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Comparative Study of Aspiration Cytology, Video-Assisted Thoracoscope and Open Biopsy in Undiagnosed Pleural Effusion

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ABSTRACT

Background: Pleural effusion is a common challenging problem in the cardiothoracic surgery. We have different modalities for diagnosis and hence establishing the management control for the pleural effusion.

Objectives: The aim of the study was to compare outcomes, in patients who underwent video-assisted thoracoscope (VATS) and patients who underwent aspiration cytology and standard thoracotomy, in diagnosis of pleural effusion.

Patients and methods: This randomized clinical (interventional) study was conducted in Cardiothoracic Surgery Department, Zagazig University Hospitals. We included 48 patients with undiagnosed pleural effusion after initial and repeated biochemical and cytological analysis of the pleural fluid, they were enrolled in this study. Patients were randomly divided into three groups. Group A**:** Where all patients were subjected to aspiration cytology, group B: 35 cases were subjected to VATS biopsy in undiagnosed pleural effusion and group C: 13 cases were subjected to open biopsy in undiagnosed pleural effusion.

Results: Pleural effusion was diagnosed by CT preoperatively and also confirmed by intra-operative findings either by VATS or by open biopsy and there were no differences between CT and intra-operative findings in presence of pleural effusion, pleural nodules and lung masses. While, there was significant difference regarding pleural thickening and mediastinal LN. 5 patients (14.3%) in VATs biopsy group failed and converted to open biopsy, 3 of them because of adhesion and 2 cases because of hemorrhage.

Conclusion: Video-assisted thoracoscope is safe and minimally invasive procedure in undiagnosed pleural effusion with less operative time, blood loss, chest tube duration, intra-operative and post-operative complications and length of hospital stay compared to open biopsy.

Keywords: Video-assisted thoracoscopic surgery, Pleural effusion.

INTRODUCTION

Pleural effusion is a collection of the fluid in the pleural space. A lot of medical disease cause pleural effusion including cancers (primary or secondary lung cancers), liver cell failure, renal disease, cardiac disease and many lung diseases as pneumonia, TB pneumonia, trauma and lung infarction [(1)].

Pleural effusion is a common challenging problem in the cardiothoracic surgery. We have different modalities for diagnosis and hence establishing the management control for the pleural effusion. The diagnosis of the pleural effusion starting from chest x-ray, CT chest, MRI, ultrasound-guided aspiration, video-assisted thoracoscopic surgery (VATS) and open thoracotomy [(2)].

CT chest is an important and mandatory tool for cases of pleural effusion to localize the site, amount and radiological opacity of the effusion and to differentiate between loculated and non loculated pleural effusion [(3)].Pleural effusion must be sent for cytological studies on a diagnostic aspiration. A little sum (10 ml) is an adequate in most circumstances. Pleural fluid cytology is accurate by 60% in most patients and decreases its accuracy by 20% in cancer cases like mesothelioma. Another sample from pleural effusion aspirate increases the diagnosis (by 10% in cancer), but there's no increase with a third sample. About 40% of cases of pleural threat will therefore remain undiscovered after cytological sampling. Advanced tests are required in this patient group [(4)]. Video-assisted thoracoscopic surgery (VATS) is a minimal recent technique for visualization of thoracic cavity aiming to diagnose and treat many intrathoracic problems and the pleural effusion is one of them [(5)].

VATS is done through port or multiple port axis through small incisions in the chest wall and the technique is associated with less intra-operative time and less post-operative morbidity, mortality and less hospital stay [(6)].

The aim of this study was to compare outcomes, in patients who underwent VATS, and patients who underwent aspiration cytology and standard thoracotomy, in diagnosis of pleural effusion.

PATIENTS AND METHODS

This randomized clinical (interventional) study was conducted at Cardiothoracic Surgery Department, Zagazig University Hospitals in the period from December 2021 to August 2022.

The study was carried out on 48 patients with undiagnosed pleural effusion. After initial and repeated biochemical and cytological analysis of the pleural fluid, they were enrolled in this study. Definition of undiagnosed pleural effusion was considered as the failure to achieve an etiologic diagnosis by initial pleural fluid microscopic and biochemical analysis including protein, sugar, lactate dehydrogenase, gram stain, acid fast bacilli smear and culture and at least three pleural fluid cytologies negative for malignant cells or other definite causes.

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All patients were subjected to aspiration cytology then patients were randomly selected (allocation by sealed envelopes) then divided into three groups.
Group A: All patients were subjected to aspiration cytology**.**
Group B: 35 cases were subjected to VATS biopsy in undiagnosed pleural effusion.
Group C: 13 cases were subjected to open biopsy in undiagnosed pleural effusion.

Inclusion criteria were: All patient seek medical advice in our thoracic OPD with undiagnosed pleural effusion were included in this study.

Exclusion criteria were: All patients with diagnosed pleural effusion. All patients unfit for surgical procedure.

All included patients were subjected to history taking and clinical examination. Routine laboratory investigations including CBC, coagulation time, bleeding time, prothrombin time and activity, aPTT, INR and platelet count in addition to blood grouping. Radiological evaluation including plain chest x-ray postero-anterior view and lateral view in some cases. Ultrasonography of the chest and computed tomography with or without contrast of the chest when needed. Electrocardiogram (ECG) in order to exclude recent myocardial infarction or significant arrhythmia.

Operative procedures:
1- Aspiration cytology: It was done by passing a small needle through chest wall, intercostal nerves and vessels that run immediately beneath the rib were avoided by inserting the needle just above the upper border of the rib, below the mark.
2-VATS: All patients underwent general anesthesia and intubated by a suitable double lumen endotracheal tube. The patients were first placed in the lateral decubitus position with the affected side up. First a ten-millimeter port was placed in the fifth intercostal space at the mid-axillary line. The second port was placed in the fourth intercostal space at the anterior axillary line.

Keeping the lung deflated and allowing adequate visualization of the pleural surfaces, all of the pleural fluid was aspirated and sent for cytology and culture. Biopsies were taken from the parietal pleura where macroscopic abnormalities were viewed. Second port axis was used whenever needed for more visualization sampling and taking tissue biopsy from the thoracic cavity. Hemostasis was controlled by electrocautery or other devices. After the procedure was completed, thoracoscope and the other port(s) were removed and a 28 to 32 Fr chest tube was inserted through the same incision. Chest drain was connected to watersealed drainage bottle. Chest X-ray was taken the next day. Once the lung had expanded and drain output decreased to less than 50 mL per 24 hours, chest drain was removed.

3-Thoracotomy: Through a limited standard thoracotomy in which pleural fluid and tissue biopsy were taken from the suspected lesion and sent for same investigation done with patients underwent VATS.
Outcomes: Operative time and intraoperative complication were collected for each patient in each group and compared with each other in terms of pain, hemothorax, air leak, hemorrhage or injury to vital structure, period of hospital stay and post-operative infection.

Ethical consent:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) software version 20 (IBM, USA). The parametric data were expressed as mean ± SD (Range) or number (%) for categorical data. Comparisons for parametric data were carried out using independent student t test. Fischer exact test and chi square test were used for categorical data. P value ≤ 0.05 was considered significant.

RESULTS

Table (1) showed that the mean age of patients was 9.1± 43.4 years ranged from 25 to 64 years, 62.5% of patients were males and 37.5% were females, 29.10% of them were administrative employees, 31.25% housewives, 18.75% industrial workers and 20.83% retired. 20.83% of them had diabetes and hypertension and 12.50% had cardiac problems.

Table (1): Demographic data of the studied patients

	All patients (n=48)
Age (Years)	43.4 ± 9.1 (25-64)
Gender	
• Male	30 (62.50%)
• Female	18 (37.50%)
Occupation	
• Administrative employees	14 (29.10%)
• Housewife	15 (31.25%)
• Industrial workers	9 (18.75%)
• Retired	10 (20.83%)
Co-morbidities	
• No	20 (41.66%)
• Cardiac	6 (12.50%)
• Diabetes	7 (14.58%)
• Hypertension	5 (10.41%)
• Diabetes & hypertension	10 (20.83%)

Data are represented as mean ± SD or Number (%).

According to biochemical findings, the pleural fluid was classified into transudate, exudate, empyema or hemorrhagic effusion.

Exudate and transudate were differentiated from each other according to the following items:
(1) Protein effusion/serum effusion > 0.5 exudate.
(2) LDH effusion / serum effusion > 0.6 exudate.
(3) Glucose level < 50 mg/dl exudate.
(4) Leukocyte count is high in exudate > 10,000 per mm^3 ($10 \times 3\ 10^9$ per L).

The hemorrhagic pleural effusion will be considered when the RBCS detected > 10 HPF. Empyema was diagnosed if there is organism or inflammatory cells and if there is atypical mesothelial cell malignancy was suspected and to be confirmed by tissue biopsy either by VATS or open biopsy as shown as table (2).

Table (2): Clinical and radiological data of the studied patients

All patients (n=48)	
Respiratory symptoms	
Dyspnea	39 (81.25%)
Cough	20 (41.66%)
Fever	5 (10.41%)
Cheat pain	14 (29.16%)
Wheeziness	2 (4.16%)
Loss weight	15 (31.25%)
Chest x ray finding (side) • Left • Right • Type of lesion A)pleural effusion B)pulmonary lesion	 15 (31.25%) 33 (68.75%) 48(100%) 3(6.25%)
Amount of pleural effusion • Mild • Moderate • Massive	 5(10.41%) 9 (18.75%) 34 (70.83%)
Color of pleural effusion • Hemorrhagic • Yellow • Straw color	 19 (39.50%) 10 (20.83%) 19 (39.50%)
CT finding • Pleural effusion • Pleural thickening • Pleural nodules • Mediastinal LN • Lung mass	 48 (100%) 31 (64.58%) 11 (22.91%) 2 (4.16%) 3(6.25%)

Data are represented as mean ± SD or Number (%). The results of laboratory examination of the pleural fluid of the studied patients showed that we had a percentage between 31% to 39% of our patients are exudative pleural effusions. We differentiated the character of pleural effusions according to protein level, glucose, LDH, leucocyte count with no significant differences between all these items (Table 3).

Table (3): Biochemical examination of pleural fluid of the studied patients

Protein	>0.5 17 patients (35.41%)	<0.5 31 patients (64.58%)
Glucose	>50mgdl 29 patients (60.41%)	<50mgdl 19 patients (39.58%)
LDH	>0.6 15 patients (31.25%)	<0.6 33 patients (68.75%)
Leucocytes count	>10000 16 patients (33.33%)	<10000 32 patients (66.66%)

The results of microscopic examination (cytological parameters) of the pleural fluid of the studied patients showed that 37.5% had mesothelium, 10.41% had inflammatory cells, and 27.08% had RBCs > 10 HPF so hemorrhagic. Operational data of studied patients: The diagnosis of pleural effusion after full biochemical and cytological study and obtaining of tissue biopsy either by VATS or open biopsy. 35 patients electively went to VATS while 13 patients went to elective open biopsy. Inclusion criteria from VATS according to our inclusion and exclusion criteria (table 4).

Table (4): Microscopic examination (cytological parameters) of pleural fluid of the studied patients

	All patients (n=48)
RBCs	13 (27.08%)
Inflammatory Cells	5 (10.41%)
Mesothelium Cells	18 (37.5%)

Data are represented as mean ± SD or Number (%). Table (5) showed that right side (68.75%) was the commonest side of operation, 72.90% went to VATS biopsy commonest, 64.58% of patients have pleural thickening, nature of lesion more specific intraoperatively than CT findings and mean operative time of VATS was less compared to open biopsy.

Table (5): Operational data of the studied patients

	All patients (n=48)
Side of operation • Left • Right	 15 (31.25%) 33 (68.75%)
Type of operation Vats Open biopsy conversion	 35(72.9%) 13(27.08%) 5(10.41%)
Nature of lesion according to intraoperative findings • Pleural effusion • Pleural thickening • Pleural nodules • Mediastinal LN • Lung mass	 48(100%) 42(87.50%) 16(33.33%) 7(14.58%) 5(10.41%)
Operation time Mean operative time in VATS Mean operative time in open biopsy	 34.6 ± 1.4 72.6 ± 3.6

Table (6) showed that pleural effusion was diagnosed by CT pre-operatively and also confirmed by intra-operative findings either by VATS or open biopsy and there was no differences between CT and intra-operative findings in presence of pleural effusion, pleural nodules and lung masses, while there was significant difference regarding pleural thickening and mediastinal LN.

Table (6): Comparison study between CT findings and intra-operative findings

	Ct findings N=48	**Intra-operative findings (N=48)**	**X^2, P**
Pleural effusion	48 (100%)	48(100%)	X^2= 0 P= 1
Pleural thickening	31 (64.58%)	42(87.50%)	X^2= 6.9 P=0.008*
Pleural nodules	11 (22.91%)	16(33.33%)	X^2= 1.28 P=0.25
Mediastinal LN	2 (4.16%)	7(14.58%)	X^2= 3.06 P=0.07
Lung mass	3(6.25%)	5(10.41%)	X^2= 0.54 P=0.46

Data are analyzed by Chi square test

Table (7) showed that the most common cause of pleural effusion in the current study was malignant pleural mesothelioma and was detected in 14 (29.16%) patients.

Table (7): Histopathological examination of the studied patients

	All patients (n=48)
Histopathological examination	
Malignant:	
Metastatic adenocarcinoma • Malignant pleural mesotheliomas	9 (18.75%) 14 (29.16%)
• Primary lung cancer	8(16.66%)
Benign	
• Chronic nonspecific pleurisy	7 (14.58%)
• Tuberculosis pleurisy	10 (20.83%)

Data are represented as mean ± SD or Number (%).

Table (8) showed that 5 (14.3%) VATs biopsy failed and converted to open biopsy, 3 of them because of adhesion and 2 cases because of hemorrhage.

Table (8): Conversion from VATs to open biopsy in the studied patients

	VATs biopsy (n=35)
Conversion from VATs to open biopsy	5 (14.3%)
Causes of conversion	(N=5)
• Adhesion	3 (60%)
• Hemorrhage	2 (40%)

Data are represented as mean ± SD or Number (%).

DISCUSSION

Our results demonstrated that the mean age of patients was 43.4 ± 9.1 years ranged from 25 to 64 years, 63% of patients were males and 37% were females, 29% of them were administrative employees, 31% housewives, 19% industrial workers and 21% retired. 23% of them had diabetes and hypertension and 13% had cardiac problems. This is in agreement with **Salim and Torky** [7] who demonstrated that the total number of patients that were included in their study was 90 patients, with 33 (73.3%) males and 12 (26.7%) females. Also, **Dadaş *et al.*** [8] demonstrated that the majority of cases were male patients (161 males and 102 females). In addition, **Puri *et al.*** [9] demonstrated that patients undergoing thoracotomy were younger and had a higher incidence of prior lung cancers. **Wang *et al.*** [10] reported that the age of the patients was 57.8 ± 14.5 years (range 17–90). There were 503 males and 330 females. **Kaushik *et al.*** [11] reported that PE was more common in males (68.3%) than in females (31.7%). **Helala *et al.*** [12] showed that their study included 28 males and 12 females with mean age of 51.3 ±16.3 years. So, undiagnosed exudative pleural effusions were more common among males more than females.

In the present study, the most common symptoms (81%) were dyspnea. 69% of patients had pleural effusion in right side with amount of pleural effusion massive in 71% of patients. color of pleural effusion was hemorrhagic in 39.5%, straw color in 39.5% and yellow in 21%. Ct finding showed that all of patients had pleural effusion and most of them (65%) had pleural thickening. This comes in agreement with **Dadaş *et al.*** [8] who demonstrated that the most common complaint was dyspnea 66.5%. There were 41 patients (45.6%) with pleural thickness ≥ 5 mm and 49 patients (54.4%) with pleural thickness < 5 mm. There were 17 patients (18.8%) with pleural nodules and there were 17 patients (18.8%) with mediastinal lymph nodes. In addition, **Salim and Torky** [7], demonstrated that there were 52 patients (57.8%) with moderate or massive pleural effusion and 38 patients (42.2%) with mild and mild to moderate pleural effusion.

Wang *et al.* [10] reported that most of patients (48.4%) had PE on the right side. In either unilateral or bilateral effusion, the proportions of small, moderate, and large size of pleural effusions were 21.1, 15.8, and 63.1%, respectively. The appearance of pleural effusions was blood-stained in 37.6%, in 62.7% it was yellow, and in 5 patients (0.6%) it was chylous.

Also, **Brun *et al.*** [13] showed that, most of patients (60%) presented by PE, followed by 40% presented with pleural effusion and pleural thickening and 20% of patients presented with pleural-based nodules or masses. So pleural effusion was the commonest findings in the computed tomography of patients followed by pleural thickening or pleural nodules.

Kaushik *et al.* [11] found in 82 patients that cough was the predominant symptom among all participants. Left sided pleural effusion was present in 64.6% of

patients and bilateral pleural effusion was found in only one male patient. Only 12 patients had massive effusion, of which eight were diagnosed with malignant effusion, one patient was diagnosed with tuberculosis and three subjects remained undiagnosed. Yellow colour fluid was present in 60 patients (among them, 50 subjects had tubercular etiology), and 22 patients had hemorrhagic effusion (among them, 15 patients had malignant etiology). **Hassanein *et al.* [14]** study reported that regarding chest X-ray findings, the pleural effusion was right-sided in 34 (56.7%), left-sided in 25 (41.6%) patients and bilateral in one (1.7%) patient. For pleural effusion in the chest x-ray, pleural collection was described as mild in 11 (18.3%) patients. Moderate effusion was detected in 31 (51.7%) patients. Large/massive pleural effusion was detected in 18 (30%). So, from both studies we could find that exudative pleural effusion was more common on the right side.

The results of laboratory examination of the pleural fluid of our studied patients showed that the mean of protein was 4.8 ± 0.63 mg/dl and of glucose was 78 ± 11.2 mg/dl and LDH was 485.08 ± 95.3. This is in agreement with **Kaushik *et al.* [11]** who found that the mean level of glucose and protein were 65.5 mg/dL and 5.6 mg/dL, respectively; also, the mean value of LDH was 476.4.

The results of microscopic examination (cytological parameters) of the pleural fluid of our studied patients showed that 75% of patients had leukocytes, 38% had mesothelium and 10% had inflammatory cells. This is in agreement with **Kaushik *et al.* [11]** who found that effusions were predominantly leukocyte (lymphocytic). The mean value of neutrophil and lymphocyte count was 29.2% and 69%, respectively. In 60 out of 82 patients there were no RBCs in the pleural fluid. In 22 patients, the fluid was frankly hemorrhagic.

In the present study, the right side (69%) was the commonest side of operation, lesions were present on the parietal pleura in 48 (100%) patients and on the diaphragmatic parietal pleura in 20 (42%) patients. The mean operation time was 44.9 ± 19.7 hours. **Alrawi *et al.* [15]** reported that the average duration of the procedure was 62 minutes (20 to 190). Also, **Klijian *et al.* [16]** reported that the mean duration of operation time was 62 min.

Regarding histopathological examination, the most common cause of pleural effusion in the current study was malignant pleural mesothelioma and was detected in 21 (44%) patients. This comes in agreement with **Wang *et al.* [10]** who found that 41.1% of patients were confirmed to have malignant pleural effusion. They reported that malignancy and tuberculosis were the two leading causes of pleural effusion. These results are also in agreement with the results obtained in several studies, in which malignancy was the final diagnosis of most of the studied patients with undiagnosed pleural effusion, such as in respective studies by **Helala *et al.* [12]** where malignant pleural effusion cases were 70, 74.4, and 83.9%, respectively.

Regarding conversion from VATs to open biopsy, the results showed that 5 (14.3%) VATs biopsy failed and converted to open biopsy, 3 of them because of adhesion and 2 cases because of hemorrhage. This comes in agreement with **Matsuoka *et al.* [17]** who demonstrated that because angioplasty is difficult by VATS, more than half of the conversions to open thoracotomy were due to the need for angioplasty. No conversions were needed because of inability to tolerate single-lung ventilation. All conversions were performed safely with minimal vascular injury, and no patient required emergency conversion due to massive intra-operative bleeding. **Augustin *et al.* [18]** demonstrated that regarding outcome one trial that considered 232 VATS procedures, of which 15 (6.5%) were converted to open thoracotomy. Early single-center cohort studies by **Krasna *et al.* [19]** showed that 11% were converted and nearly one-third of conversions were for non-oncologic reasons. Continued experience has led to a decrease in reported conversion rates. **Puri *et al.* [9]** demonstrated that 7% of patients were converted to open operation.

CONCLUSION

In conclusion, Video-assisted thoracoscope is safe and minimally invasive procedure in undiagnosed pleural effusion with less operative time, blood loss, chest tube duration, intra-operative and post-operative complications and length of hospital stay compared to open biopsy.

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