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VATS (Video Assisted Thoracoscopic Surgery) Pleural Biopsy in the Diagnosis of Unexplained Pleural Effusion

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Abstract:

Introduction: *An unexplained pleural effusion is a difficult diagnostic dilemma that needs further histological study for a definitive etiological diagnosis. Video assisted thoracoscopic (VATS) pleural biopsy is a minimally invasive procedure that could resolve this problem. The study is conducted to determine the efficacy of VATS pleural biopsy in the diagnosis of unexplained pleural effusion.*

Methods: *This cross-sectional study was to investigate our experience of VATS pleural biopsy for unexplained pleural effusion which was conducted at our center. All patients who underwent VATS pleural biopsy for unexplained pleural effusion during the period of January 2019 to December 2019 were included in the study. Epidemiological, clinical, radiological & histopathological data of the patients were collected and analyzed*

Results: *The overall diagnostic yield of VATS pleural biopsy in our study was 95%. Malignancy was the most common histological diagnosis for unexplained pleural effusion followed by tuberculosis. In patients with malignant effusion, metastatic adenocarcinoma was commonly observed finding followed by metastatic squamous cell carcinoma. Minor complications related to the procedure were noticed with no mortality.*

Conclusion: *VATS pleural biopsy has high definitive diagnostic accuracy in the evaluation of unexplained pleural effusions.*

Key words: *Unexplained pleural effusion, Video assisted thoracoscopic (VATS) pleural biopsy, Malignancy, Tuberculosis.*

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Introduction:

The patients of pleural effusion are frequently encountered conditions in thoracic surgery. Approximately 1.5 million new pleural effusions are diagnosed and around 180 000 thoracentesis are performed annually in the United States.[1] After routine and radiological investigations, the diagnostic workup of patients with pleural effusion usually begins with thoracentesis. Thoracentesis provides a definitive or presumptive diagnosis in 59% to 73% of cases, and additional diagnostic investigations are often needed.[2]

Unexplained pleural effusion is defined as failure to achieve an etiologic diagnosis by biochemical, microbiological, microscopic analysis of pleural fluid and/or percutaneous needle biopsies of pleura. Biochemical analysis included sugar, protein, adenosine deaminase [ADA] test of pleural fluid. Microbiological analysis included Gram stain, Acid-fast bacilli [AFB], culture and sensitivity, Nucleic Acid Amplification Test [NAAT] (Gene Xpert for Mycobacterium tuberculosis) of pleural fluid. Microscopic analysis included total count, differential count, malignant cell of the pleural fluid.

VATS (Video Assisted Thoracoscopic Surgery) pleural biopsy is a minimal invasive procedure with a minor morbidity and mortality risk that involves access to the pleural space with a rigid telescope and allows direct visualization of the pleural space and intra thoracic

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structures and aids in obtaining tissue under direct visual guidance. Pleural biopsy is helpful to reach an etiological diagnosis of exudative pleural effusion, particularly when malignancy is suspected or when results of the detailed pleural fluid study are inconclusive.

Pleural Biopsy can also be done by medical pleuroscopy, which is the endoscopic evaluation of the pleural space. VATS is a minimally invasive procedure that was first invented in 1910 by Hans Christian Jacobeus, a Swedish internist who is also regarded as the "father of thoracoscopy." In recent years, thoracoscopy has gained a lot of interest and popularity among thoracic surgeons mainly in the etiological diagnosis of pleural effusions.[3]

The equipments used in VATS are trocar, cannula, telescope, light source, monitor and biopsy forceps. Trocar and cannula usually range in size from 7 to 13 mm in external diameter and are made from single-use disposable plastic or reusable stainless steel. The rigid telescope is made of stainless steel and is 27 to 31 cm in length with a diameter of 5 to 12 mm. The rigid telescope can be a straight (0^o) or oblique (30^o and 50^o) angle of vision. A cold (xenon/ helium/LED) light source with a camera is attached to the eyepiece of the telescope.[4,5]

VATS pleural biopsy is an overall safe procedure with a very low complication and mortality rate when performed by a trained thoracic surgeon in conscious sedation patients under local anesthesia and/or under general anesthesia.

In 2010, British Thoracic surgery (BTS) Pleural Disease Guideline reported an overall mortality of 0.34%.[7]

In a study done by Md Billal Hossain in the Department of Internal Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbagh, Dhaka, Bangladesh stated that out of 100 patients with pleural effusion, 52 had tuberculosis,16 patients had malignancy, 32 patients had other causes and 4 patients were undiagnosed. Among the malignant cases 14 were found to have bronchial carcinoma and 2, had lymphoma. Tuberculosis is the predominant cause of pleural effusion in our country and the second leading cause is malignancy.[29]

In Bangladesh, VATS pleural biopsy is being practiced for unexplained pleural effusion. But no study has yet been done on the efficacy of VATS pleural biopsy for unexplained pleural effusion. The purpose of our study is to research the effectiveness of VATS pleural biopsy in the definitive diagnosis of unexplained pleural effusions in a tertiary hospital in Bangladesh.

Methods:

This cross-sectional study was conducted in the department of Thoracic Surgery, NIDCH, Mohakhali, Dhaka from January 2019 to December 2019. We performed VATS for diagnosis of undiagnosed pleural effusions in 75 patients admitted to our institute. All the cases of pleural effusion that remained unexplained were enrolled in this study according to inclusion and exclusion criteria. As a part of review work up, we recorded detailed history including age, sex, address, smoking habits, significant co morbidity history and all the necessary laboratory hematological and radiological investigations. VATS pleural biopsy was done by the different thoracic surgeons of similar skills and experiences in all eligible patients. Decisions about regional or general anesthesia were made by anesthesiologist. Informed written consent was taken.

Patients were kept nil by mouth for 8 hours prior to the procedure. Intravenous access was achieved in the upper limb same to the side of VATS. Regional anesthesia by means of intercostal nerve block and subcutaneous infiltration of 10 ml solution of 2% lignocaine & bupivacaine at the desired incision site with intravenous Propofol and Pethidine were administered by anesthesiologist to increase patient's comfort without compromising respiration. And for general anesthesia patients were intubated by a suitable double lumen endotracheal tube. Patient's vital parameters such as pulse, blood pressure, and oxygenation were monitored continuously throughout the procedure. Patients were then made to lie in lateral decubitus position with affected side facing upward and both the arms were placed above and below the head.

This was uniportal VATS where port of site was usually 4th or 5th intercostal space in between anterior & mid axillary line. 3–5 cm sized incision was made and the subcutaneous tissue and muscles were bluntly dissected to reach the pleura. Then a trocar with cannula was inserted through the chest wall, pleural fluid was aspirated and systemic exploration of the pleura was

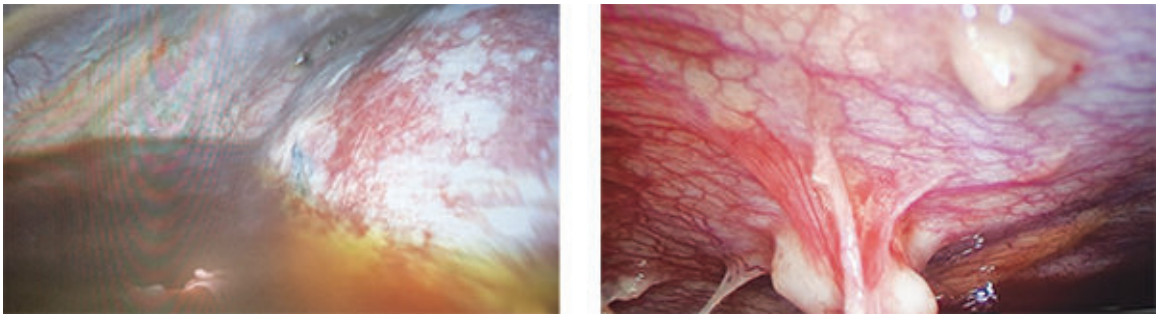

Fig.-1: *View of pleural pathology during VATS.*

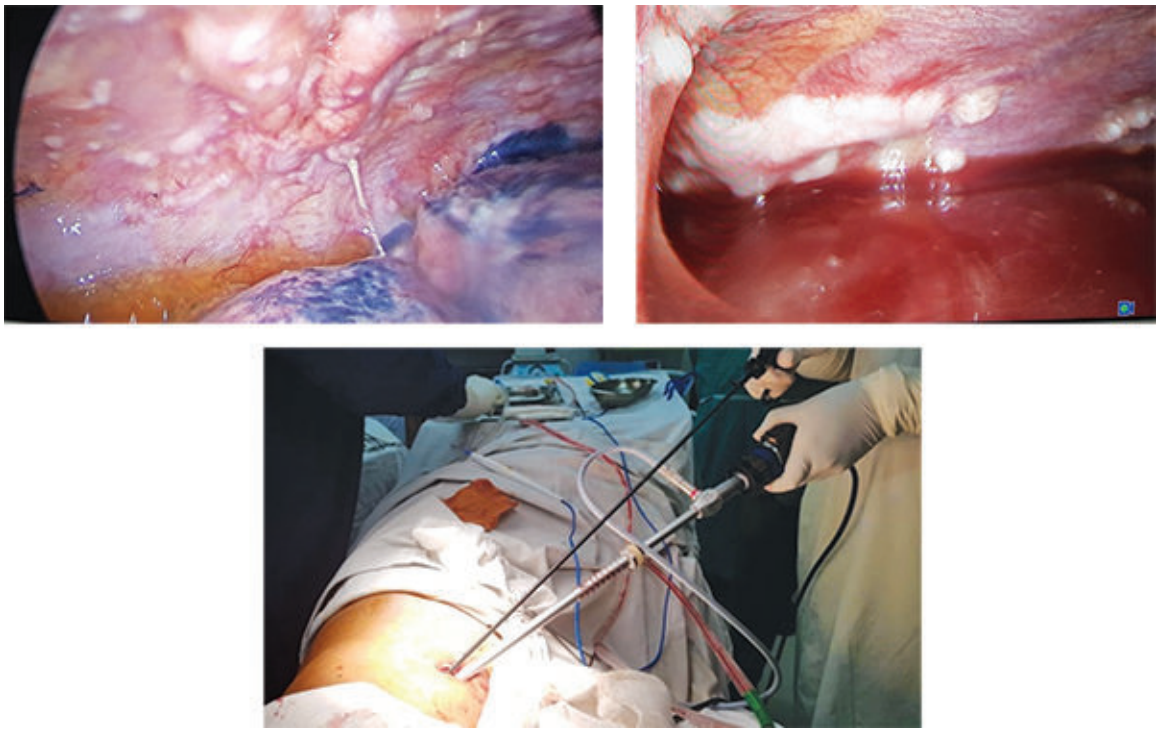

Fig.-2: *Technique of taking pleural biops*

done by rigid thoracoscope Hopkins II (Karl storz Germany, 30°) 5 mm or 10 mm diameter. Typically more than 3 biopsies from the abnormal lesions of parietal pleura were taken by rigid biopsy forcep which was introduced through the same port. If no gross abnormalities were visible on parietal pleura, multiple biopsies were taken from different sites. Chest tube size 28 F to 32 F was introduced through trocar site and connected with under water seal followed by proper suturing of the wound. All patients who were intubated, extubated immediately after surgery. Chest X-ray was taken the next day. Once the lung had expanded and drainage decreased to less than 100mL per 24 hours for three consecutive days, chest drain was removed after doing chemical pleurodesis in malignant effusion.

Descriptive statistics were used to describe the demographic characteristics of the patients. Percentages and mean ± SD were used for the categorical variables.

Results:

Total 75 patients with unexplained pleural effusion were evaluated. Age range was from 20 to 70 years with mean ± SD was 45.22 ± 12.33 years.. 40% of population belongs to 41-60 years age group. In our research, fifty-seven

(76%) were males and eighteen (24%) were females, with an overall male to female ratio of 3.1:1 was found and 79% patients were from rural areas. Characteristics of the study population shown in table 1

Pre procedure pleural fluid study findings were, protein mean value 3.98 ± 0.31 gm/dl and glucose mean levels 57±0.9 mg/dl with insignificant ADA levels 30.6 ± 5.7 to reach a definitive etiological diagnosis.

Observations during VATS pleural biopsy for unexplained effusion of 75 patients are shown in the table II.

Gross VATS findings observed were pleura-parenchymal adhesions were the most common findings seen in 63 (84%) of the patients followed by thickened non smooth pleura in 42 (56%) and parietal pleural nodularity in 37 (49%) of patients. Malignancy in 46 patients (61%) was the most common histological diagnosis for unexplained pleural effusion followed by tuberculosis in 17 patients (23%). Chronic nonspecific inflammation was found in 8 patients (11%). In 4 patients (5%) definitive etiological diagnosis could not be reached. In patients with malignant effusion (46 patients), metastatic adenocarcinoma (n = 23) was the most common followed by metastatic squamous cell carcinoma (n=18). Others included small cell carcinoma, malignant melanoma and lymphoma. That's 30 % and 24 % of total population finally diagnosed as metastatic adenocarcinoma and metastatic squamous cell carcinoma respectively. Out of total 75 patients of our study, definitive etiological diagnosis was reached by VATS pleural biopsy in 71 patients and 4 patients were non diagnostic. The overall diagnostic yield of VATS pleural biopsy in our study was 95%. Duration of the chest tube drains in situ for different etiologies after VATS pleural biopsy is shown in table 3 where for malignant pleural effusion, the duration of keeping the chest drain tube in situ was most lengthy; the mean ± SD value was 12 ± 1.9 days.

Table-I

Characteristics of the study population (n= 75) (Values are expressed as n (%) or mean ± SD.)

Smoking status:	Smoker	52%
	Non smoker	48%
Comorbidities:	Diabetes mellitus	8%
	Hypertension	10.66%
	IHD	4%
	COPD	5.33%
	Other diseases	8%
	No diseases	64%
Clinical presentations:	Breathlessness	87%
	Chest pain	69%
	Cough	65%
	Fever	25%
	Others	10%
Duration of clinical presentations	< 1 month	11%
before definitive diagnosis:	3-6 months	54%
	6-12 months	31%
	>12 months	4%
Preprocedure empirical	Taking anti TB treatment.	31%
treatment for Tuberculosis:	Not taking anti TB treatment.	69%
CXR findings:	Pleural effusion	70%
	Massive effusion	10%
	Encysted effusion	20%
Chest CT Scan Findings:	Encysted effusion/multiloculations	66%
	Lung mass with effusion	14%
	Pleural nodularity with effusion	10%
	Mediastinal lymphadenopathy with effusion	15%

Table-II

Observations during VATS pleural biopsy (n= 75)

Site of the procedure:	Right	52%
	Left	48%
Appearance of pleural fluid during VATS:	Serous	37%
	Haemorrhagic	48%
	Purulent	15%
Procedure time:	Mean ± SD (min)	52.86 ± 7.49
Length of hospital stay:	Mean ± SD (Days)	12.89 ± 1.85

(Values are expressed as n (%) or mean ± SD.)

We found no major complications, few patients had minor complications like subcutaneous emphysema (3 patients, 4%), wound infection (4 patients, 5.33%). Post-operative haemothorax (4 patients, 5.33%) and prolonged air leakage (2 patients, 2.6%), Port site tumour implantations (1 patient, 1.33%) All complications improved with conservative management (Total 18.65 %). There was no procedure related mortality.

Discussion:

In general, more than 50% of all patients with PE cannot be diagnosed after the initial diagnostic thoracentesis.[20] In such cases pleural biopsy is mandatory.

The pleural biopsy can be performed under the guidance of computed tomography (CT) or ultrasound (USG). According to Metintas et al, diagnostic sensitivity of the CT guided-needle pleural biopsy in patients with pleural effusion (PE) is approximately 82% and USG-guided needle pleural biopsy has a 66% diagnostic sensitivity.[19] But the image-guided pleural biopsies require experienced interventional radiologists.

For this reason, in many centers including ours, thoracentesis without any definite diagnosis is followed by VATS pleural biopsy.

In our study, we presented the data of 75 patients who underwent VATS pleural biopsy for unexplained pleural effusions. Most of the patients of our study population were between 40 to 50 years of age with a mean ± SD of 45.22 ± 12.33 years, which is similar to other studies.[13, 22.] This may be related to the fact that the study was done in a tertiary center and most of the pleural effusions in the older age group were difficult to diagnose or remain undiagnosed in a primary or secondary health center and subsequently were sent to a higher referral center for further workup.

In our study the male female ratio was 3.1:1. An article by Sodhi R et al in 2016 found that among 47 patients with undiagnosed exudative pleural effusion underwent VATS Pleural biopsy 66.96% were male and 34.04% were female.[21] The majority of cases were male patients (161 males and 102 females) in another study by Erdogan D et al.[20] These data correlated with our study.

Among the 75 patients, 36% (27) patients have different co-morbidities. Similar results were seen in a study done by Nattusamy L et al. [26] Minimum morbidity & mortality in that study were due to less percentage of associated co morbidities in the study population as there is direct association between co morbidities with morbidity & mortality. [26] Similar observations were found in our research. However any co relation between associated co morbidities and complications of VATS pleural biopsy was not done in our study.

Evaluation of symptoms in patients with unexplained pleural effusion revealed that the most common symptom was breathlessness in 87 patients (67.4%), followed by chest pain in 69 (53.4%). A study conducted by Erdogan D at el showed breathlessness in 66.5% and chest pain in 15.6% of patients[20] and Prabhu VG et al found breathlessness in 75. 4% and chest pain in 42.8% patients.[14]

The duration of symptoms in our study is mostly for 3-6 months. Fifty four percent [54%] of patients (n= 41) suffered for this duration. This short duration of symptoms reflected predominant malignant causes of unexplained pleural effusion. Beheshtirouy S. et al showed in their study done in Iran, the meantime before the patient referral for VATS pleural biopsy was 4.85 months.[16] These data co-related with our study.

In our study, 23 patients were having empirical treatment with anti TB drugs for weeks to 5 months duration and with no improvement. Only 5 (26.3%) patients among them proved to be TB following VATS biopsy. In most of these patients, the final diagnosis wasnon-tubercular etiology, which included malignancy. This is because tuberculous pleural effusion is the second most common form of extrapulmonary tuberculosis after lymph node tuberculosis.[23] On the other hand, tuberculosis is always considered as the leading etiology of pleural effusions in developing countries.[23] According to WHO Global TB Report 2016, Bangladesh as a developing country, is one of the world's 30 high TB burden countries with an annual occurrence of 362,000 new Tuberculosis cases. So in many cases of unexplained pleural effusions, anti TB treatment was prescribed empirically. Those patients were referred to higher centers after no improvement with initial management of anit-TB therapy. In China Wang et al experienced a similar observation in their study.[23] So VATS pleural biopsy should be done in all the patients getting empirical anti tubercular drug, where ever facilities available.

In our study, the most common chest X ray findings were pleural effusion in 70% of cases followed by encysted effusion in 20 %. Among the Chest CT scan findings, encysted effusion/multiple loculations with thickened pleura was the most common findings, in 66% (n=50) patients. Only in 10% (n=8) of cases, pleural nodularity was seen. All patients who had pleural nodularity on the CT chest were detected to have pleural nodules during the VATS procedures and were positive for malignancy on histopathological examination.

Right-sided and left-sided VATS pleural biopsies for unexplained pleural effusion were done in 52 % & 48% of patients respectively in our study which was similar to other studies.[3],[24] In our no simultaneous bi lateral VATS pleural biopsy was found.

The physical appearance of pleural fluid during VATS was an interesting finding. The color of fluid was straw in 37% of patients, hemorrhagic in 48% of patients, and purulent in 15% of patients. In a study, Wang X et al found that the appearance of pleural effusions was blood stained, yellow, and chylous in 306(36.7%), 522 (62.7%), and 5 (0.6%) patients respectively.[23] In another study of India,Nattusamy et al showed that the color of pleural fluid was straw-colored in 52.08%, hemorrhagic in 43.75%, and purulent in 4.17% of patients.[24]

In our study, predominant hemorrhagic-colored fluid signifies more in favor of malignancy. But the presence or absence of hemorrhagic pleural effusions was not found to be useful in predicting cancer. Because in a study evaluating 390 patients who were diagnosed with cancer, 82.5% of the cytological positive fluids were not hemorrhagic.[25]

In our research, procedure time and length of hospital stay were respectively 52.86 ± 7.49 minutes, 12.89 ± 1.85 days (Mean± SD). Length of stay in hospital and duration of operation were respectively 2.67 days (SD ± 1.56) days and 51.93 ± 8.85 min (40–80 min.) among VATS pleural biopsy patients in a study done by Mertol G. et al[29]. Beheshtirouy S. et al in their study found Mean hospital stay was 5.35 days (range: 2-17).[16] All these data reflected the fact that VATS pleural biopsy was a minimum invasive procedure with shorter operation time and length of hospital stay.

Gross VATS findings observed by us were pleura-parenchymal adhesions were seen in 63 (84%) patientfollowed by thickened non-smooth pleura in 42 (56%) patients and pleural nodularity in 37 (49%) patients. Prabhu V. G et al, in their study, described that nodules were found in 33 patients, adhesions were seen in 26 patients, and 8 patients had sago grain appearance.[13] In another study done by Dar KA et al described that the gross thoracoscopic visual findings were multiple variable-sized nodules in 67 (53.6%) patient, followed by sago granular appearance in 19 (15.2%) patients, adhesions in 14 (11.2%) patients, mass lesion in 9 (7.2%) patients, diffuse pleural thickening in 6 (4.8%) patients, apparently healthy smooth pleura in 2 (1.6%) patients.[26] These data correlated with our data.

Pleural fluid studies were performed before VATS pleural biopsy in all of our patients. Cytological examination of the pleural fluid was inconclusive in all patients. And pleural fluid protein mean value was 3.98 ± 0.31 gm/dl and glucose mean levels 57±0.9 mg/dl with insignificant ADA levels 30.6 ± 5.7 to reach a definitive etiological diagnosis. These data helped differentiate between transudative and exudative effusions. But achieving a definitive diagnosis in exudative pleural effusion is always been a challenge for thoracic surgeons.

In the present study, the overall diagnostic yield was 95%, similar results were experienced in multiple other studies across the globe. In a study, Patil CB presented

an overall diagnostic yield of rigid thoracoscopic pleural biopsy was 85.3%.[3] The success rate of VATS pleural biopsy for definitive diagnosis was 97% in another study done by Erdogan D at al.[20] All these data are similar to our data.

However, in a recent comparative study, while the success rate of closed pleural biopsies was only 21.7% and that of medical thoracoscopic pleural biopsies were found to be 78.3%.[27] Choosing between VATS and medical thoracoscopy (MT) for unexplained pleural effusions has been one of the most important controversies and a source of debate between interventional pulmonologists and thoracic surgeons. While VATS is considered the gold standard, MT has been reported to be a less invasive, simpler, and cost-effective alternative, without significantly compromising the diagnostic yield.

A study directly comparing MT and VATS was recently published by McDonald et al.[28] They retrospectively compared MT (78 cases) and VATS (99 cases). The authors reported an overall diagnostic yield for MT at 92%, while 96% for VATS. Both medical thoracoscopic (MT) and VATS carry an acceptable safety profile with low morbidity rates reported in the literature. VATS allows for more efficient drainage of loculated effusions trapped in dense fibrous bands. The biopsy size from the VATS is larger than that with the MT; this has been quoted as a reason for the superiority of the former.

Our study showed the most common histological diagnosis for unexplained pleural effusion was malignancy followed by tuberculosis, 61% and 23% of cases respectively. Chronic nonspecific inflammation contributes to 13% of cases. Five percent (5%) of the total cases were non-diagnostic. The non diagnostic patients were probably due to the inadequate/defective collection of tissue. Erdogan et al found malignancy in 55%, chronic nonspecific inflammation in 26.9%, tuberculosis in only 7.6%, and ndiagnostic in 3% of cases.[20] In India, Patil C B showed in a study of 129 cases that histopathological diagnosis confirmed malignancy in 66.4% patients (both primary and metastatic pleural carcinoma), tuberculosis in 28.2%.[3] So world wide data from VATS pleural biopsy for unexplained pleural effusion is similar to our study.

In our study patients with malignant effusion, metastatic adenocarcinoma (n = 23) was the most common findings followed by metastatic squamous cell carcinoma (n=18). Others included small cell carcinoma, malignant melanoma and lymphoma. In a study by Dar KA et al metastatic adenocarcinoma was the most common malignancy (50%) followed by mesothelioma (36.84%), squamous cell carcinoma (9.21%), small cell carcinoma (2.63%), and non-Hodgkin's lymphoma (1.31%).[26] In an article, Jamal U A.et al found metastatic adenocarcinoma was the most frequent type (70%) of the malignant case for unexplained effusion.[18] Those results were similar to our study.

The lengthiest mean duration of chest drain tube in situ was for malignant pleural effusion (mean ± SD 12 ± 1.9 days). And for tuberculosis, it was 8 ± 1.7 days (mean ± SD). This difference was due to the longer duration of time required for pleurodesis in the case of malignant pleural effusion.

The postoperative morbidity rate was detected as 9% in a study by Erdogan D et el.[20] The morbidities included prolonged air leak, prolonged drainage, pneumonia, atrial fibrillation, expansion defect, hemorrhage, wound infection. We found no major complications, few patients had minor complications like subcutaneous emphysema (3 patients, 4%), wound infection (4 patients, 5.33%). Post-operative haemothorax (4 patients, 5.33%) and prolonged air leakage (2 patients, 2.6%), Port site tumour implantations (1 patient, 1.33%) All complications improved with conservative management. (Total 18.65 %)

There was no procedure related mortality. Studies around the world also reported no major complications or mortality. In the study by Dar KA, there was also no reported mortality.[26]

Conclusion:

VATS pleural biopsy has high diagnostic yield for patients with unexplained pleural effusion as it facilitates targeted biopsy under direct visualization. It has also minimum morbidity with no mortality.

Limitations of the study:

- The study is based on a single thoracic surgery center and therefore may not apply to those with different patient population.
- Non diagnostic patients were not reevaluated.
- Cost analysis was not done.
- Long-term follow-up is beyond the scope of this study.

Recommendations:

VATS pleural biopsy can be routinely practiced in the diagnosis of all exudative unexplained pleural effusions.

In Bangladesh with high tuberculosis prevalence, VATS pleural biopsy should be done in the patients even with clinically suspected Tuberculosus pleural effusion.

VATS pleural biopsy is preferable when adhesionlysis may be needed in the aim of obtaining pleural biopsies.

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Conflict of interest:

None declared.

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