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MINIMALLY INVASIVE SURGERY FOR PLEURAL EMPYEMA: ASSESSMENT OF EFFICACY

Summary of Doctoral Dissertation

Biomedical Sciences, Medicine (06 B)

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VILNIAUS UNIVERSITETAS

ŽYMANTAS JAGELAVIČIUS

PLEUROS EMPIEMOS MINIMALIAI INVAZYVAUS CHIRURGINIO GYDYMO EFEKTYVUMO ĮVERTINIMAS

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List of abbreviations

PE – pleural empyema
ATS – American Thoracic Society
VATS – video-assisted thoracic surgery
ICU – intensive care unit
VU – Vilnius University
LDH – lactate dehydrogenase
WBC – white blood cell
CCI – Charlson comorbidity index
CT – computed tomography
HU – Hounsfield unit
IU – international unit
US – ultrasound
CRP – C reactive protein
PCT – procalcitonin
NPRS – numeric pain rating scale
OR – odds ratio
CI – confidence interval
ROC – receiver operating characteristic
AUC – area under the curve

Introduction

Pleural empyema (PE) or infected (purulent) pleural effusion is known from the time of Hippocrates [1]. Despite the evolution of medicine and development of modern diagnostic and treatment methods, PE is still an increasing incidence all over the world and is associated with substantial morbidity and mortality in patients of all ages [2-7].

Infection in the pleural cavity is usually a secondary process. Its causes may include a direct or indirect spread of infection (from the lung, mediastinum or abdomen), chest trauma or it could be secondary to any kind of intervention or surgical procedure to the chest [2, 4]. So, the ideal management of empyema should primarily be its prevention. Pathophysiologically, according to the classification of American Thoracic Society (ATS) [8], empyema evolve through three stages of development, which include accumulation of fluid (exudative, stage I), loculation of pleural fluid, formation of adhesions (fibrinopurulent, stage II) and formation of inelastic fibrotic pleural peels (organisational, stage III) [4, 9]. There is no definitive diagnostic test to identify the transition of an empyema from stage to stage, especially from stage II to III [4]. The majority of patients with pleural empyema are not cured by medical therapy and usually require surgical intervention, especially from the stage II disease, when different fibrin formations (septas, peels and loculations) appear in the pleural fluid and it becomes nonhomogeneous [6, 10, 11].

The principal aims of managing pleural empyema are to control the infection and to evacuate the infected material [12]. The control of infection is reached with antibiotics. For the evacuation of infected material and refiling residual pleural space with the lung. any kind of surgical intervention is usually required. Hence, surgical management of PE plays an important role in the treatment of this disease [4, 9, 13].

Current management of empyema is still based on local empirical practice as there is no consensus on an optimal regimen [4, 11, 14]. There is a lack of adequate research data regarding treatment of pleural infections [5, 7, 9, 14]. Patient history, choice and condition still often direct the appropriate surgical management [4, 14]. The precise role of video assisted thoracic surgery (VATS) within the treatment of PE remains controversial and no consensus is currently in place on which of the surgical options and for what patient are first line [5, 10, 11, 15].

Traditionally, open thoracotomy represents the main stay of treatment for this condition, but recently, numerous attempts have been performed to replace it by a minimally invasive approach [4, 16-18]. In the era of minimally invasive techniques becoming more and more common, thoracoscopic surgery for PE increasing in popularity, even in the advanced cases. Although there are some basic principles what should be done during the operation, the way to perform it and its methods sometimes vary depending on the center or surgeon experience, available equipment or patient status.

What could be the advantages of thoracoscopic surgery for PE? It may be found in scientific literature that the VATS approach offers equivalent outcomes in terms of the resolution of disease when compared with open surgery. Some recent studies suggest that VATS and open thoracotomy are showing similar treatment success rates and are equally effective. Some studies mentioned that a successfully done VATS, being less invasive, provides additional advantages and decreases the length of hospital stay, postoperative complications, patient morbidity and mortality, postoperative discomfort, has better cosmetics and higher patient satisfaction [10, 11, 15, 16, 19, 20]. However,

thoracoscopy also has some disadvantages. There are possible complications, such as bleeding, prolonged air leak, residual pleural space, wound infection or recurrence of disease. In up to 59 % of patients, VATS is inadequate and a conversion to open thoracotomy is necessary during the same operation [6, 11, 21]. Conversion by itself leads to longer operating time and hospital stay. Thoracoscopic surgery may also fail or be incomplete, requiring additional invasive treatment later [10]. Re-do surgery after VATS (when the disease remains or a complication occurs) reaches up to 11.5 % and is higher as compared to direct open thoracotomy [11, 16]. So, any kind of failed VATS empyemectomy may result in longer operating time, prolonged hospital stay, higher need of additional surgery or a treatment at the Intensive Care Unit (ICU). All that may significantly increase patient morbidity and the general treatment cost. The identification of preoperative factors that might facilitate surgeons to select appropriate successful operation could be of great interest in clinical practice.

With this research we would like to add some more experience to the attempts at solving the serious problem of PE.

Research purpose

The purpose of the research is to evaluate early and late results of VATS empyemectomy, the rate and reasons of failed VATS (in terms of conversion) and to identify preoperative factors that could facilitate surgeons to select an appropriate successful operation for a pleural empyema.

Research tasks

1. To compare preoperative data and postoperative clinical, blood laboratory and chest X-ray data between successful VATS and conversion groups.
2. To investigate the reasons of conversion and its dependence on a patient's preoperative data.
3. To compare postoperative complications between VATS and conversion groups.
4. To identify perioperative factors that have influence on postoperative complications.
5. To evaluate complications, the recurrence of disease and outcomes in the late postoperative period.

Propositions to be defended

1. Minimally invasive (VATS) surgery could be effective enough for pleural empyema management.
2. Some preoperative factors could help select patients for minimally invasive surgery and could help predict its failure.

Significance and novelty of the research

Global perspective

Pleural empyema is known as high impact orphan disease on public health perspectives. This definition refers to medical conditions associated with substantial morbidity and mortality, yet still lacking adequate scientific attention [5]. The morbidity of pleural infections is increasing, whereas the mortality of hospitalised patients is reported to be up to 33 % [22-26].

Why is it a high impact disease? The elderly population is increasing due to the progress of medicine. Therefore, the lifespan of people with various chronic diseases is prolonged. There is also an increase of numerous immunosuppressive conditions due to larger amounts of immunosuppressive medicines used, development of organ transplantation and unrelenting consumption of drugs, especially among younger people. The increase of antibiotic resistant bacteria is noticed.

Why is it an orphan disease? The insufficient interest of scientists and, possibly, insufficient funding for research limit our knowledge and establish the lack of high-quality evidence-based data on the diagnosis and treatment of pleural infection [5, 27, 28]. The vast majority of studies is retrospective. There is a serious lack of high-quality evidence-based guidelines of treatment; furthermore, much is still dependent on the individual experience of the surgeon, requests of the patients as well as facilities of the hospital. A considerable portion of traditional 'truths' on the pathophysiology and treatment of PE is not evidence-based and therefore passes from generation to generation without any detailed revision and analysis [29].

Upon searching for the term 'empyema' in keywords, titles or abstracts in the Cochrane Database, which contains highest quality evidence-based research, one can only find 5 studies, whereas the term 'pneumonia' is found in 186, and the term 'lung cancer' – in 95 studies.

In recent literature, two multi-centered prospective randomised trials on the use of fibrinolytic agents in intrapleural sepsis management in adults were published [30, 31]. However, the surgical management for PE is the most controversial [4, 5]. All experts agree with certain fundamental principles of the pleural infection management. Nevertheless, there are plenty of different opinions in different centers on when and how the PE patient should be treated.

National perspective

Pleural empyema is not an uncommon, unknown or threatened pathology in Lithuania as well as in the rest of the world. In addition to those already mentioned causes of increased morbidity regarding the progress of medicine and certain social circumstances, our population faces a common problem of careless attitude towards ourselves and our health. Lithuanians sometimes tend to avoid and delay seeking medical help in due time, keep on working while being ill and try to cure themselves in various ways. Sometimes, an unfounded faith that everything will pass by itself is noticed. Therefore, it is common to become anxious with one's health only when the disease has already advanced. On the other hand, the management of health services appears not to be working properly for a patient seeking for timely and immediate help. Often a patient with

advanced PE meets the surgeon only after a long journey through different medical professionals. In our country, the prevalence of purulent pleural pathology is also determined by the lifestyle of certain social layers, where alcohol and drug abuse is common. The statistical analysis of the last decade reveals that, on average, 76 patients per year are operated on for various purulent pleural pathology at the Centre of General Thoracic Surgery, Vilnius University (VU). However, moving towards the new millennium, the tendency of increasing morbidity was observed [32].

Minimally invasive thoracic surgery is a quite new technique in Lithuania. Thoracoscopic operations for thoracic patients were started to be performed in 2006 in the Centre of General Thoracic Surgery, VU, when appropriate equipment became available. One of the indications for VATS was PE. In medical literature, there are only few publications from Lithuanian authors regarding pleural infection [32-36] and another few regarding VATS for other indications [37-39]. In spite of that, minimally invasive surgery for PE is a new field in Lithuania and there are no other reports as we know regarding this topic from the country.

The question is how to select the appropriate candidate for minimally invasive intervention out of a very disperse population of pleural infection patients? On which of the patients is it better to perform classic open thoracotomy straight away in order to provide maximum benefits and the lowest cost? All of this information is still unknown and thus far there are many debates on this topic in Lithuania and in the world.

Practical benefits

Modern surgery is mainly developed in three directions – organ transplantation, development of artificial agents and minimally invasive techniques. Thoracoscopic surgery is a minimally invasive thoracic surgery. The main aims of minimally invasive surgery are to reduce the postoperative discomfort, pain, provide better cosmetics and higher patient satisfaction in comparison with classic open surgery [40]. Minimally invasive techniques become more and more common and VATS for PE is also getting more and more popular, even in advanced cases. A successfully done VATS operation may reduce postoperative pain, need for analgesics, shorten hospitalisation time as well as overall recovery time, providing positive effects on national social and economic policy. However, VATS requires additional input, including adequate equipment and instruments as well as disposable medical supplies [40]. Minimally invasive surgery for PE sometimes fails and leads to conversion to open thoracotomy. This leads to longer operating time, longer general anesthesia, consumption of more medication and medical supplies.

With this research, we aim to determine certain preoperative factors that might define the guidelines for successfully selecting the patient for minimally invasive surgery. That could help avoid ‘double’ surgery. With our research, we aim to contribute to the attempts further analyzing this problematic topic.

Patients and methods

Patients

In order to evaluate the efficacy of VATS for PE and to identify preoperative factors that could predict VATS failure in term of conversion, a clinical observational study was performed, prospectively including patients with PE. Patients were included in the study during the period from January 2011 till June 2014 irrespectively of chronicity of disease (stage II/III according ATS classification) who were treated at the Centre of General Thoracic Surgery, VU.

The diagnosis of PE was confirmed in all cases if any kind of infected pleural effusion was identified (according inclusion criteria) and if the general clinical or blood laboratory signs of infectious inflammatory process in the organism were assessed.

Inclusion criteria

Inclusion criteria (at least one from four):

- Pus on pleural aspiration;
- Positive culture from pleural space;
- Encapsulation of the fluid in pleural space;
- Pleural fluid laboratory analysis:
    - pH<7.3;
    - Lactate dehydrogenase (LDH) > 1000 IU/l;
    - Glucose < 2,22 mmol/l;
    - Protein > 10 g/l;
    - White blood cell (WBC) count > 500/µl.

Mandatory clinical and blood laboratory signs of infection.

Exclusion criteria

Pleural empyema is a multivariable disease according its etiology, clinical course and is often associated with other different pathological conditions. In order to compose a more homogeneous study group, we excluded patients from the study according the next criteria.

Exclusion criteria:

- Previous thoracic surgery (during the last 2 years);
- Presence of bronchopleural fistula;
- Presence of empyema necessitatis;
- Lung or pleural malignancy;
- Known tuberculosis;
- Mediastinitis;
- Time of illness >3 months;
- Severe neurological or psychiatric condition.

All patients before and after surgery were examined and managed routinely.

The aim of the surgery is: (1) to evacuate purulent debris from the pleural space and (2) to achieve total lung reexpansion. Surgical operation in all patients was started as VATS procedure. Sometimes during the operation, we assessed that there was impossible to perform it successfully by VATS and to reach surgical aims. In these cases, conversion to the open thoracotomy was considered.

According to the success of VATS, two groups were formed and analysed later:

→ **Successful VATS** group (operation ended by VATS);
→ **Conversion** group (VATS was converted and ended as open thoracotomy).

Conversion to the thoracotomy was considered if there were any of the following:

- Inability to enter the pleural cavity or to release whole lung safely due to firm adhesions;
- Inability to make proper decortication and to achieve total lung reexpansion;
- Intraoperative bleeding (>500 ml / 30 min);
- Intolerance of single lung ventilation.

Collected and analysed preoperative data

Different preoperative factors that could influence conversion and postoperative outcome were collected and analysed (Table 1).

Time of illness – time (in days) from the beginning of the disease (clinical signs and symptoms after which radiologically infected pleural effusion was identified) till hospitalisation at the Department of General Thoracic Surgery.

Treatment before that refers to surgery was evaluated: if a patient was treated at all, if he was treated at a hospital, if he received antibiotics or underwent any therapeutic intervention (thoracocentesis or chest tube placement).

Comorbidities were assessed calculating Charlson comorbidity index (CCI) [41].

Radiological variables were collected on computed tomography (CT) scan images: number of loculations, total volume of empyema, density of pleural fluid collection (in Hounsfield units (HU)), thickening of parietal pleura and presence of air bubbles in the empyema cavity. The percentage of opacified hemithorax was recorded by evaluating the chest X-ray. Pleural ultrasound (US) was performed in all patients only for diagnostic purposes, in order to assess fibrin formations (nonhomogeneous fluid) in the pleural cavity.

The assessed laboratory blood variables were preoperative hemoglobin concentration, WBC count, serum C-reactive protein (CRP) and procalcitonine (PCT) levels. The assessed laboratory pleural fluid variables were positive culture, pH, protein, glucose, LDH levels, WBC count and leukogram.

Table 1. Collected and analysed preoperative factors

Group of factors	**Factor**
Demographic data	Age (years)
	Sex
Anamnesis data	Time of illness (days)
	Symptoms on admission
	Previous treatment:
	at the hospital (yes/no)
	with antibiotics (yes/no)
	therapeutic intervention – thoracocentesis or chest tube placement (yes/no)
	Comorbidities (CCI score)
Objective clinical examination	Temperature on admission (°C)
Radiological features	Opacified hemithorax on X-ray (%)
	CT scan: empyema volume (ml)
	number of encapsulates
	parietal pleura thickness (mm)
	density of empyema (HU)
	air bubbles in empyema (yes/no)
Pleural fluid features	Visually frank pus (yes/no)
	pH
	LDH (IU/l)
	Protein (g/l)
	Glucose (mmol/l)
	WBC count (/µl)
	Leucogram: neutrophils (%)
	lymphocytes (%)
	Bacteriological culture (positive/negative)
Blood laboratory features	WBC count (u/µl)
	Hemoglobin concentration (g/l)
	Protein (g/l)
	CRP (mg/l)
	PCT (µg/l)

Surgery

All surgical procedures have been performed under general anesthesia. All patients were managed with a double-lumen endotracheal tube for single lung ventilation and were placed on the lateral decubitus position. A small antidecubitus mattress was placed below the dependent hemithorax to obtain a slight splitting of the intercostal spaces.

Usually, two 12 mm diameter trocars have been used. However, in some cases, it was impossible to remove all of the debris and to make a complete decortication of the lung through two ports. In these cases, an additional 10 mm diameter trocar was used. A 30° camera was preferred to allow easier exploration of the pleural cavity and better visualisation of infected material collections. The initial port was performed in the

sixth or seventh intercostal space in the mid-axillary line, independently of the location of empyema cavities. After digital exploration, the first 12 mm thoracoscopic trocar was placed. If no free pleural space was found, firstly, the lung around the initial port was blindly dissected from the chest wall using the index finger and a peanut pusher for trying to move it gently and as close to the thoracic wall as possible. Then, after introducing the camera through the first port, the remaining one or two ports were made according to the empyema cavities location under thoracoscopic vision to avoid injury to the underlying lung parenchyma. Fluid, loculations, septa, all solid debris and adherent peel from parietal and visceral pleura were removed using an endoscopic aspirator – irrigator, a special thick and rigid 10 mm diameter aspirator, Winter forceps and curettes. The lung was completely mobilized from the apex to the diaphragm. If the lung was seen not to re-expand completely, then additional decortication of the lung (removing the cortex from the lung) was performed using a small peanut dissector and Kelly or thoracoscopic forceps. Material for microbiological analysis and pieces of parietal pleura for histological examination were collected in all patients.

After decortication was accomplished, the pleural space was irrigated with an antiseptic solution; an assessment of lung re-expansion and an air leak were made. The lung was ventilated with 40 cmH_2O pressure and evaluation was made if it would reach the inner surface of the chest wall. If the lung was to reach the inner surface of the chest wall, it would have been decided that re-expansion is sufficient and the operation would end as VATS; otherwise, there was decided that decortication is not sufficient and conversion to open thoracotomy was performed.

At the end of the procedure, usually two 32 French gauge size chest tubes were placed. Neither suction nor irrigation via chest tubes were directly used postoperatively.

Subsequently, analgesics were administered after the operation on demand. An intensive respiratory rehabilitation program was started since the first postoperative morning. Antibiotics were given empirically (Cefuroxime and Metronidazole) if there was no established bacteriological agent or according to the microorganism and its sensitivity. Chest tubes were removed when there was no air leak and drainage output was less than 200 ml per 24 hours.

Early postoperative period

The early postoperative period was the time from surgery to discharge from the hospital. In order to evaluate treatment results and outcomes, total hospital stay, postoperative hospital stay, time spent at the ICU, operating time, postoperative chest tube time, morbidity and mortality were also recorded.

Prolonged air leak (>5 days), wound infection, hemothorax, persistence or recurrence of disease (when clinical signs remained and a significant amount of effusion in the chest cavity was observed) and death were considered as complications. Additional interventional treatment required for complications was also assessed.

Evaluation of recovery from the disease, changes in blood laboratory findings (WBC, CRP and PCT), chest X-ray (what part (in per cent) of opacified hemithorax diminished) and clinical signs were analysed. A patient was considered recovered if there were no clinical signs of infection, diminishing laboratory blood inflammatory features,

opacification of hemithorax on chest X-ray and the amount of residual effusion on pleural US was less than 20 mm.

The chest X-ray was evaluated prior to and after operation by two independent radiologists having no information about the patient and operation. Preoperatively, the area of opacified hemithorax (expressed in percentage) was assessed. Postoperatively, the diminishing of opacification (expressed in percentage from the preoperative X-ray) was assessed.

Postoperatively, pain was evaluated using the numeric pain rating scale (NPRS) (Figure 1). Patients were asked to assess their pain on the scale the next day after the last chest tube was removed. The need of narcotic analgetics in the early postoperative period was also assessed. It was counted how many daily doses of narcotics were necessary in average during the early postoperative period. A single dose was considered to be 10 mg 1 ml of Morphine solution. Pain and the need of analgetics were compared between successful VATS and conversion groups.

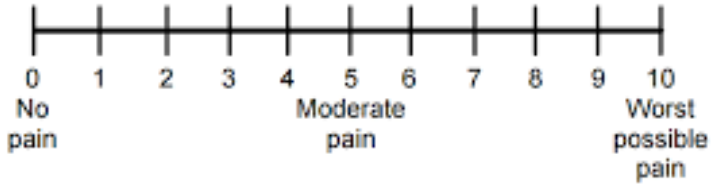

Figure 1. Numeric (0-10) pain rating scale.

All postoperative data was compared between successful VATS and conversion groups.

Late postoperative period

The late postoperative (follow-up) period was considered as the time from discharge till the last day of the follow-up (17 of March 2015). A control chest X-ray and pain evaluation according to NPRS were made in 1 and 6 months after the operation. Late complications, recurrences of disease and death were also recorded. This data was also compared between successful VATS and conversion groups.

Statistical analysis

Statistical analysis was performed using SPSS 19.0 for windows (SPSS Inc. Chicago, Illinois, USA). Categorical data was presented as a frequency (%) and continuous variables were expressed as a mean ± standard deviation if the distribution was a normal and as median and quartile range if otherwise. Normal distribution of continuous data was tested by Shapiro-Wilk test. Categorical data were compared using χ^2 test or Fisher exact test. Continuous variables, according to cases if they were independent or dependent, were compared using an independent or dependent t-test respectively on normally distributed variables; Mann-Whitney and Wilcoxon tests were performed comparing non-normally distributed continuous variables respectively.

Potential outcome predictive factors were evaluated using univariate and multivariate binary logistic regression analysis models, counting the odds ratio (OR) and 95 % confidence interval (CI).

General surveillance was evaluated using Kaplan-Meier analysis. Influence of different factors to morbidity was analysed using Cox regression analysis.

A statistical significance level was set at 0.05.

Bioethics

The study was approved by Vilnius Regional Bioethical Committee (No. 158200-06-312-89).

Results (research findings)

General descriptive data

There were 71 patients prospectively included in the study, on whom VATS for stage II/III nonspecific PE were attempted to perform.

Video assisted thoracic surgery was successfully performed in 53 (74.6 %) cases, whereas in 18 (25.4 %) cases conversion to the open thoracotomy was required (Figure 2).

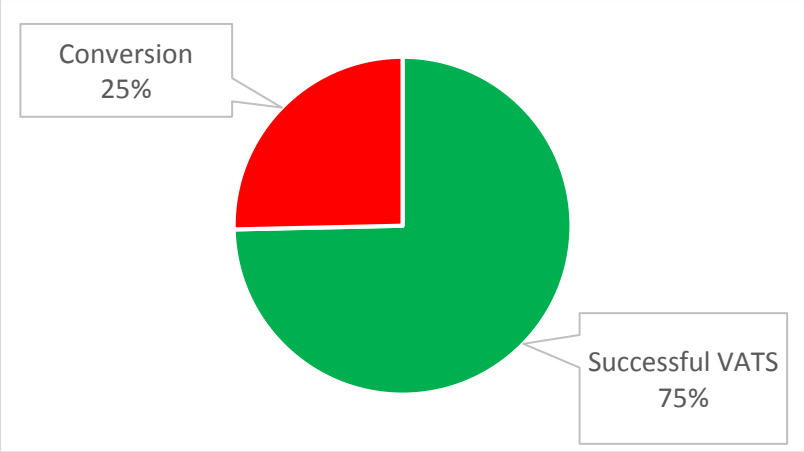

Figure 2. Surgery: success of VATS for pleural empyema.

There were 62 (87.3 %) males and nine (12.7 %) females and there was no significant difference between successful VATS and conversion groups (Figure 3).

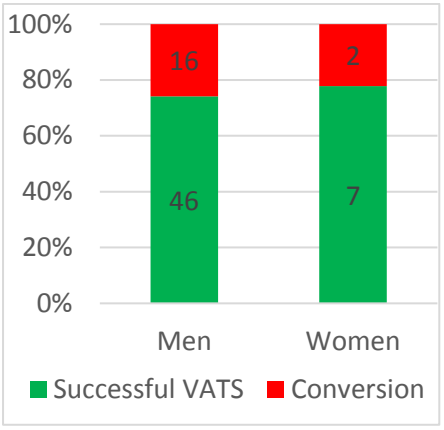

Figure 3. Success of VATS for PE according to sex (p=1.0).

The mean age was 52 ± 16 years and did not differ significantly between the two groups (52 ± 17 in VATS and 53 ± 11 years in conversion group, p=0.85). Looking into age groups every ten years we can see that morbidity is very similar from 31 to 70 years (Figure 4).

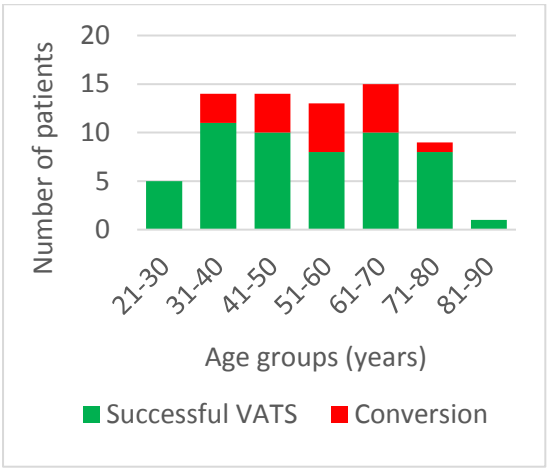

Figure 4. Distribution of patients according to age.

The median duration of hospital stay was 11 (9 – 16) days. The median postoperative hospital stay was 7 (6 – 10) days. The median ICU time was 1 (0-1) day (mean 0.7 ± 0.6 days). Converted cases spent more time after the operation at the ICU, the mean duration was 0.94 ± 0.54 days comparing to 0.62 ± 0.66 days in successful VATS group, p=0.045. But there was no difference between groups according to hospital or postoperative times (Figure 5). Converted cases more often required treatment at the ICU – 83.3 % vs. 52.8 % of cases respectively, p=0.022.

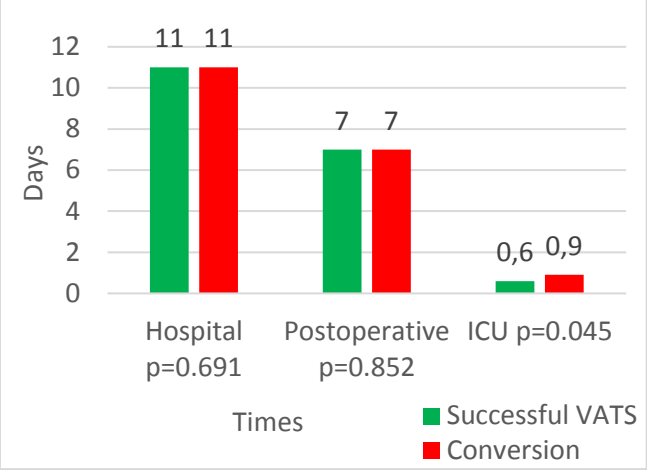

Figure 5. Surgical treatment time between groups.

The median time of illness was 19 (10-25) days. However, a significant difference was found between successful VATS and conversion groups – 14 (9-23) and 28 (20-32) days respectively, p<0.001 (Figure 6).

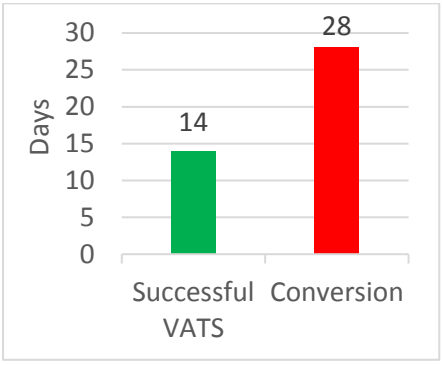

Figure 6. Median time of illness in successful VATS and conversion groups, p<0.001.

The main symptoms presented on admission are shown in Table 2. There was no significant difference in presented symptoms between successful VATS and conversion groups.

Table 2. Symptoms presented on admission.

Symptom	Total n=71 (%)	Successful VATS n=53 (%)	Conversion n=18 (%)	p-value
Fever	65 (92)	50 (94.3)	15 (83.3)	0.166
Chest pain	60 (85)	43 (81.1)	17 (94.4)	0.269
Dyspnea	50 (70)	39 (73.6)	11 (61.1)	0.316
Weakness	38 (54)	27 (50.9)	11 (61.1)	0.455
Cough	30 (42)	24 (45.3)	6 (33.3)	0.375
Sputum production	8 (11)	7 (13.2)	1 (5.6)	0.670
Sweating	7 (10)	5 (9.4)	2 (11.1)	1.000
Weight loss	3 (4)	2 (3.8)	1 (5.6)	1.000

Since median time of illness was 19 days, naturally most patients were treated in some way before admission. According to anamnesis data, 61 of all patients (86 %) were previously treated. Of all patients, 58 (82 %) were treated at the hospital and 59 (83 %) received antibacterial treatment. Of all patients, 21 (30 %) underwent therapeutic intervention (thoracocentesis or chest tube placement). The comparison of previous treatment between successful VATS and conversion groups is shown in Figure 7.

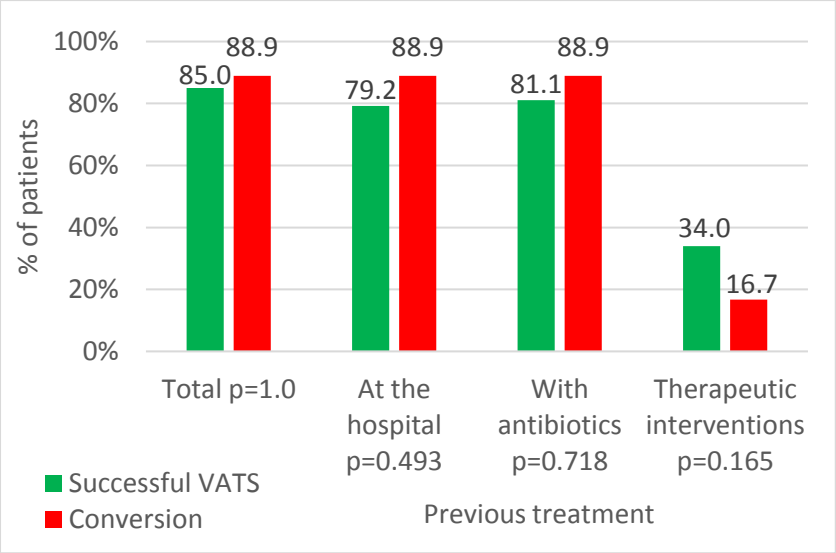

Figure 7. Treatment until the admission to the department of General Thoracic Surgery.

In evaluating co-morbidities according to the CCI score, we did not find any significant difference between successful VATS and conversion groups. There were 58.5 % of patients in successful VATS and 61.1 % pf patients in conversion groups in whom CCI score was 0 (p=0.845).

The mean temperature on admission was 38.0 ºC ± 0.7 ºC and there was no significant difference between successful VATS and conversion groups – 38.0 ± 0.6 ºC and 37.7 ± 0.8 ºC respectively, p=0.118.

Bacteriology of pleural fluid

Infected material from pleural cavity was examined for bacteriology in all patients. However, only in 17 of all patiens (23.9 %) positive culture was identified. Mixed culture was identified in one of the patients. The variety of identified bacterial families is shown in Figure 8. The main causative microorganisms were from *Streptococcaceae* (5 cases), *Enterobacteriaceae* (4) and *Staphylococcaceae* (3) families.

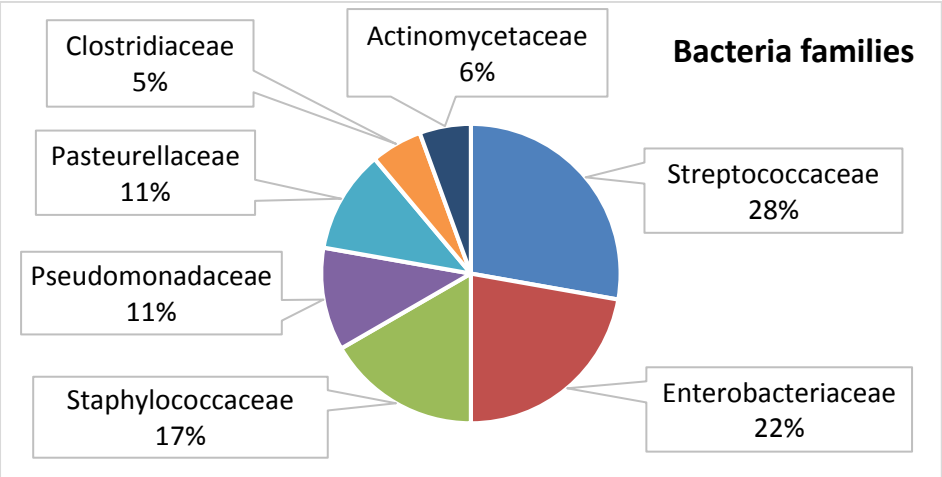

Figure 8. Bacteria families identified from pleural space.

Positive pleural culture did not differ significantly between successful VATS and conversion groups – 20.8 % and 33.3 %, p=0.341 (Figure 9).

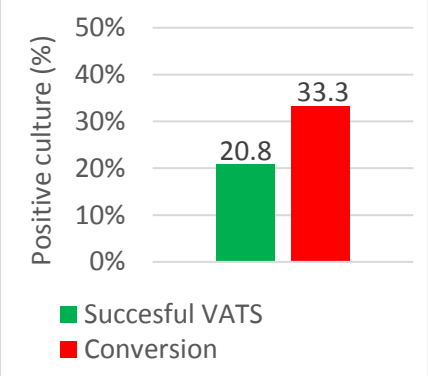

Figure 9. Positive pleural culture comparison between two groups, p=0.341.

Laboratory blood tests

Preoperative laboratory blood test findings and their comparison between successful VATS and conversion groups are shown in Table 3.

Table 3. Analysed preoperative blood tests and comparison between groups.

Variable	Total n=71	Successful VATS n=53	Conversion n=18	p-value
Hemoglobin (g/l)	121 ± 20	120 ± 21	122 ± 17	0.718
WBC count (/µl)	12.2 (8.9-16.6)	13.2 (9.6-16.9)	10.8 (8.4-13.9)	0.129
CRB (mg/l))	143.6 (91-203)	155.1 (100.7-211.5)	111.2 (59.9-176.2)	0.081
PCT (ng/ml)	0.19 (0.11-0.43)	0.21 (0.09-0.41)	0.17 (0.12-0.84)	0.761
Protein (g/l)	66.9 ± 7.6	66.9 ± 8.2	66.8 ± 5.5	0.963

The comparison of preoperative and postoperative blood laboratory findings is shown in Table 4. There was a significant decrease in hemoglobin, WBC, CRP and PCT levels in both groups and there was no significant difference noticed in postoperative findings, comparing between successful VATS and conversion groups.

Table 4. Blood laboratory tests before and after the operation in successful VATS and conversion groups.

Variable	Operation	Before operation	After operation	p-value
Hemoglobin (g/l)	Successful VATS	123 (107.5-134)	116 (104-123.5)	0.011
	Conversion	123 (111.9-131.5)	114 (101.5-123.5)	0.016
WBC count (/µl)	Successful VATS	13.2 (9.6-16.9)	8.3 (6.6-10.3)	<0.001
	Conversion	10.8 (8.4-13.9)	7.9 (6.9-9.5)	0.001
CRP (mg/l)	Successful VATS	155.1 (100.7-211.5)	46 (22.0-58.1)	<0.001
	Conversion	111.2 (59.9-176.2)	41.6 (23.7-53.6)	<0.001
PCT (ng/ml)	Successful VATS	0.21 (0.09-0.41)	0.08 (0.04-0.12)	<0.001
	Conversion	0.17 (0.12-0.84)	0.06 (0.05-0.07)	0.022

Pleural fluid analysis

Pleural fluid after aspiration was firstly evaluated visually, whether it is frank pus or not. Frank pus was found in 23 of all patients (32.4 %). By comparing the presence of frank pus in pleural cavity between successful VATS and conversion groups, we found a significant difference – 24.5 % and 55.6 % of patients respectively, p=0.015 (Figure 10).

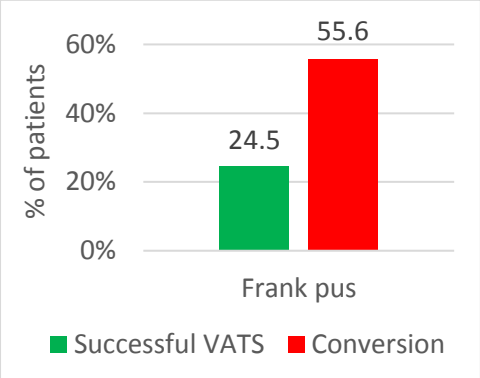

Figure 10. Visual characteristic of pleural fluid in both groups, p=0.015.

Preoperative pleural fluid laboratory findings and their comparison between successful VATS and conversion groups are shown in Table 5. There was no significant difference in any of the analysed factors between two groups.

Table 5. Preoperative pleural fluid laboratory findings and their comparison between the groups

Factor	Total n=71	Successful VATS n=53	Conversion n=18	p-value
pH	7.1 ± 0.3	7.12 ± 0.31	7.05 ± 0.26	0.419
LDH (IU/l)	4352 (751-8206)	4052 (729-7584)	6046 (1415-9896)	0.165
Glucose (mmol/l)	1.95 (0.28-3.53)	2.14 (0.29-3.54)	1.70 (0.25-3.63)	0.995
Protein (g/l)	44.6 (41.9-49.7)	44.9 (43.5-49.5)	42.9 (40.1-51.4)	0.258
WBC count (/µl)	4120 (1030-28400)	3200 (965-22600)	10955 (1175-40200)	0.247
Neutrophils (%)	85 (59-91)	86 (49-91)	84.5 (65-93)	0.900
Lymphocytes (%)	13 (6-36)	13 (7-48)	10.5 (6-25)	0.716

Preoperative radiological data

Preoperatively, a chest X-ray, pleural US and chest CT were performed in all patients. By evaluating the chest X-ray, it was found that median opacification of hemithorax was 50 (30-70) %. In comparing opacification between successful VATS and conversion groups, the difference was not significant – 50 (31-70) % and 47 (29-71) % respectively, p=0.591 (Figure 11).

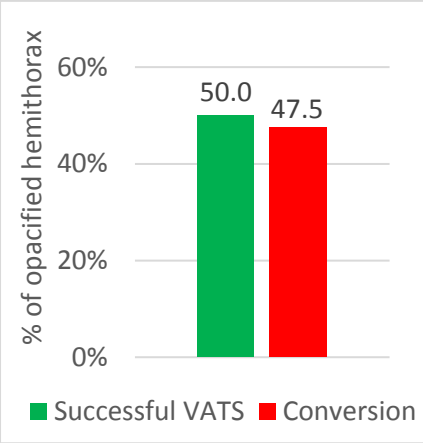

Figure 11. Opacification of the hemithorax on chest X-ray before the operation in both groups, p=0.591.

On the chest CT scan, the median amount of encapsulates was 2 (1-3). The median volume of empyema was 780 (618-1121) ml. The median thickness of parietal pleura was 4 (3-5) mm. The mean density of empyema was 14.8 ± 5.0 HU. Air bubbles in the empyema cavity were identified in 21 of all patients (29.6 %). By comparing all of the analysed CT scan features between successful VATS and conversion groups, no significant difference was found (Table 6).

Table 6. Features from CT scan compared between two groups.

Factor	Successful VATS n=53	Conversion n=18	p-value
The amount of encapsulates	2 (1-3)	2 (1-3)	0.573
Empyema volume (ml)	801 (644-1084)	752 (463-1427)	0.653
Thickness of parietal pleura (mm)	4 (3-4.5)	4 (3.8-5)	0.362
Density of empyema (HU)	14.8 ± 5.4	14.8 ± 3.9	0.987
Presence of air bubble in empyema	14 (26.4 %)	7 (38.9 %)	0.316

Pleural US was performed only for diagnostic purposes and any US factors were not further analysed.

Surgery

For all patients, surgery was started as VATS. However, in 18 of all patients (25.4 %), a conversion to open thoracotomy was required. Obliterated pleural space by

firm adhesions, an inability to release the whole lung (in 12 patients) and failure to achieve total lung re-expansion (in 6 patients) were the main reasons for conversion.

The mean operating time was 82 ± 26 minutes and there was a significant difference between successful VATS and conversion groups – 76 ± 22 and 100 ± 28 minutes respectively, p<0.001.

Influence of preoperative factors on conversion (logistic regression analysis)

According to the univariate binary logistic regression analysis on possible predictors of conversion, we have found that the time of illness and frank pus in aspiration significantly increased the conversion rate. By looking for independent predictors of conversion on multivariate logistic regression analysis, we have found that each day of illness spent before surgery (OR 1.1, 95% CI 1.0-1.2, p=0.004) and frank pus in aspiration (OR 4.4, 95% CI 1.2-15.3, p=0.021) had significantly increased the chance of conversion (Table 7).

According to the receiver operating characteristic (ROC) analysis, the time of illness had a high predictive value for conversion (area under the ROC curve (AUC) – 0.8, 95% CI 0.7-0.9, p<0.001). The cut-off value for time of illness was 16 days with sensitivity at 94.4% and specificity at 54.7% (Figure 12).

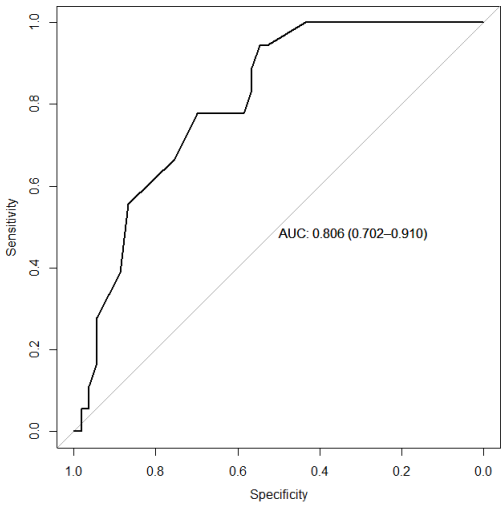

Figure 12. ROC curve for time of illness, p<0.001 (AUC 0.8 (0.7-0.9, 95 % CI), p<0.001).

Conversion was necessary in 41.5 % of patients that were ill for 16 or more days and only in 3.3 % for those who were ill for less than 16 days. For patients who were ill for 16 or more days, the chances of conversion were 19.1 times higher as compared to those who were ill for a shorter time (p=0.002). The conversion rate according to the time of illness is shown in Figure 13.

Table 7. Influence of different preoperative factors on conversion.

Factor	Univariate analysis		Multivariate analysis	
	OR (95 % CI)	p-value	OR (95 % CI)	p-value
Demographic data				
Sex: man	1.217 (0.229-6.475)	0.818		
Age	1.003 (0.969-1.038)	0.876		
Anamnesis data				
Time of illness	1.091 (1.029-1.157)	0.003	1.097 (1.031-1.167)	0.004
Symptoms: pain	3.953 (0.469-33.299)	0.206		
Fever	0.300 (0.055-1.644)	0.165		
Dyspnea	0.564 (0.183-1.742)	0.320		
Cough	0.604 (0.197-1.850)	0.378		
Weakness	1.513 (0.509-4.501)	0.456		
Prior treatment at the hospital	2.095 (0.418-10.513)	0.369		
Prior treatment with antibiotics	1.860 (0.367-9.430)	0.453		
Prior thoracocentesis or chest tube placement	0.389 (0.099-1.521)	0.175		
CCI score	1.085 (0.672-1.750)	0.738		
Objective clinical examination				
Temperature (°C)	0.525 (0.233-1.185)	0.121		
Blood laboratory findings				
Hemoglobin concentration	1.005 (0.978-1.033)	0.714		
WBC count	0.940 (0.845-1.047)	0.261		
Protein	0.999 (0.930-1.072)	0.969		
CRP	0.994 (0.986-1.001)	0.093		
PCT	0.970 (0.684-1.376)	0.864		
Pleural fluid findings				
Visually frank pus	3.846 (1.254-11.796)	0.018	4.374 (1.249-15.320)	0.021
pH	0.471 (0.077-2.875)	0.414		
LDH	1.000 (1.000-1.000)	0.190		
Glucose	0.961 (0.751-1.228)	0.748		
Protein	1.007 (0.956-1.061)	0.786		
WBC count	1.000 (1.000-1.000)	0.468		
Leukogram: neutrophils %	1.006 (0.988-1.025)	0.510		
lymphocytes %	0.992 (0.973-1.011)	0.417		
Positive pleural culture	1.909 (0.684-6.236)	0.284		
Gram+ bacteria	1.667 (0.210-13.223)	0.629		
Radiological findings				
Opacification of the hemithorax on chest X-ray	0.993 (0.969-1.017)	0.563		
CT scan: thickness of parietal pleura	1.322 (0.727-2.407)	0.360		
empyema volume	1.000 (0.999-1.001)	0.866		
density of empyema	1.001 (0.899-1.115)	0.986		
number of encapsulates	1.121 (0.703-1.787)	0.631		
presence of air bubbles	1.773 (0.574-5.473)	0.320		

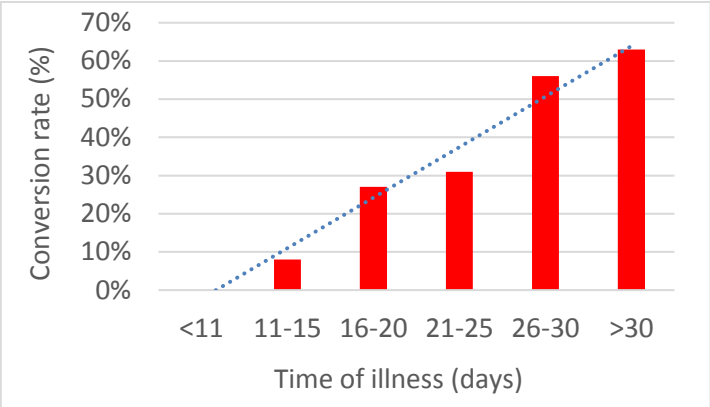

Figure 13. Conversion rate according to the time of illness

Early postoperative period

The median chest tube time after the operation was 4 (3-6) days and it did not differ significantly between successful VATS and conversion groups, p=0.909 (Figure 14).

By analysing the changes on postoperative chest X-rays (what part (in per cent) of opacified hemithorax diminished), we found that median diminishing of opacification was 90 % (79-93). We did not find any significant difference in comparing chest X-ray changes between successful VATS and conversion groups, p=0.526 (Figure 15).

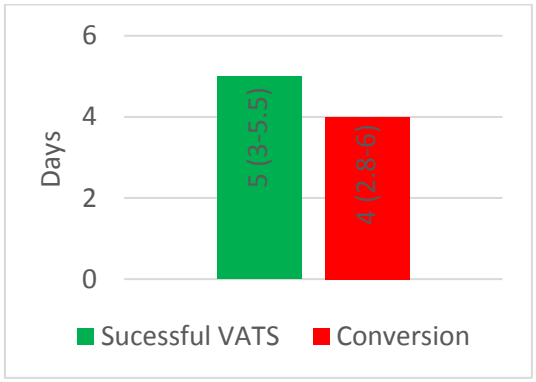

Figure 14. Median chest tube time after operation in both groups, p=0.909.

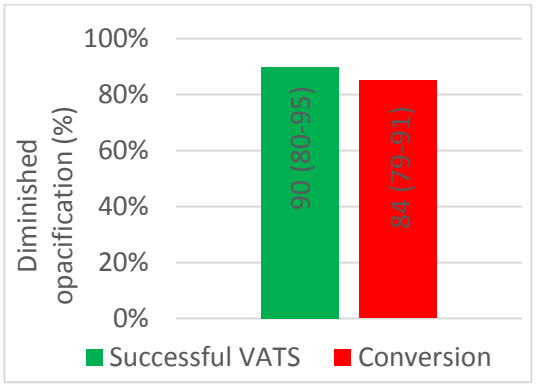

Figure 15. Chest X-ray changes (part (in per cent) of opacified hemithorax diminished) from preoperative opacification, p=0.526.

By evaluating postoperative pain according NPRS in an early postoperative period, we found a significant difference between successful VATS and conversion groups – 2 (1.3-3) and 5 (3-6) respectively, p<0.001 (Figure 16).

The median need of analgetics was 1.1 (0.8-1.6) doses per day. A significant difference was found by comparing the need between successful VATS and conversion group, respectively 1 (0.7-1.4) and 1.6 (0.9-2.4) doses, p=0.019 (Figure 17).

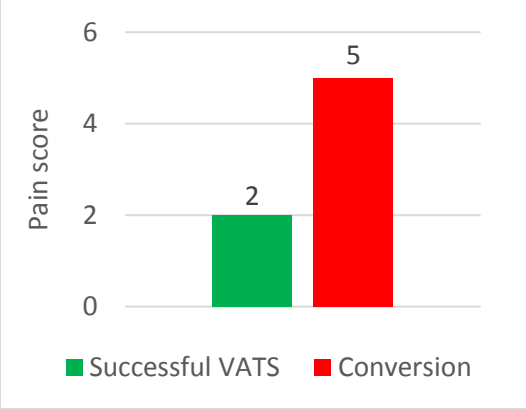

Figure 16. Postoperative pain score according NPRS in early postoperative period in two groups, p<0.001.

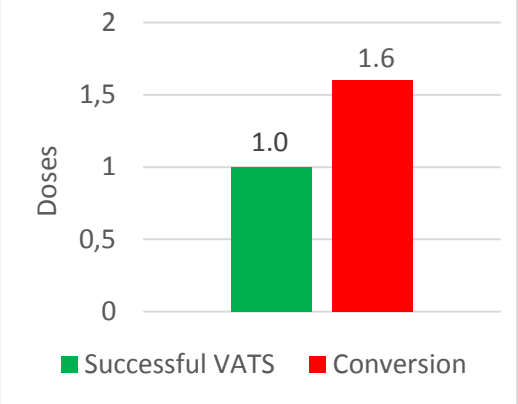

Figure 17. The median demand of narcotic analgetics per day in the early postoperative period in both groups, p=0.019.

Complications

Fourteen patients (19.7 %) had postoperative complications during the early postoperative period (Table 8). Six of them (8 %) required additional surgery: three due to postoperative hemothorax and the other three due to persistence of disease. All six patients that required re-do surgery in the early postoperative period underwent primary successful VATS operations. There was no patient that required re-do surgery after conversions. Two patients returned during the first month after discharge with recurrences of disease, both being from the VATS group and both of the patients required re-do surgery as well (Table 8). As we looked further into re-operations, we found that in the majority of the patients (7 out of 8), the time of illness was ≥16 days (Table 9). According to the logistic regression analysis, we discovered that if the time of illness is ≥16 days, the chance of re-do surgery increases by six times (p=0.104).

Table 8. Postoperative complications.

Complication	Successful VATS n=53	Conversion n=18	p-value
Total	10 (18.9 %)	4 (22.2 %)	0.742
Recurrence (persistence) of disease	4 → 3*	0	
Prolonged air leak	2	1	
Wound infection	1	2	
Hemothorax	3 → 3*	0	
Death	0	1	
Recurrence after discharge**	2 → 2*	0	

*cases that required re-do surgery in the early postoperative period; **recurrence after discharge is not included in the total count of postoperative complications

There is a tendency for the time of illness to not only have influence on VATS failure, but also for increasing the risk of postoperative complications that require re-do surgery (Table 9).

Table 9. Reoperations according to time of illness.

Operation	Successful VATS		Conversion	
Time of illness	<16 days	≥16 days	<16 days	≥16 days
	n=29	n=24	n=1	n=17
Complications	3	7	0	4
Re-do due to complication	1	5	0	0
Recurrence after discharge	0	2	0	0
Total re-do surgery	1	7	0	0

Complications were associated with longer hospitalisation time (11 (8 – 13) days (patients without complications) vs. 23 (18 – 29) days (patients with complications), p<0.001), postoperative time (7 (6 – 8) vs 20 (14 – 25) days, p<0.001) and ICU time (1 (0 – 1) vs 1 (1 – 2) days, p=0.028).

One of the patients died and he was from the conversion group. The reason of death was severe hepatic cirrhosis and liver insufficiency. Thirty day mortality was 1.4 %.

Predictors for complications (logistic regression analysis)

Preoperative and operative factors were analysed for the influence on postoperative complications. According to the multivariate logistic regression analysis for preoperative factors, we have found that the CCI score (1.8 times (95 % CI 1.1-3.1), p=0.028) and positive pleural culture (4.4 times (95 % CI 1.1-16.9), p=0.032) significantly increase the chance of postoperative complications (Table 10). By looking at operative factors, we found that only time spent at the ICU significantly increased the chance of postoperative complications (Table 11).

Late postoperative period and follow-up

On the follow-up, we evaluated general surveillance. The start point was the day of operation and the last day of follow-up was March 17, 2015. The median follow-up was 858 (498-1147) days. Observed were late recurrences of the disease, the fact itself, date and reason of death.

All patients were examined in one and six months after the operation. At one month follow-up, we checked 94 %, and at six months – 83 % of all patients. Later we followed them only for mortality or late recurrences.

During the follow-up, 11 (15.5 %) patients died. The reasons of death were not associated with previous pleural infection. Cox regression analysis revealed that only the CCI score had significant independent influence on general mortality (Table 12). There was no late recurrence.

General surveillance according to Kaplan-Meier analysis is shown in Figure 18. There was no significant difference between successful VATS and conversion groups (p=0.526). Thirty day surveillance was 98.6 %, six months – 95.8 %, one year – 93.0 %, three years – 84.5 %.

Table 10. Preoperative predictors of complications

Factor	Univariate analysis		Multivariate analysis	
	OR (95 % CI)	p-value	OR (95 % CI)	p-value
Demographic data				
Sex: man	0.840 (0.155-4.566)	0.840		
Age	1.021 (0.983-1.060)	0.292		
Anamnesis data				
Time of illness	1.031 (0.983-1.082)	0.203		
Symptoms: pain	0.350 (0.086-1.424)	0.143		
fever	1.250 (0.134-11.641)	0.845		
dyspnea	0.702 (0.204-2.419)	0.576		
cough	1.031 (0.316-3.362)	0.959		
weakness	1.200 (0.369-3.903)	0.762		
Prior treatment at the hospital	3.467 (0.411-29.210)	0.253		
Prior treatment with antibiotics	3.109 (0.367-26.361)	0.298		
Prior thoracocentesis or chest tube placement	0.941 (0.259-3.422)	0.927		
CCI score	1.585 (0.974-2.579)	0.064	1.806 (1.065-3.060)	0.028
Objective clinical examination				
Temperature (ºC)	0.583 (0.244-1.390)	0.224		
Blood laboratory findings				
Hemoglobin concentration	0.986 (0.957-1.015)	0.329		
WBC count	1.028 (0.925-1.144)	0.606		
Protein	1.028 (0.949-1.113)	0.505		
CRP	0.997 (0.990-1.004)	0.414		
PCT	0.646 (0.134-3.122)	0.586		
Pleural fluid findings				
Visually frank pus	1.765 (0.531-5.865)	0.354		
pH	0.689 (0.097-4.872)	0.709		
LDH	1.000 (1.000-1.000)	0.114		
Glucose	1.046 (0.819-1.336)	0.718		
Protein	1.031 (0.966-1.101)	0.356		
WBC count	1.000 (1.000-1.000)	0.618		
Leukogram: neutrophils %	1.000 (0.982-1.019)	0.974		
lymphocytes %	0.999 (0.980-1.018)	0.894		
Positive pleural culture	3.136 (0.902-10.906)	0.072	4.386 (1.137-16.921)	0.032
Gram+ bacteria	6.000 (0.516-69.754)	0.152		
Radiological findings				
Opacification of the hemithorax on chest X-ray	1.008 (0.981-1.034)	0.571		
CT scan: thickness of parietal pleura	1.310 (0.684-2.509)	0.415		
empyema volume	1.001 (0.999-1.002)	0.302		
density of empyema	0.917 (0.803-1.047)	0.198		
number of encapsulates	0.746 (0.418-1.330)	0.320		
presence of air bubbles	2.100 (0.625-7.054)	0.230		

Table 11. Influence of operative factors on complications.

Factor	Univariate analysis		Multivariate analysis	
	OR (95 % CI)	p-value	OR (95 % CI)	p-value
Conversion	1.229 (0.332-4.540)	0.758		
Operating time	0.990 (0.966-1.013)	0.390		
Single chest tube	1.023 (0.246-4.259)	0.975		
ICU time	3.172 (1.178-8.541)	0.022	3.172 (1.178-8.541)	0.022

Table 12. Influence on general mortality

Factor	Univariate analysis			Multivariate analysis		
	OR	95 % CI	p-value	OR	95 % CI	p-value
Re-do surgery	6.214	1.518-25.440	0.011	1.919	0.161-22.895	0.606
ICU time	2.612	1.132-6.029	0.025	1.152	0.310-4.280	0.833
CCI	3.251	1.975-5.350	<0.001	3.142	1.695-5.821	<0.001
Hospitalization time	1.063	1.006-1.123	0.031	1.018	0.920-1.126	0.730

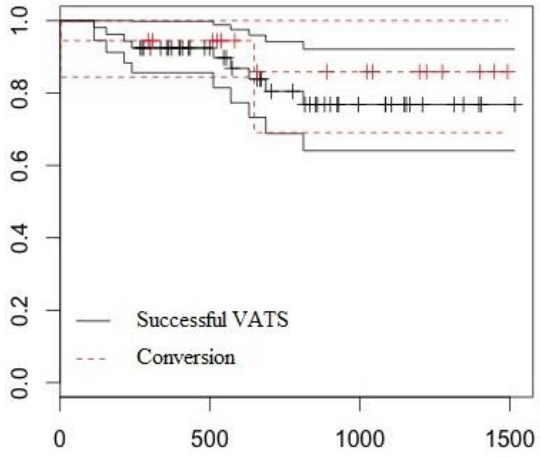

Figure 18. General surveillance in successful VATS and conversion groups, p=0.526.

Further diminishing of opacification was observed in analysing the changes of opacification in chest X-rays in one and six months after the operation, and there were not any significant differences between successful VATS and conversion groups (Figure 19).

By analysing postoperative pain according to the NPRS, we found a significant difference between successful VATS and conversion groups straight after and in one month after surgery (in both comparisons p<0.001); however, there was no significant difference in six months after the operation (p=0.156), Figure 20.

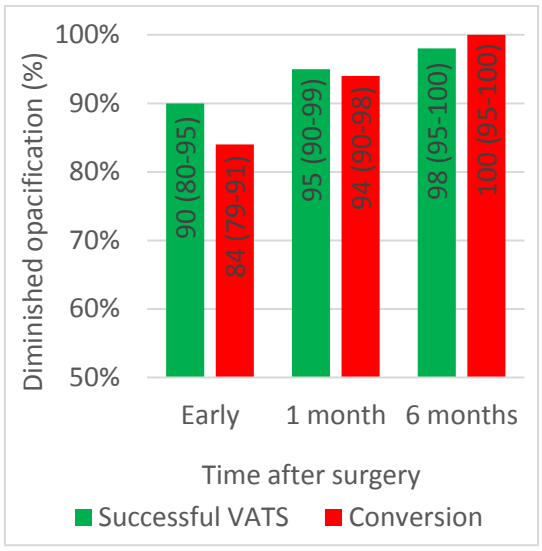

Figure 19. Diminishing of opacification on chest X-ray in different time periods in both groups (p=0.526; p=0.884; p=0.632, respectively).

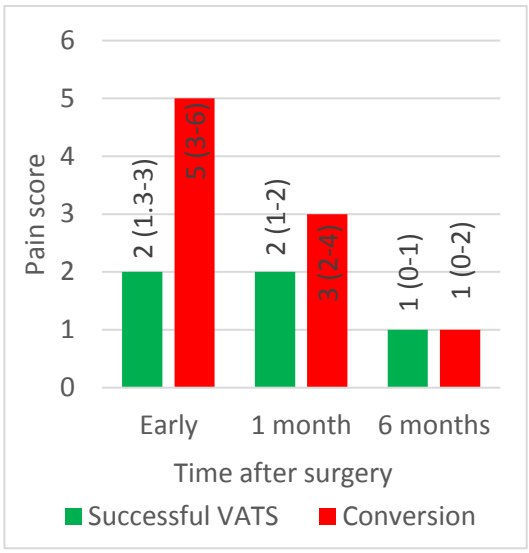

Figure 20. Pain after the operation according to the NPRS in different time periods in both groups (p<0.001, p<0.001, p=0.156, respectively).

Discussion of the findings

Pleural empyema is a complex clinical entity that has defied randomised controlled trials and efforts to define the best clinical practices because of the multitude of patient factors that determine treatment outcomes [7, 13]. Even with moderate or minimal infectious or respiratory symptoms, PE exposes the patient to devastating morbidity if neglected or operated on too late. This study was not a randomised comparative trial of different therapeutic options. However, an understanding of preoperative prognostic factors for conversion and complications is, nevertheless, critical to choosing the best therapeutic attitude.

Patient selection for the time and the type of surgical intervention usually remains a matter of expert opinion and varies widely between institutions [42]. Despite the advantages of VATS, according to different authors including different groups of patients, it is associated with up to 59 % of conversion to open thoracotomy [6, 7, 11-13, 16-19, 20, 21, 43-50]. The conversion rate in our study, according to the fact that we included stage II/III empyema cases, was 25.4 %. Conversion to thoracotomy is usually considered if it is impossible to enter the pleural cavity safely due to firm adhesions, to completely dissect and remove the peel from the underlying lung surfaces to achieve sufficient lung re-expansion or in cases of severe bleeding or significant air leak [13, 21, 44-46, 48]. The first two were the reasons for conversion in our study. Because of a higher rate of conversion to open thoracotomy and technical difficulties during the surgery, VATS empyemectomy would clearly show better results if applied at the appropriate time. Unfortunately, there is a lack of data regarding the optimal timing of surgical intervention, so there is no consensus regarding this issue. Some recent studies identified that delayed referral to surgery or longer anamnesis lead to a higher conversion rate, consequently increasing morbidity and mortality [7, 12, 13, 21, 46, 49, 50]. Chung and colleagues, in their recent retrospective analysis of 120 cases of VATS empyemectomies, stated that

patients whose duration of symptoms was less than four weeks showed better early results, as compared to those whose duration of symptoms was greater than four weeks [42]. Lardinois and colleagues, in their study, suggested to use conversion thoracotomy when the duration of symptoms is more than two weeks before surgery [50]. However, Waller and colleagues stated that the success of VATS decortication is not related to either the delay between the onset of symptoms or hospital admission and surgery [19]. In our study, we have found that longer time off illness and frank pus in pleural aspiration had significantly increased the rate of conversion. On the basis of our results, the importance of early VATS in the management of PE, which was also reported in other previous studies [42, 43, 49, 51], seems to be more justified. Clinically, it may provide better clues for the decision to perform early surgical approach.

Positive culture from pleural space is assessed by different authors in 10 – 60 % of patients [7, 15-17, 49-55]. Such a low percentage of positive cultures may represent effective antibiotic treatment prior to sample collection. It may also suggest that continual presence of bacteria is not necessary to sustain the ongoing inflammatory response after the initial bacterial invasion [12]. In our study, positive pleural fluid culture was observed only in 23.9 % of all patients. The sterility of pleural fluid may reflect to the chronicity of the process as well as being associated with prior antibacterial treatment, which was used in 83.1 % of our patients. According to our data, positive culture did not have any significant influence to the rate of conversion. Stefani and colleagues have also not found any significant influence of positive culture on conversion [49]. Lardinois and colleagues stated that only Gram-negative bacteria significantly increased the rate of conversion, but, in general, positive culture had no influence on conversion [50]. On the other hand, according to our data and to Okiror and colleagues study [54], positive culture significantly increased the risk of postoperative complications.

The average length of hospitalization usually varies from 5.7 to 18.5 days, but is significantly longer if VATS fails or if complications occur [11, 13, 15, 17, 43, 55-57]. Postoperative stay, as stated by Waller and colleagues, is significantly longer in the conversion group vs. the successfully done VATS group (8.5 and 5.5 days) [19]. In our study, as well as showed by Stefani and colleagues [49], postoperative time did not differ significantly between successful VATS and conversion groups. We have found a significant difference in postoperative time only if complications occurred. However, time spent at the ICU after the operation was significantly higher in the conversion group.

In our study, mean operating time was 82 ± 26 min. However, this time was significantly longer if the operation was converted to thoracotomy (76 ± 22 vs 100 ±28 min, $p<0.001$). Similar significant differences are shown in the studies made by Waller and colleagues [19] and Stefani and colleagues [49].

The complication rate after VATS empyemectomy varies from 9 % to 40.2 % [11, 15-17, 20, 43-45, 49, 50, 55]. A prolonged air leak, bleeding, recurrence or persistence of the disease, surgical wound infection and residual pleural space are the most common complications. In our series, the complication rate was 19.7 % (14 out of 71 patients): recurrences of disease (four patients), prolonged air leaks (three), wound infections (three), hemothoraxes (three) and in-hospital death (one). Terra and colleagues [16] as well as Stefani and colleagues [49] mentioned in their studies that VATS is associated with a significantly lower rate of postoperative complication, as compared to the converted to open thoracotomy cases. Differently from these authors, we have not found any difference in complication rate between the successfully done VATS and converted groups.

However, by analysing the treatment that was necessary to cure complications, we have found that all six patients (8.5 %) who required re-do surgery (three due to recurrence of disease and three due to hemothorax) were patients from the successful VATS group. Moreover, during the first month after discharge, two patients returned due to recurrences of disease, both were from the VATS group and both required re-do surgery. According to Lardinois and colleagues, recurrence of empyema that required re-do surgery was found in 2.4 % of cases and did not differ between VATS and open thoracotomy groups [50]. Marra and colleagues identified 6.5 % of recurrence after VATS empyemectomy that required re-do surgery [55]. Terra and colleagues, similarly to our data, have found that the reintervention rate was higher, yet not in a significant way, in a VATS group, as compared with an open thoracotomy group (11.5 % (13/113) vs. 6.5 % (6/93)) [16]. According to other authors, treatment failures requiring any post-VATS reintervention occur in 2.4 – 9.2 % [11, 16, 50]. Nonetheless, all eight patients that required re-do surgery were from the VATS group; the time of illness in seven of them was ≥16 days. These figures are not significant, probably because of too small numbers, but they show a tendency that time of illness could also be an important factor for re-do surgery.

In our study, one patient died before discharge postoperatively (1.4 %). The reason of death, similarly to data gathered by Marra and colleagues [55], was not associated with pleural empyema.

Recent studies indicate a poor association of imaging results with patient outcomes with therapy [5]. Abnormalities on CT scan do not predict the stage of empyema nor its likelihood of requiring surgical intervention [12]. Furthermore, radiological features on CT are not predictive on which patients require conversion to thoracotomy from VATS [17, 18, 58]. That was also confirmed in our study: radiological features on CT scan had no influence to the rate of conversion.

Finally, empyema is an infectious pleural space disease with a broad clinical spectrum. It is essential to fully understand its dynamic process and approach it with the most efficient treatment modality at the most appropriate time.

Conclusions

1. Minimally invasive (VATS) surgery for pleural empyema is as equally effective as a converted to open thoracotomy managing pleural empyema.
2. Prognostic factors for conversion:
    - Time of illness (≥16 days) and frank pus in aspiration are independent predictors of conversion.
    - Clinical, blood and pleura fluid laboratory and radiological features identified before operation have no significant prognostic value for conversion.
3. The rate of postoperative complications is similar after thoracoscopic and converted operations, but after a thoracoscopic procedure, if the time of illness is longer, re-do surgery is more often required.
4. Comorbidities and positive culture from pleural space are independent predictors of postoperative complications.
5. On the late postoperative period, recurrences of disease occur early (during the two months after primary operation).

Practical recommendations

1. If time of illness of pleural empyema is less than 16 days, minimally invasive surgery is indicated.
2. If pleural empyema lasts 16 or more days and frank pus in aspiration is found, open thoracotomy operation is worth to be recommended for the patient.
3. Early reference to surgery could help avoid converted, open and re-do surgical procedures for pleural empyema; that helps reach a faster and easier recovery, an earlier return to a normal life and lesser treatment costs.
4. If pleural empyema is suspected, pleural ultrasound must be performed for a better evaluation of the content and possible treatment options. If fibrin formations is already found reference to thoracic surgeon is mandatory.
5. Further prospective multicenter studies are necessary in order to get more evidence and recommendations in choosing the most appropriate surgical treatment for pleural infection.

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Publications and reports by the author of the doctoral dissertation

Publications

1. Jagelavicius Z, Jovaisas V, Danila E. Parapneumonic effusion and pleural empyema: etiology and peculiarities of the course. Paediatric Pulmonology and Allergology 2011; 14(2): 66(4868)-74(4876).
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Scientific reports

1. Zymantas Jagelavicius, Ricardas Janilionis, Edvardas Danila. Empyema thoracis – very old but still a problem. International conference "Evolutionary Medicine: New Solutions for the Old Problems", Vilnius, Lithuania, June 12-15, 2012. (*oral presentation)*
2. Zymantas Jagelavicius. Possibilities of minimally invasive surgery in the treatment of pleural empyema. 15th congress of Lithuanian Society of Cardio-Thoracic Surgeons, Birstonas, Lithuania, November 15, 2013. (*oral presentation*)
3. Zymantas Jagelavicius, Ricardas Janilionis, Narimantas Evaldas Samalavicius. Minimally invasive surgery for pleural empyema. International scientific conference "Evolutionary Medicine: Perspective in Understanding Health and Disease", Vilnius, Lithuania, May 27-30, 2014. (*oral presentation*)
4. Zymantas Jagelavicius, Gediminas Vaitenas, Vytautas Jovaisas, Ricardas Janilionis. Localized pyopneumothorax treated with vacuum assisted closure system. 17th Congress of Lithuanian Society of Cardio-Thoracic Surgeons and Scientific practical conference "Innovations in Cardiothoracic Surgery. Clinical Cases", Kaunas, Lithuania, October 16, 2015. (*oral presentation*)
5. Zymantas Jagelavicius, Vytautas Jovaisas, Mindaugas Mataciunas, Ricardas Janilionis. Preoperative predictors of conversion in thoracoscopic surgery for pleural empyema. 24th European Conference on General Thoracic Surgery, Naples, Italy, May 29 – June 01, 2016. (*oral presentation*)

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2012-06-12 – 2012-06-15	Vilnius University Faculty of Medicine, International conference "Evolutionary Medicine: New Solutions For The Old Problems", Vilnius, Lithuania (*oral presentation* – Empyema thoracis – very old but still a problem).
2013-11-15	15th Congress of Lithuanian Society of Cardio-Thoracic Surgeons, Birstonas, Lithuania (*oral presentation* – Possibilities of minimally invasive surgery in the treatment of pleural empyema).
2014-05-27 – 2014-05-30	Vilnius University Faculty of Medicine, International scientific conference "Evolutionary Medicine: Perspective in Understanding Health and Disease", Vilnius, Lithuania (*oral presentation* – Minimally invasive surgery for pleural empyema).
2015-10-16	Lithuanian University of Health Sciences, Lithuanian Society of Cardio-Thoracic Surgeons, scientific practical conference "Innovations in Cardiothoracic Surgery. Clinical Cases" and 17th

	Congress of Lithuanian Society of Cardio-Thoracic Surgeons, Kaunas, Lithuania (*oral presentation* - Localized pyopneumothorax treated with vacuum assisted closure system).
2016-05-29 – 2016-06-01	ESTS, AATS, STS, JACS, 8th Collaborative Symposium on General Thoracic Surgery, Postgraduate Course organized by ESTS-AATS-STS-JACS and 24rd European Conference on General Thoracic Surgery, Naples, Italy (*oral presentation* - Preoperative predictors of conversion in thoracoscopic surgery for pleural empyema)

PRINTED ARTICLES	
1	Samalavicius NE, Poskus T, Drasutis RK, Jagelavicius Z, Kervys L. Treatmen of rectal prolapse. Sveikatos mokslai (Health Sciences) 2003; 1(24): 81-85.
2	Samalavicius NE, Poskus T, Jagelavicius Z, Kervys L, Vaitkus A, Radziunas G. Long Term Results After Surgical Treatment of Haemorrhoids, Anorectal Abscess and Anal Fissure (1985-1999). Sveikatos mokslai (Health Sciences) 2003; 2(25): 96-99.
3	Jagelavicius Z, Samalavicius NE, Poskus T, Kervys L, Drasutis RK. Milligan-Morgan hemorrhoidectomies: experience of the Center Branch of Vilnius University Hospital "Santariskiu Klinikos". Lietuvos Chirurgija (Lithuanian Surgery) 2004; 2(4): 293-299.
4	Jovaisas V, Gruslys V, Jagelavicius Z, Kiskis G, Janilionis R. Temporary bronchus occlusion in the treatment of pyopneumothorax and bronchopleural fistula, data of the last 10 years. Lietuvos Chirurgija (Lithuanian Surgery) 2007; 5(3): 250-254.
5	Jagelavicius Z, Jovaisas V, Zilinskas A, Kybartas A. Kiskis G, Gruslys V, Liubertiene I, Janilionis R. Penetrating cardiac injuries: evaluation of a 25-year experience. Lietuvos chirurgija (Lithuanian Surgery) 2010; 8(2): 83-93.
6	Jovaisas V, Janilionis R, Gruslys V, Kiskis G, Kybartas A, Zilinskas A, Jagelavicius Z, Liubertiene I. Radical surgical management of the necrotizing lung infections complicated with pleural empiema (10 years data). Medicinos teorija ir praktika (Medicine theory and practice) 2011; 17(2): 195-202.
7	Jagelavicius Z, Jovaisas V, Danila E. Parapneumonic effusion and pleural empyema: etiology and peculiarities of the course. Paediatric Pulmonology and Allergology 2011; 14(2): 66(4868)-74(4876).
8	Jagelavicius Z, Danila E. Tools for the diagnosis and management of parapneumonic effusion and pleural empyema. Paediatric Pulmonology and Allergology 2012; 15(1): 61(4967)-68(4974).
9	Janilionis R, Falcoz PE, Jovaisas V, Jagelavicius Z, Valancius R. Sternal pseudoarthrosis after resternotomy treated with the Strasbourg Thoracic Osteosyntheses System: a case report. Acta Medica Lituanica 2013; 20 (3): 129-134.
10	Jagelavicius Z, Budra M, Jovaisas V, Kiskis G, Kybartas A, Zilinskas A, Liubertiene I, Gruslys V, Janilionis R. Penetrating cardiac injuries: 28-year data analysis. Kardiochirurgia i Torakochirurgia Polska 2013; 10 (1): 415-421. (ISI)
11	Janilionis R, Jagelavicius Z, Petrik P, Kiskis G, Jovaisas V, Kybartas A, Zilinskas A, Liubertiene I, Navickas G, Valancius R. Diffuse descending necrotizing mediastinitis: surgical treatment and outcomes in a single-centre series. Acta Medica Lituanica 2013; 20 (3): 117-128.
12	Sileika N, Sileikiene I, Jagelavicius Z, Jovaisas V, Navickas G, Zilinskas A, Janilionis R. Boerhaaves syndrome presented and managed as an acute coronary syndrome. Eur J Intern Med 2013; 24 (e88).
13	Sileika N, Jovaisas V, Jagelavicius Z, Janilionis R. Management of acquired benign tracheoesophageal fistula in adults: a twelve-year experience. Lietuvos chirurgija (Lithuanian Surgery) 2013; 12 (4): 196-203.

14	Janilionis R, Falcoz PE, Jovaisas V, Jagelavicius Z. Titanium implants in the management of chest instability: first experience in Lithuania. Health Sciences 2014; 24 (2): 30-34.
15	Jagelavicius Z, Jovaisas V, Kybartas A, Zilinskas A, Lukoseviciute L, Janilionis R, Samalavicius NE. Successful video-assisted thoracic surgery for pleural empyema. Lietuvos chirurgija (Lithuanian Surgery) 2014; 13(3): 168-176.
16	Jagelavicius Z, Vaitenas G, Jovaisas V, Janilionis R. Localized pyopneumothorax treated with vacuum assisted closure system. Lietuvos chirurgija (Lithuanian Surgery) 2015; 14 (1): 46-51.
17	Jagelavicius Z, Jovaisas V, Mataciunas M, Samalavicius NE, Janilionis R. Video-assisted thoracic surgery in pleural empyema: predictors of complications and treatment failures. Acta Medica Lituanica 2015; 22 (2): 102-110.