

To Study the Diagnostic Yield of Medical Thoracoscopy in Patients with Pleural Effusion of Undetermined Etiology

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ABBREVIATIONS: **ADA:** Adenosine Deaminase; **AFB:** Acid Fast Bacilli; **ALP:** Alkaline Phosphatase; **CPB:** Closed Pleural Biopsy; **CT:** Computerized Tomography; **HAI:** Hospital Acquired Infection; **HIV:** Human Immunodeficiency Virus; **LDH:** Lactate Dehydrogenase; **MM:** Malignant Mesothelioma; **NPV:** Negative Predictive Value; **PPV:** Positive Predictive Value; **SGOT:** Serum Glutamic Oxaloacetate Transaminase; **SGPT:** Serum Glutamic Pyruvic Transaminase; **SLE:** Systemic Lupus Erythematosus; **TB:** Tuberculosis; **TTP:** Thoracoscopic Talc Poudrage; **USG:** Ultra Sonography; **VATS:** Video Assisted Thoracoscopic Surgery; **DM:** Diabetes; **SHT:** Systmic Hypertension; **IHD:** Ischemic Heart Disease; + / -: Present / Absent.

INTRODUCTION

In clinical practice, Pulmonologists commonly encounter large number of patients with pleural diseases like pleural effusion, pneumothorax and pleural thickening or pleural mass. Worldwide, approximately a million patients develop pleural effusion annually [1]. Diagnosis of pleural effusion usually begins with detailed history taking, physical examination and chest radiography. Pleural fluid aspiration and its microbiological, biochemical and cytological analysis is the initial investigation of choice to determine the etiology of pleural effusion. Blind pleural biopsy may establish the diagnosis in some additional cases [2-3]. 25-40% of pleural effusions

remain undiagnosed even after thoracentesis and closed pleural biopsy. Thus, the accurate diagnosis of pleural diseases is very challenging [4-5]. Almost 50% of these undiagnosed patients will ultimately be diagnosed with a malignancy [6].

Medical thoracoscopy also known as pleuroscopy today remains the gold standard technique for diagnosing and managing undiagnosed pleural effusion cases because of its high sensitivity in malignant and tubercular pleural effusions [7]. This procedure was first performed for diagnosis purpose in 1910 by H. C. Jacobsen, the Swedish internist [8]. Medical thoracoscopy has received an overwhelming interest among respiratory physicians in the last decade as a tool for diagnosing pleural diseases [9].

Medical thoracoscopy, in the trained hands of a pulmonologist is a safe, effective and minimally invasive procedure that can be performed under local anesthesia or conscious sedation in an endoscopy suite, unlike video assisted thoracoscopic surgery (**VATS**) which is performed under general anesthesia with single lung ventilation. It allows one to visualize the pleural space and intrathoracic structures and perform limited diagnostic and therapeutic procedures [3].

Major indication of medical thoracoscopy is evaluation of undiagnosed, lymphocyte predominant exudative pleural effusions where tuberculosis (**TB**) and malignant pleural effusion are clinical possibilities and initial pleural fluid analysis is inconclusive [10]. Pleural effusion of unknown etiology remains the commonest indication of medical thoracoscopy which has the highest diagnostic yield in “aspiration cytology negative exudative effusion” as per the recent British Guidelines, with an efficacy almost compatible to VATS [11].

Medical thoracoscopy helps to take pleural biopsy from suspicious sites under direct vision and allows greater diagnostic yield up to 95% for malignancies and 100% for benign diseases [3]. Yield of thoracoscopic pleural biopsy is higher in patients with suspected pleural TB. A diagnosis of pleural TB could be achieved in 99% patients as against 51% patients using closed pleural biopsy. Diagnosis of malignant pleural effusion can be achieved in 95% of patients with thoracoscopy, which is higher than the 44% yield for closed thoracoscopy [12].

In the past, rigid instruments were used for thoracoscopy that might have been considered relatively invasive in the setting of conscious sedation and local anesthesia. While using rigid thoracoscope, it was difficult to visualize posterior and mediastinal aspects of pleural cavity without creating an extra port of entry especially when a lung was only partially collapsed [13]. Moreover, most pulmonary physicians are not familiar with rigid thoracoscope and hence procedure was not much popular [14].

The diagnostic yield achieved by the semirigid thoracoscope is similar to that of the conventional rigid thoracoscope despite the smaller biopsy size. Both rigid and semirigid thoracoscope remain valuable in the evaluation and management of pleural disease [15].

Medical thoracoscopy can be used for therapeutic purposes like adhesiolysis, evacuation of pleural fluid in empyema patients, chemical pleurodesis in case of malignant pleural effusion and spontaneous pneumothorax [16].

This study aims to assess diagnostic yield of medical thoracoscopy in patients with pleural effusion of undetermined etiology presented to a tertiary care center in central India. Study also assesses the therapeutic outcome, complications and safety of the procedure in such a setup.

AIMS & OBJECTIVES

1. To assess the diagnostic yield of medical thoracoscopy in patients with pleural effusion of undetermined etiology presenting at Get well Hospital & Research Institute, a tertiary respiratory referral centre in Nagpur.
2. To observe the correlation in gross thoracoscopic findings and pleural biopsy reports among patients with undiagnosed pleural effusion.
3. To study the extent of therapeutic outcomes of medical thoracoscopy in patients with pleural diseases.
4. To review adverse events and to evaluate safety of thoracoscopy in patients with pleural diseases.

REVIEW OF LITERATURE

The role of medical thoracoscopy has been evaluated in various studies over the years. Many studies have arrived at varied conclusions over the usefulness of this procedure in undiagnosed pleural effusion. I reviewed the literature through pubmed and national & international journals. After reviewing literature, I have mentioned outcomes of many other similar studies beginning from oldest to new in chronology as per years of publication. I considered more than 10 national and international studies related to semirigid thoracoscopy which were published in last 5 years.

In 1991, Menzies and Charbonneau [17] from Canada reported a study in which 104 thorascopies were done on 102 patients. The thoracoscopy was 96% accurate with a sensitivity of 91%, a specificity of 100% and a negative predictive value of 93% for the diagnosis of pleural malignancy. Thoracoscopy was well tolerated under local anesthesia and entailed hospitalization for less than 24 hours in most cases. No deaths occurred, although 1.9% of patients had major complications, and 5.5% had minor complications.

In 1993, a study in Germany by Boutin et al [18] suggested that thoracoscopy is useful for diagnosis of a number of lung diseases. Thoracoscopy in pleural effusion was 92-97%, and specificity was 99%. This is much better than needle pleural biopsy and/or fluid cytology. In malignant mesothelioma, thoracoscopy allows accurate staging.

In 1995, Colt [19] reported prospective study of safety and outcome of thoracoscopy; Fifty-two procedures were performed in 50 patients at San Diego medical center, California. Median age was 60 years (range, 18 to 88 years). A diagnosis in 93% patients with pleural disease of unclear origin was made via thoracoscopy. Pleurodesis by thoracoscopic talc insufflation was successful in 95% of cases. Thoracoscopic drainage of empyema was successful in 6 of 7 patients. There were no procedure-related deaths or intra operative accidents occurred in the study. Minor adverse events, noted in ten instances (19%) included fever, asymptomatic pneumothorax, and minor wound infection in a patient with empyema.

Harris et al [20] reviewed a retrospective study in which 182 patients underwent thoracoscopy for pleural disease over a 5-year period at Cleveland Clinic, Ohio in the year 1995. Final diagnoses were 98 (54%) malignant, 58 (32%) benign and 26 (14%) idiopathic. Thoracoscopy had 95% sensitivity for malignancy and 100% for benign disease.

In 1996, Viallat et al [21] reviewed a study to assess the efficacy, permanence and safety of thoracoscopic talc poudrage (**TTP**) for pleurodesis in malignant effusions. Out of the 360 patients: 88 had mesothelioma, while 272 had pleural metastases. The mean follow-up time in this study was 12 months (2 to 120). Of the 327 patients, 90.2% had a successful pleurodesis at 1 month, and 82.1% had a lifelong pleural symphysis. Adverse effects involved 1 death 3 days after the procedure in a patient with end-stage disease, fever (9.8%), empyema (2.5%), pulmonary infection (0.8%), and malignant invasion of the scar (1 patient).

In 1998, A study by Wilsher and Veale at Green Lane Hospital, Auckland, New Zealand [22] In 1998, A study by Wilsher and Veale at Green Lane Hospital, Auckland, New Zealand, 2258 patients had thoracoscopy, most having had 2 (range: 1–6) non-diagnostic pleural aspirations and biopsies of the pleura. 19 patients were found to have mesothelioma and 9 metastatic malignancies. 3 patients were considered likely to have tuberculous pleural disease, 6 had asbestos-related benign pleural fibrosis, and 3 post-cardiotomy syndrome. There was 1 chylous effusion of uncertain etiology, one post-traumatic and 2 benign effusions, which resolved without clear etiology. There were 5 false negative diagnoses of malignancy, but no false positives. In pleural malignancy diagnosis, sensitivity was 85% and specificity 100%.

In 1998, de Groot and Walther [23] from Cape Town, South Africa, reported a study of thoracoscopy in undiagnosed pleural effusion among 34 patients. 17 (50%) had malignant disease, 6 (18%) tuberculosis and 9 (26%) 'negative' pathology. In 2 (6%), further intervention was required to make a conclusive diagnosis. The diagnostic sensitivity for malignant disease was 89% and the specificity 100%. For pleural tuberculosis both the sensitivity and specificity were 100%. For 'negative' diagnoses the negative predictive value was 82%. There was 1 in-hospital death (3%), and 9 patients (26%) had major complications related to the procedure.

In a retrospective study in Denmark by the Hansen et al, [24] the results of medical thoracoscopy in 147 patients were reviewed; 136 of the patients had pleural effusion and 11 patients had diffuse pulmonary infiltration. All the pleural exudates were initially screened three times successively and found to be sterile and without tumour cells. All thorascopies were performed with local anaesthesia, with the 'open technique', and nine different doctors performed the thorascopies. The overall diagnostic sensitivity was 90.4%. The results demonstrated 62% with malignancy of the pleura, and 38% revealed benign pleural diseases, among them 2% with tuberculosis. The sensitivity for malignancy was found to be 88% and the specificity 96%. The most common primary lung cancer with involvement of the pleura was the adenocarcinoma (62%), and the most common metastatic tumour originated from the breast (28%). The sensitivity for tuberculosis was 100% and the specificity 100%. No mortality was found, and the morbidity was low at about 0.6% (empyema, pleuro-cutaneous fistula, transcutaneous growth of tumour (mesothelioma)). In 64% of the patients the thoracoscopy resulted in treatment (pleurodesis, antituberculous treatment, chemotherapy and peroral steroid therapy). The medical diagnostic thoracoscopy in local anaesthesia is a simple low-cost investigation with a relatively high diagnostic accuracy, no mortality and a low morbidity.

A study in 2002 by Guska [25], thoracoscopy was performed among 74 patients with the pleural effusions of unknown origin. The malignancy was found in 47.3% (35/74) patients. Diagnostic sensitivity of the method for malignancy was 89.7% and the specificity 100.0%. The positive predictive value of the thoracoscopy for malignancy was 100.0% and negative predictive value 89.7%.

In 2002, Blanc et al [26] from France, reported a study in which 168 medical thorascopies were performed on 154 patients (123 men; mean age $\pm$ SE, 61 $\pm$ 1 years), of which 149 were diagnostic and 19 were indicated for therapeutic assessment in malignant mesothelioma. Prior to thoracoscopy, at least one closed pleural biopsy (**CPB**) had been performed in 120 of 149 cases, yielding a diagnosis in 96 cases. Thoracoscopy challenged the CPB-based diagnosis in 43 of 96 cases. In 66 cases of nonspecific inflammation diagnosed by CPB, thoracoscopy revealed Malignant Mesothelioma (**MM**) in 16 cases, adenocarcinoma in 10 cases, undetermined carcinoma in 3 cases and pleural tuberculosis in 3 cases. In 18 cases in which the diagnosis was MM, thoracoscopy, performed for precise staging, challenged the diagnosis in 4 cases. In 12 cases of carcinoma diagnosed by CPB, thoracoscopy specified the histologic type in 7 cases. Thoracoscopic diagnoses were found to be erroneous in 10 of 149 cases, mainly owing to pleural adhesions that limited access to the pleural cavity. There was one thoracoscopy-related death, one case of sepsis, and six cases of empyema.

A retrospective study in year 2005 was done by Tettey et al [27] from Ghana to establish the effectiveness of tetracycline pleurodesis in 38 patients with malignant pleural effusion using the powder from tetracycline capsules and compare the results with other studies done elsewhere. Of the 38 cases, 32 were diagnosed as breast cancer (84%), 4 were ovarian cancer (10%), one

endometrial carcinoma (3%), and one fallopian tube cancer (3%). Sixty one percent of patients achieved complete symphysis of the pleura with no recurrence. There was recurrence with loculation in 16% of the cases. These patients were left alone since they did not develop significant dyspnoea on exertion. In 23% of patients, the procedure was unsuccessful and significant re accumulation of pleural fluid occurred.

In 2007, A study by Lee et al, [28] all patients with unilateral exudative pleural effusions of unknown aetiology underwent diagnostic flex-rigid pleuroscopy at Singapore General Hospital, Singapore. Fifty-one patients were recruited (20 male and 31 female). Median age was 53 years (range 45-67). Flex-rigid pleuroscopy was 96% accurate and yielded a diagnosis in 49 out of 51 patients. It was safely carried out without need for surgical intervention, blood transfusion or endotracheal intubation. Culture-negative fever was observed in eight patients (16%), and five patients (10%) required additional analgesia for postoperative pain. Duration of chest tube drainage and length of stay for patients who underwent diagnostic pleuroscopy were 1 and 2 days, respectively, while they were both 3 days when talc poudrage was carried out. Success rates with pleuroscopic talc pleurodesis for malignant pleural effusions were 94%, 92% and 89.5% at 3, 6 and 12 months, respectively, and the 30-day mortality was 0%.

A study from Hong kong by Law et al, [29] a total of 20 patients (16 males and 4 females; mean age, 63 years) underwent the procedure and were followed up for a mean of 19 weeks. For the 14 patients having diagnostic pleuroscopy, the yield was 79% (11 patients). The 3-month success rate for the six patients undergoing pleurodesis was 83% (five patients). Complications were mild and included self-limiting fever (20%, four patients) and localized subcutaneous emphysema (20%, four patients). No major complications or mortality were noted.

A comparative retrospective study in China in year 2008 by Wang et al [30], 27 patients with undiagnosed pleural effusion who underwent medical thoracoscopy revealed tuberculous pleurisy in 6 patients, adenocarcinoma in 7, squamous-cell carcinoma in 2, metastatic carcinoma in 3, mesothelioma in 2, non-hodgkin's lymphoma in 1, and others in 4. Only 2 patients could not get definite diagnosis. Diagnostic efficiency of medical thoracoscopy was 93% (25/27). Medical thoracoscopy could be well tolerated by all the patients. The semi-rigid thoracoscope could be easily controlled by chest physicians. The most common complication was transient chest pain (20 of 27 patients) from the indwelling chest tube, which would be managed with conventional analgesics. One case of subcutaneous emphysema and 2 cases of postoperative fever were self-limiting. No severe complications occurred.

Ng et al [31] from Pahang, Malaysia reported the yield of medical thoracoscopy to be 45.5% (10/22 patients). Ten patients were confirmed carcinoma (eight cases of adenocarcinoma, one case of non small cell carcinoma, one case of osteosarcoma). Eight patients had inconclusive thoracoscopic pleural biopsy results. Three patients underwent pleurodesis for malignant effusion. One patient had adhesiolysis for empyema. There were no procedure-related deaths or intra operative accidents.

A study was carried out by Tscheikuna et al [32] in Thailand during 1998 to 2007. There were 142 procedures of medical thoracoscopy performed. There were 86 procedures for the indication of undiagnosed pleural effusion. The diagnostic yield was 95.2%. The malignancy was diagnosed by thoracoscopy in 45.35% procedure. 15 patients who had loculated pleural effusion underwent medical thoracoscopy. Mean hospital stay was 9.1 days after thoracoscopy. There was no serious complication from procedure.

In 2010, Mohan et al [17] retrospectively evaluated outcomes of rigid thoracoscopy in pleural effusion of undetermined etiology at AIIMS, India and Royal Preston Hospital, UK. One hundred fifty procedures were analyzed. Ninety-two patients (62.3%) were diagnosed as having a malignant disorder, of which mesothelioma was the most common (26%). Pleural thickening and nodularity were the most common abnormalities noted. The combined presence of nodules and hemorrhagic fluid increased the likelihood of malignancy 9-fold. Overall, thoracoscopy provided a diagnostic accuracy of 91.3%, sensitivity of 87%, and specificity of 100%. The addition of a second procedure in selected patients improved the diagnostic accuracy for malignancy by 8.7%. The procedures were well tolerated and only 6 patients developed minor and transient complications such as pain, hypoxia, and bradycardia.

A study in year 2010, thoracoscopy was done by Thangakunam et al [33,34] in 21 patients using a flex-rigid thoracoscope at Christian Medical College, Vellore, India. The indication was pleural effusion with inconclusive or negative pleural fluid cytology and blind pleural biopsy in 18 of the 21 patients. Thoracoscopic biopsy was positive in 12 of the 18 patients (66.7%): Six had adenocarcinoma, three had necrotizing granulomatous inflammation suggestive of tuberculosis and one each had non-Hodgkin's lymphoma, mesothelioma and inflammatory pseudotumour. Of the six who had a negative biopsy, the procedure indirectly helped in patient management in five. There were no significant procedure-related complications.

Mehta et al [35] reported a study of semirigid thoracoscopy performed in 25 consecutive patients with pleural effusions of unknown etiology at AIMS, Cochin, Kerala in year 2010. Out of the 20 patients who underwent diagnostic thoracoscopy: 9 were malignancy, 7 were chronic pleuritis, 2 were tuberculosis and 1 each of empyema and endometriosis. Patients with diagnosis of chronic pleuritis were followed up. Two patients were found to have malignancy by means of bronchoscopic and CT guided biopsy respectively. One patient was found to have metastatic malignancy on lymphnode biopsy. One patient died of sepsis after 1 month for whom final diagnosis remained elusive. Overall diagnostic yield of the series was 80% (16/20). Five patients underwent thoracoscopy for talc poudrage. There were no significant procedure-related complications.

In 2010, Mootha et al [10] from North India reported a study in which 35 patients (71% men and 28.6% women; mean age 48.68 years) with undiagnosed pleural underwent thoracoscopy for diagnostic purposes, effusion overall diagnostic yield of thoracoscopic pleural biopsy was 74.3% in patients with undiagnosed pleural effusions. Pleural malignancy was diagnosed in 48.6% of

patients. There was only one case of mesothelioma and the rest were due to pleural metastasis. Lung cancer and breast cancer were the most common sites of primary malignancy. Tuberculosis was diagnosed with pleural biopsy in 22.8% of patients. Study showed very low complication rate after thoracoscopy.

In 2011, a study in China reported by Huang et al, [36] Thoracoscopy identified lesions in the pleural and/or diaphragm in 42 patients and no lesions in 5 patients. Malignancy was confirmed in 21 (44.7%), tuberculosis in 17 (36.2%), idiopathic hypereosinophilic syndrome in 1 (2.1%), nocardiosis in 1 (2.1%), constrictive pericarditis in 1 (2.1%), chronic empyema in 2 (4.3%), splenic artery embolization in 1 (2.1%), and negative result in 3 (6.4%) of the cases. The diagnostic accuracy rate of flexirigid thoracoscopy reached 93.6%, and no serious complications in relation to the examination was found.

Rozman et al [37] from Slovenia made a retrospective analysis of 129 thorascopies which were performed in 125 patients in a 5-year period. All patients had pleural effusion or a pleural mass, which failed to be diagnosed by less invasive diagnostic methods. In the study group, there were 90 (72.0 %) men and 35 (28.0 %) women. Their median age was 63years (from 28 to 81 years). All procedures were performed under local anaesthesia with a video thoracoscope Olympus A5252A. Pleurodesis was performed by insufflation of 5g of talc. Results: 78 (62.4 %) of patients had malignant infiltration of the pleura and 47 (37.6 %) had a benign pleural disease. The diagnostic accuracy of thoracoscopy was 91.5 %. The sensitivity in the diagnostics of malignant pleural disease was 86.1 %, the negative predictive value was 82.0 %. Talc pleurodesis was performed in 14 patients with malignant pleural infiltration. Complications were detected in 33 (26.4 %) patients, most of them were not severe. Severe complications, such as empyema, bronchopleural fistula, prolonged duration of drainage, perforation of the diaphragm and trapped lung, occurred in 8 (6.4 %) patients. 30-day mortality rate after the procedure was 0%.

In 2012 in a study by Prabhu and Narasimhan [38] from India during a three-year period, a total of 68 patients (55 males and 13 females; mean age 49 years) underwent pleuroscopy. 66.1% patients had left sided and 33.9% patients had right sided pleural effusion. Symptomatically 75.4%, 67.3%, 45.3%, 42.8% patients had breathlessness, cough, fever and chest pain respectively. On pleuroscopic findings, nodules were found in 33 patients, 26 patients had adhesions, 8 patients had sago grain appearance, and 1 patient had normal pleura. Malignancy was diagnosed in 24 patients, 22 patients had non-specific inflammation, tuberculosis was found in 16 patients, empyema was found in 2 patients, 1 patient had sarcoidosis, 1 patient had normal pleura and it was non-diagnostic in 2 patients. The diagnostic yield was 97%. In 24 patients who had malignancy, 15 patients had Metastatic adenocarcinoma, three patients had Mesothelioma, three patients had undifferentiated carcinoma, one patient had lymphoma, one patient had Metastatic clear cell carcinoma and one patient had Metastatic squamous cell carcinoma. There were no major complications, only four patients had minor complication like subcutaneous emphysema (three patients) and prolonged air leak (one patient).

In year 2012, a study by Mehta et al, [39] majority of the patients had pleural nodules while empyema, pleural thickening, patchy pleuritis and apical blebs were the findings in the rest. Normal pleuroscopy findings were observed in 2 patients. Therapeutic pleuroscopy (Adhesionolysis and/or pleurodesis) was performed in 16 patients. Pleurodesis was performed in 5 patients and adhesionolysis was performed in 9 patients, while in 2 patients, adhesionolysis and pleurodesis was performed. Sclerosing agents used for pleurodesis were betadine solution (6 cases) and oxytetracycline (1 case). Success rate of betadine pleurodesis was 83.3 % (5 of 6 cases). Pleuroscopy along with biopsy demonstrated diagnostic yield, sensitivity and specificity of 100 %. Minor complications related to the pleuroscopy procedure were bleeding, surgical emphysema and infection with overall incidence rate of <1 %. Procedure related mortality was zero.

A study in Pakistan, Saifullah and Rizvi [40] reported results of 120 pleuroscopies and were able to reach a diagnosis in 116 patients. Yield of pleuroscopic biopsy in the diagnosis of exudative pleural effusion is 96.7%. Specific diagnosis through pleuroscopic biopsy have shown 45% cases of tuberculosis, 41.7% cases of adenocarcinoma, 8.3% cases of chronic non specific inflammation, 1.7% cases of lymphoma and one case of hemagioendothelioma was also diagnosed. No major complications were occurred.

In 2012, Retrospective case note, radiology and laboratory result analysis of patients undergoing thoracoscopy was done by Brims et al [41] from UK. Fifty-seven of 58 case notes were available for analysis. Median (interquartile range) age was 73.0 (66.5–79.0) years and 44 (77.2%) were male. Median time with chest drain post-procedure was 3.0 (2.0–5.0) days, and length of stay (**LOS**) was 4.0 (2.0–8.0) days. Malignant histology was reported in 40 (70.2%), with 25 (62.5%) cases of mesothelioma. There were no deaths related to the procedure. Hospital-acquired infection (**HAI**) occurred in six (10.5%: pneumonia four, empyema two), all had malignancy. The presence of HAI significantly prolonged the LOS 9.0 (7.5–23.5) vs no HAI 4.0 (2.0–7.0) days; $P = 0.006$. Four patients died within 1 month of the procedure, three had a malignant diagnosis, and all had suffered HAI. Trapped lung (persistent hydropneumothorax 5 days post-procedure) occurred in 11 (19.2%), six of whom had benign histology. Performance status (European Cooperative Oncology Group) prior did not differ with reported histological type: benign 2.0 (2.0–2.0), malignant 2.0 (2.0–3.0), $P = 0.170$.

A retrospective analysis of 2380 patients with unexplained pleural effusion (1320 males and 1060 females; age 15-94 years) in China was done by Jiang et al. [42]. The endoscopic findings of malignant pleural effusion mostly showed nodules of varying sizes. The nodules could be grape-like, cauliflower-like, fused into masses, or diffused small nodules. The appearance of cancerous nodules was more diversified compared to tuberculous nodules. Tuberculous pleurisy was manifested as diffuse pleural congestion and miliary changes, multiple small gray-white nodules, fibrin deposition and adhesion in the pleural cavity, pleural thickening and loculation.

The pathological diagnosis was as follows: pleural metastases in 899 (37.8%), primary pleural mesothelioma in 439 (18.4%), tuberculous pleurisy in 514 (21.6%), non-specific inflammation in 226 (9.5%), empyema in 190 (8.0%), hepatic pleural effusion in 36 (1.5%) and pleural effusion of unknown causes in 76 (3.2%) cases. The diagnostic positive rate of medical thoracoscopy was 96.8%. No serious complications were observed.

A study by Helala et al, [43] Medical thoracoscopy was performed on 40 patients (28 males, 12 females, mean age 51.3 year) Kobri El-Kobba Military Hospital, Egypt. Study gave a definitive diagnosis in 38 out of 40 patients with diagnostic yield 95%. Malignancy was diagnosed in 28 patients (70%), one patient was diagnosed as empyema (2.5%), tuberculosis was found in 9 patients (22.5%), and it was non diagnostic in 2 patients (5%). Nodules were found in 28 patients (70%), sago-grain nodules were found in 5 patients (12.5%), adhesions were found in 3 patients (7.5%), collection of pus in one patient (2.5%), mass was found in one patient (2.5%), Violaceous lesions were found in one patient (2.5%) and there were no specific findings in only one patient (2.5%). 92.9% of patients with nodules were malignant, while only 3.6% were non-malignant and this difference was statistically highly significant. 100% of patients with sago grain nodules were non-malignant (all diagnosed as tuberculous pleural effusion), it was of high statistical significance. Also 100% of patients with adhesions were non-malignant. It was statistically significant. The post-thoracoscopic complications in the studied group have occurred only in 4 patients (10%).

Shaheen et al [44] reported a study in which forty patients were enrolled including 15 males (37.5%) and 25 females (62.5%) presenting with undiagnosed exudative pleural effusion. The mean age of the patients was 53 years (range 26-72). The diagnostic yield of flexible thoracoscope and that of rigid thoracoscope was 80% (32/40) and 95% (38/40), respectively. All thoracoscopy procedures were safely without serious complications. 19 patients presented with hemorrhagic pleural effusion (47.5%), 20 (50%) presented with straw colored and one (2.5%) presented with green colored pleural effusion. The majority (79%) of patients with hemorrhagic effusions were finally diagnosed as malignant, other diagnoses were tuberculous and parapneumonic effusions.

In 2014, a study by Gao et al, [45] a total of 215 patients with undiagnosed exudative pleural effusion were underwent thoracoscopy under local anesthesia at Yichang Central People's Hospital, China. All patients, Karnofsky performance status >70, could tolerate both the thoracoscopic surgery and pleural biopsy; there were no severe complications. Thoracoscopic findings included pleural hyperaemia, fibrinous adhesion, nodular bulge and fester. The pathological biopsy confirmed diagnoses of malignant tumor (97 cases), tuberculous pleuritis (91 cases), tuberculous empyema (one case), pulmonary schistosomiasis (one case) and unknown etiology (25 cases). The total diagnosis rate was 88.4%. Subcutaneous emphysema occurred in ten cases and fever in six cases, all of which recovered completely with conservative treatment.

In 2014, a study by Rozman et al [46] One hundred fifteen thorascopies were performed on 111 patients. The median age was 65 years (range 28–86 years), 14.4% were female and 85.6% male. Seventy-three (65.8%) patients had malignant pleural disease (malignant mesothelioma, metastatic cancer) and 38 (34.2%) had benign disease. The sensitivity, negative predictive value, and accuracy of the procedure for malignancy were 96.0%, 93.0%, and 97.4% respectively. Pleurodesis was carried out in 34 patients; in 32 (94.1%) it was assessed as successful after 1 month. There were 24 adverse events: three empyemas/pleural infections, three bronchopleural fistulae after chest tube placement and lung re-expansion, five patients had excessive pain after pleurodesis, six patients had sedation-associated hypotension, and seven patients had self-limited fever after pleurodesis. One patient died 11 days after a procedure for advanced carcinoma.

A study was published in year 2014 by Haridas et al [47] at AIMS, Kochi, India to compare the efficacy of closed pleural biopsy and medical thorascopic pleural biopsy in the diagnosis of undiagnosed exudative pleural effusions in a tertiary care setting. Medical thoracoscopy has a diagnostic yield of 86.2% with complication rate of 10.3% compared to 62.1% and 17.2% respectively in closed pleural biopsy group.

MATERIALS AND METHODS

Study settings: This study was conducted at a 100-bed tertiary care teaching hospital, Get well Hospital & Research Institute, Nagpur. The hospital provides health care to the nearby area, mainly from the urban and the rural areas of Nagpur district and other parts of Central India. Our hospital is tertiary care center with advanced infrastructure for disease management especially for respiratory diseases. Most of our patients with pleural diseases were referred to us and many of them remained undiagnosed after initial assessment. Hence we choose to study role of medical thoracoscopy in patients with undiagnosed pleural effusion. The present study is first of its kind study to be carried out in this part of central India analyzing data on Medical Thoracoscopy which itself is done in very few centres around here.

Study Design: This study is a hospital-based, prospective cross sectional study.

Study period of recruitment: The study period of recruitment was from January 2013 to December 2014.

Sample size: 45 patients with pleural effusions of undetermined etiology were enrolled in study with prior consent. Sample size was calculated by formula using sensitivity, specificity and prevalence of disease. Following is the formula used for the calculation of sample size:

FORMULA

$$n = \frac{Z^2 * P(1 - P)}{\Delta^2} \quad (1)$$

n will be $(a+c)$ if we use Sensitivity as P , and n will be $(b+d)$ if we use Specificity as P in formula (1).

$$N = \frac{(a + c)}{\text{Prevalence}} \quad (2)$$

$$N = \frac{(b + d)}{(1 - \text{Prevalence})} \quad (3)$$

Where $a+c$ is number of diseased patients and $b+d$ is number of non diseased patients and Δ is precision.

Ethical Issues: The study protocol was approved by the Ethical Review Committee and Scientific Committee, Get well Hospital, Nagpur, Maharashtra, India. Written informed consent was obtained from the study participants.

Study Population: The subjects of the study group were chosen from the patients admitted in the Pulmonary Medicine Ward at Get well hospital, Nagpur. We performed medical thoracoscopy in patients with undiagnosed pleural effusion. We followed Light's criteria for the diagnosis of pleural effusion. Undiagnosed pleural effusion was defined as failure to achieve diagnosis by initial pleural fluid report including its microbiological, biochemistry and cytological analysis. To consider undiagnosed pleural effusion, Pleural fluid must be sterile, exudative with lymphocyte predominant, ADA level <70 IU/L and cytology negative for malignant cells. Pleural fluid was considered as an exudate if one or more of the following Light's criteria were met

1. Pleural fluid protein/serum protein - >0.5
2. Pleural fluid LDH/serum LDH - >0.6
3. Pleural fluid LDH more than two-thirds of the upper limit of normal serum LDH.

All selected patients followed inclusion criteria as described.

Inclusion criteria:

- Age 18 -70 years including both male & female
- To consider undiagnosed pleural effusion, Pleural fluid must be

- Exudative pleural effusion as per Light's criteria
- Lymphocyte predominant
- ADA levels must be less than 70 IU/L
- Cytology must be negative for malignancy
- No known underlying lung pathology causing pleural effusion like pulmonary tuberculosis or malignancy.
- Patients willing to give consent for thoracoscopy
- Surgically fit

Exclusion criteria

- Age less than 18 years or more than 70 years
- Diagnosed pleural effusion including following pleural fluid analysis
 - Transudative pleural effusion as per Light's criteria
 - Neutrophil predominant exudative pleural effusion as per Light's criteria
 - Pleural fluid ADA levels more than 70 IU/L
 - Pleural fluid cytology positive for malignancy
- Smear positive pulmonary tuberculosis
- Known primary malignancy
- Pregnant female patients
- Surgically unfit
- Patients with bleeding diathesis
- Patients with history of recent myocardial infarction or cardiac arrhythmias
- Patients with severe dyspnea or intractable cough
- Patients with history of hemodynamic instability.
- Non cooperative patients
- Patients who were not given consent for thoracoscopy
- Patients who are not affordable since this was a private self funded hospital.
- Patients with excess rib crowding with narrow intercostal space

All patients were subjected to the following:

- Detailed history and clinical assessment as per study proforma
- Investigations
 - Routine blood investigations: Complete blood count, liver and kidney function test , test for HIV and HbsAg and coagulation profile
 - Sputum smear examinations for the presence of Acid-Fast Bacilli (**AFB**) on 3 consecutive days
 - Electrocardiography
 - Radiological examination including plain chest X-ray postero-anterior view and lateral view, ultra sonography (**USG**) of chest and CT scan of chest
 - Diagnostic thoracocentesis: pleural fluid was sent for microbiological, chemical and cytological analysis
 - Thoracoscopic examination of the pleural space using a fiberoptic thoracoscope.

After a detailed clinical history, thorough physical examination and routine investigations, patients were assessed on the grounds of fitness for the procedure of thoracoscopy. A written informed consent was obtained from all the patients undergoing thoracoscopy procedure. The purpose of the study was explained to the patients and those who consented to participate were included. Others, who didn't fall in the inclusion criteria due to various reasons, were excluded from the study.

Fourty five such indoor patients were included in this prospective cross sectional study. Thoracoscopy was performed on 45 consecutive patients with undiagnosed pleural effusion who presented to KRIMS hospital, Nagpur. Thoracoscopy was performed by the faculty from Pulmonary Medicine department. Thoracoscopy was done with Olympus LTF 160 semirigid thoracoscope shown in figure 1. Pleural biopsy was taken among all 45 patients in study. In addition, therapeutic procedure was carried out for 22 patients. Thoracoscopic adhesinolysis was done among 10 patients. Pleurodesis was done in 12 patients.



Figure 1: Olympus semirigid thoracoscope with plastic cannula & trocar.

Procedure: All patients were kept nil orally for six hours prior to the procedure. Though medical thoracoscopy can be performed very efficiently in bronchoscopy suite we preferred to do the procedure in operation theatre. The patients were positioned in the lateral decubitus position with the normal lung in the dependent position and arm raised above the head. The involved side was disinfected and draped with sterile cloth. Patients were hemodynamically monitored including pulse rate, blood pressure, oxygen saturation and oxygen supplementation was provided as required. Thoracoscopy was performed under conscious sedation with local anaesthesia. Intravenous midazolam (0.5mg/kg body weight) was used for sedation and titrated according to the needs of patients. At the point of entry, local anaesthesia was achieved by injecting 10-15 ml 2% lignocaine through all the layers of chest wall till the pleura. A 1cm long incision in the mid-axillary line between 4th to 7th intercostal spaces of the chest wall was done using sterile surgical blade and track was created by blunt dissection using artery forceps. A cannula with blunt trocar (Figure 1) was inserted and port was made. The trocar was then removed and semirigid thoracoscope was introduced through cannula (Figure 2). Pleural fluid was suctioned to allow better visualization of pleural surface. Pleural cavity was thoroughly examined. Biopsy forcep was introduced through working channel of the thoracoscope and multiple (5-6) biopsy samples were obtained under vision from suspicious areas over costal and diaphragmatic parietal pleura.

Biopsy specimens were placed in formalin for histopathology. Adhesiolysis was done among the patients in whom there were multiple septations causing adhesions which prevented complete lung expansion using thoracoscope or biopsy forceps. In cases with suspected malignant lesions, pleurodesis was done once lung expanded completely and pleural fluid drain was less than 100 ml/day. Pleurodesis was done using talc poudrage (5gm) – Steritalc or oxytetracycline (35mg/kg body weight). At the end of procedure, cannula and thoracoscope were removed and chest tube was inserted. Chest drain was connected to under water seal drainage. Patients were kept under close observation and dealt with any complications which were reported. A chest X-ray was taken after 24 hours of procedure. Drain was removed once lung expansion was confirmed radiographically and drain output had decreased to less than 50 ml per 24 hours.



Figure 2: Procedure of thoracoscopy.

Data collection: All indoor patients with undiagnosed pleural effusion who underwent thoracoscopy and enrolled during study period were reviewed. All indoor patients in the study group were interviewed to obtain history in detail and physical examination was performed. All investigations and inpatient records including thoracoscopic procedure and pleural biopsy reports were reviewed. Data was collected in predesigned Proforma (Annexure 1) and was analysed to determine demographic characteristics and comorbid conditions, thoracoscopic findings, pleural biopsy reports, and other therapeutic outcomes.

Data entry & analysis: The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (**SPSS**) version 21.0.

Analysis of this data was done in accordance to previous related studies. Categorical variables were presented in the form of frequency and percentage (%) and continuous variables were presented as Mean $\pm$ SD and Median. Graphical representation of the results was done and appropriate statistical methods were employed to ascertain the diagnostic yield of medical thoracoscopy.

Qualitative variables were compared using Chi-Square test /Fisher’s exact test. Diagnostic test was performed to calculate sensitivity, specificity, NPV, PPV and diagnostic accuracy.

Test of Significance was applied to study the diagnostic yield of thoracoscopy. A p value of less than or equal to 0.05 was considered statistically significant.

OBSERVATIONS & RESULTS

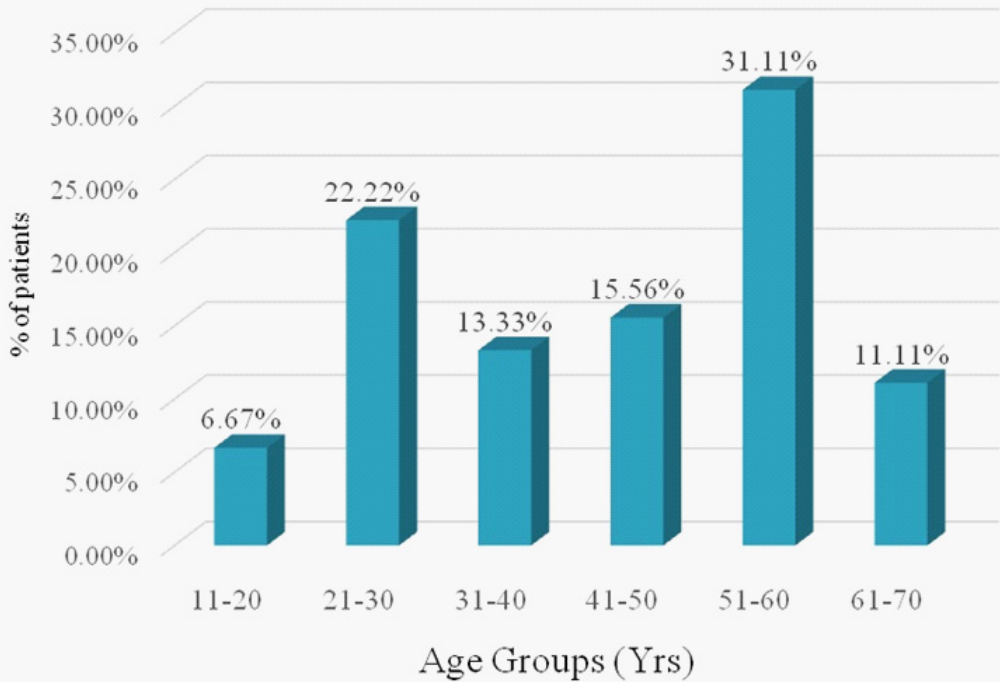
The clinico-radiological profile, gross thoracoscopic and pleural biopsy histopathology findings, therapeutic outcome and post thoracoscopy complications among 45 patients were tabulated and following observations were made.

Table 1: Age wise distribution of patients.

Age Group(Yrs)	Frequency	Percentage
11-20 yrs	3	6.67%
21-30 yrs	10	22.22%
31-40 yrs	6	13.33%
41-50 yrs	7	15.56%
51-60 yrs	14	31.11%
61-70 yrs	5	11.11%
Total	45	100.00%
Mean $\pm$ SD	43.49 $\pm$ 43.59 yrs	

In the present study the age of the patients ranged from 21-64 years. The mean age was 43.49 years. The median age was 45 years. The youngest patient’s age was 21 and the oldest patient’s age was 64 years. The maximum numbers of patients were from age group 51-60 years. This is depicted in Graph 1.

Graph 1 : AGE WISE DISTRIBUTION



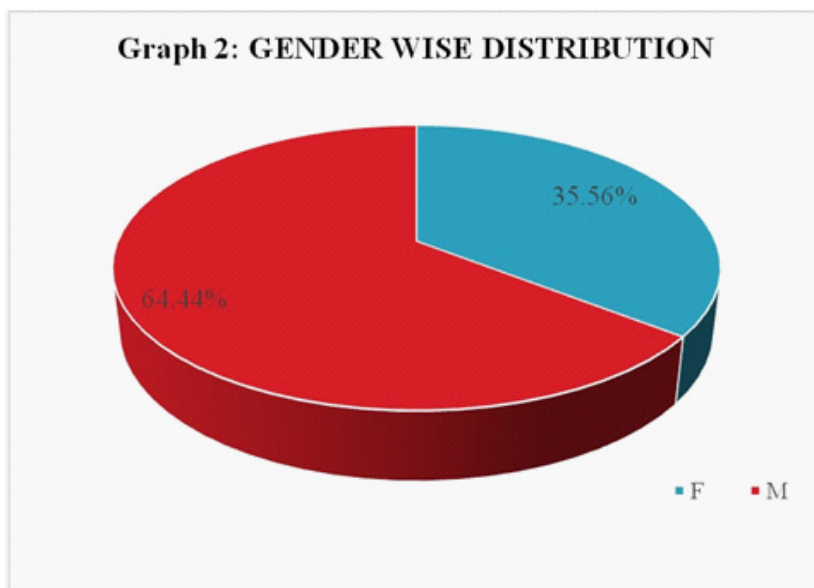
Gender wise distribution of the patients has been studied according to the **Table 2**.

Table 2: Gender wise distribution of patients.

Gender	No of patients	Percentage
Female (F)	16	35.56%
Male (M)	29	64.44%
Total	53	100.00%

In this study 29 (64.44%) were males and 16 (35.56%) were females.

It is shown in graph 2

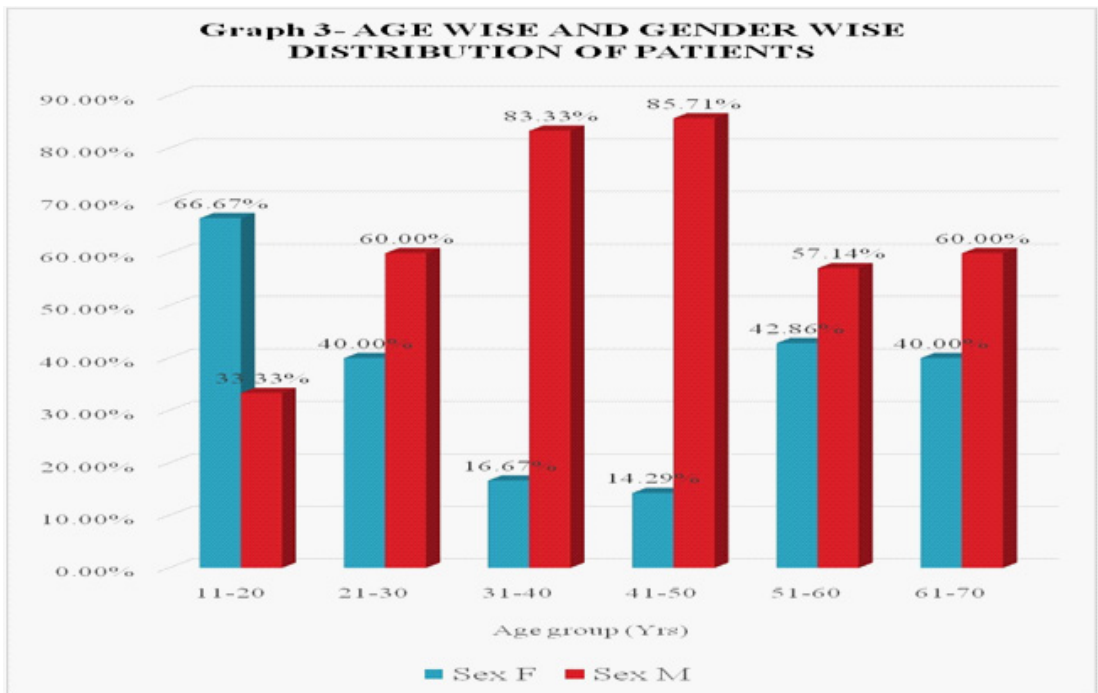


Age and gender wise distribution of patients was shown in **Table 3**.

Table 3: Age wise and gender wise distribution of patients.

		Sex		Total	P value
		Female	Male		
Age groups (Yrs)	11-20	2 (66.67%)	1 (33.33%)	3 (100.00%)	0.544
	21-30	4 (40.00%)	6 (60.00%)	10 (100.00%)	
	31-40	1 (16.67%)	5 (83.33%)	6 (100.00%)	
	41-50	1 (14.29%)	6 (85.71%)	7 (100.00%)	
	51-60	6 (42.86%)	8 (57.14%)	14 (100.00%)	
	61-70	2 (40.00%)	3 (60.00%)	5 (100.00%)	
Total		16 (35.56%)	29 (64.44%)	45 (100.00%)	

In this study, maximum patients belonged to age group 51-60 years (31.11%) and 57.14% patients were male. Maximum males and females were from age group 51-60 years. P value is 0.544 which means distribution of gender in various age groups is not significantly different. This is depicted in Graph 3.



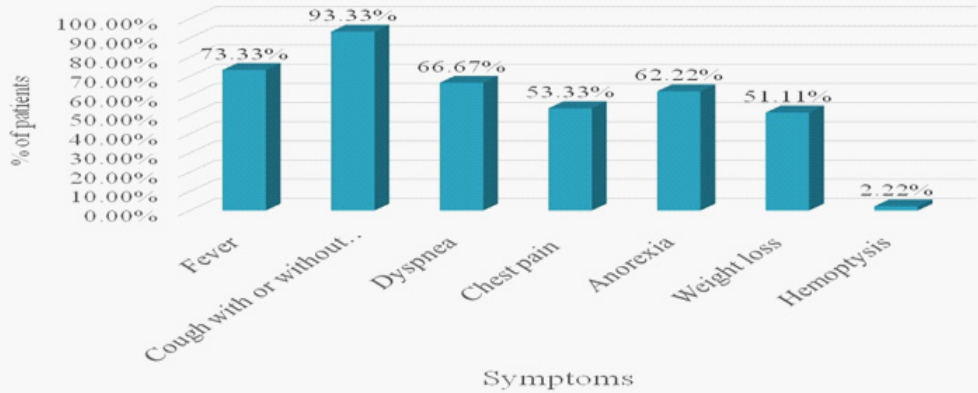
Patients were distributed according to presenting symptoms in the frequency distribution **Table 4.**

Table 4: Distribution of patients according to symptoms.

Symptoms	Frequency	Percentage
Fever	33	73.33%
Cough with or without expectoration	42	93.33%
Dyspnea	30	66.67%
Chest Pain	24	53.33%
Anorexia	28	62.22%
Weight loss	23	51.11%
Hemoptysis	1	2.22%

Out of total 45 patients, 33 (73.33%) patients had complaints of fever, 42 (93.33%) patients had cough with or without expectoration, 30 (66.67%) patients had dyspnea, 24 (53.33%) patients had complaints of chest pain, 28 (62.22%) patients had associated anorexia, 23 (51.11%) patients had weight loss, and 1 patient (2.22%) had hemoptysis. This is shown in Graph 4.

Graph 4: DISTRIBUTION OF PATIENTS ACCORDING TO SYMPTOMS



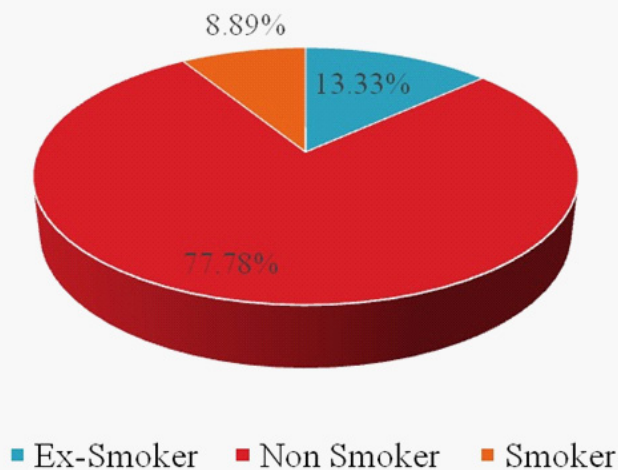
Distribution of patients was done on basis of personal habits as shown in **Table 5**.

Table 5: Distribution of patients according to history of smoking.

History of Smoking	Frequency	Percentage
Ex-Smoker	6	13.33%
Non Smoker	35	77.78%
Smoker	4	8.89%
Total	45	100.00%

In the present study, Out of 45 patients 4 (8.89%) were smokers, 35 (77.78%) patients were non smokers and 6 (13.33%) patients were Ex-Smokers. This is shown in Graph 5.

Graph 5 : DISTRIBUTION OF PATIENTS ACCORDING TO HISTORY OF SMOKING

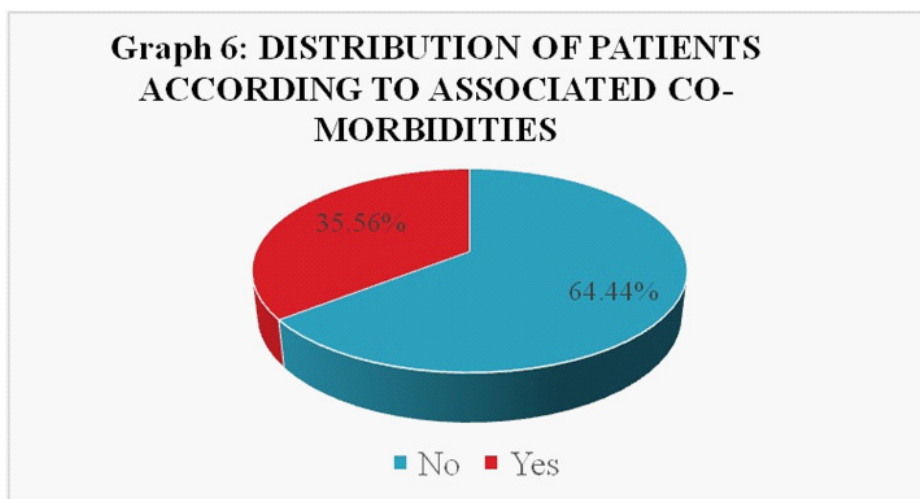


Distribution of patients was done according to associate Co-Morbidities as shown in **Table 6**.

Table 6: Distribution of patients according to associated Co-Morbidities.

Co-Morbidities	Frequency	Percentage
No	29	64.44%
Yes	16	35.56%
Total	45	100.00%

Out of 45 patients, 16 patients had associated Co-Morbidities. 5 patients had diabetes, 5 had systemic hypertension, 4 patients had both systemic hypertension and diabetes, 4 patients had ischemic heart disease, one patient had asthma, one patient had hypothyroidism and one patient had Hepatitis B virus infection. This is shown in graph 6.



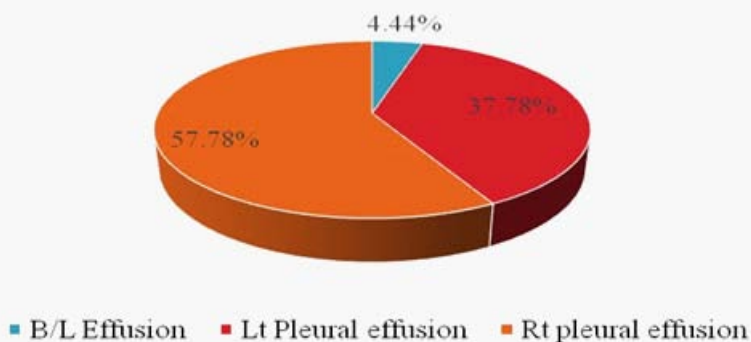
Distribution of patients was done according to Chest X-ray findings as shown in **Table 7**.

Table 7: Distribution of patients according to Chest-X-ray findings.

Chest X-ray findings	Frequency	Percentage
B/L Effusion	2	4.44%
Left Pleural effusion	17	37.78%
Right pleural effusion	26	57.78%
Total	45	100.00%

Out of 45 patients, 26 patients (57.78%) had Right sided pleural effusion where 17 patients (37.78%) had left sided pleural effusion. 2 patients (4.44%) had bilateral pleural effusion. This is shown in graph 7.

**Graph 7: DISTRIBUTION OF PATIENTS
ACCORDING TO CHEST X-RAY
FINDINGS**



Patients were distributed into simple versus multi loculated pleural effusion according to USG findings as shown in **Table 8 & 9**.

Table 8: Distribution of patients into simple versus multi loculated pleural effusion.

USG Findings	Frequency	Percentage
Multi loculated pleural effusion	19	42.22%
Simple pleural effusion	26	57.78%
Total	45	100.00%

In this study out of 45 patients, 24 patients (42.22%) had multi-loculated pleural effusion where 21 patients (57.78%) had simple pleural effusion. This is depicted in graph 8.

**Figure 8- DISTRIBUTION OF PATIENTS
ACCORDING TO USG FINDINGS**

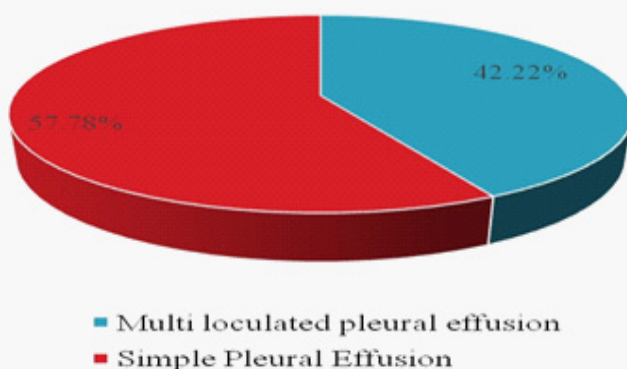
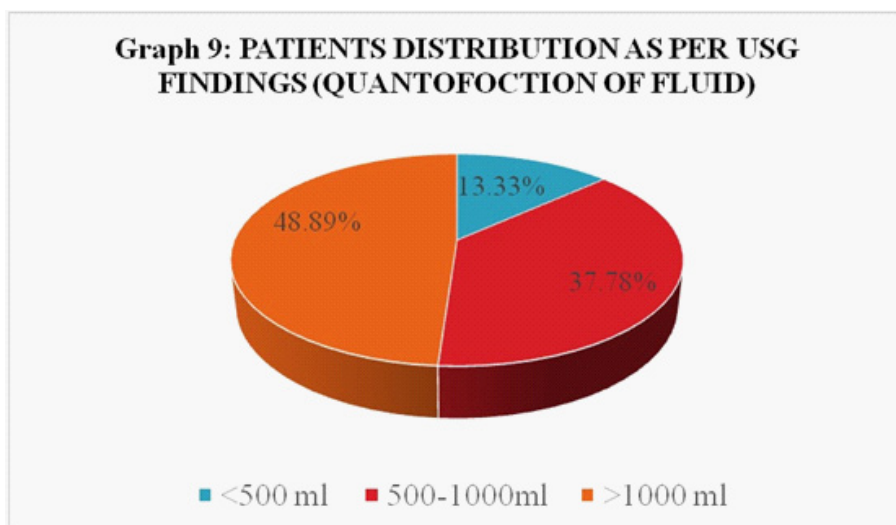


Table 9: Distribution of patients according quantification of pleural fluid by USG.

Quantification of pleural fluid	Frequency	Percentage
<500 ml	6	13.33%
500-1000ml	17	37.78%
>1000 ml	22	48.89%
Total	45	100.00%

In this study out of 45 patients, 22 patients (48.89%) had pleural effusion with more than 1000 ml fluid, 17 patients (37.78%) had pleural effusion with 500-1000 ml fluid while rest 6 patients (13.33%) had pleural effusion with less than 500 ml fluid. This is shown in graph 9.



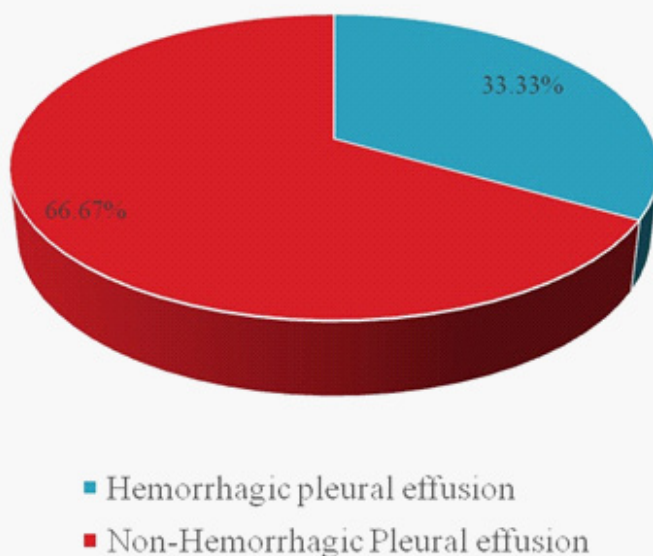
Distribution of patients was done according to type of pleural effusion on the basis of gross appearance of the pleural fluid as shown in **Table 10**.

Table 10: Distribution of patients according to type of pleural effusion on basis of gross appearance of the fluid.

Type of pleural effusion	Frequency	Percentage
Hemorrhagic pleural effusion	15	33.33%
Non-hemorrhagic pleural effusion	30	66.67%
Total	45	100.00%

In this study out of 45 patients, 15 patients (33.33%) had hemorrhagic pleural effusion where 30 patients (66.67%) had non-hemorrhagic pleural effusion. This is shown in graph 10.

Graph 10: DISTRIBUTION OF PLEURAL EFFUSION



Patients were distributed according to gross thoracoscopic findings, as shown in Table 11.

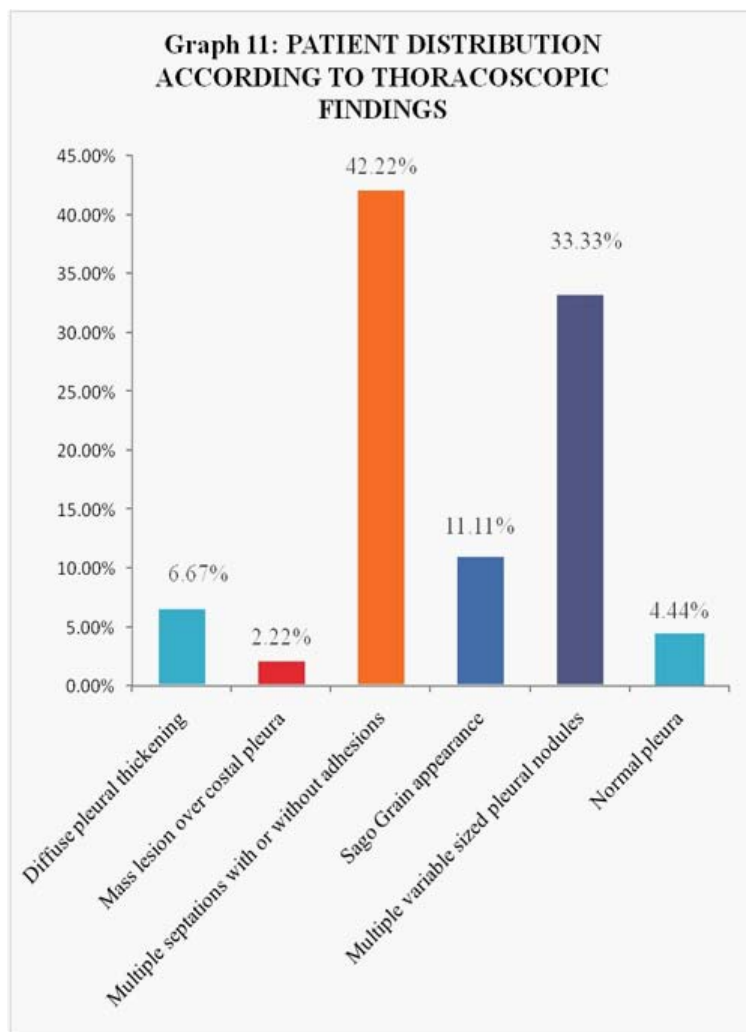
Table 11: Gross thoracoscopic findings in the studied group.

Thoracoscopic Findings	Frequency	Percentage
Diffuse pleural thickening	3	6.67%
Mass lesion over costal pleura	1	2.22%
Multiple septations with or without adhesions	19	42.22%
Sago grain appearance	5	11.11%
Multiple variable sized pleural nodules	15	33.33%
Normal pleura	2	4.44%
Total	45	100.00%

In this study out of total 45 patients, 2 patients (4.44%) had normal thoracoscopic findings.

Total 43 patients (95.56%) had abnormal findings. Among them 3 patients (6.67%) showed diffuse pleural thickening, 1 patient (2.22%) had mass lesion over costal pleura, 19 patients (42.22%) showed multiple septations with or without adhesions, 5 patients (11.11%) had sago grain appearance, 15 (33.33%) had multiple variable sized pleural nodules.

This is shown in Graph 11.



Patients were distributed according to pleural biopsy histopathology findings, as shown in **Table 12**.

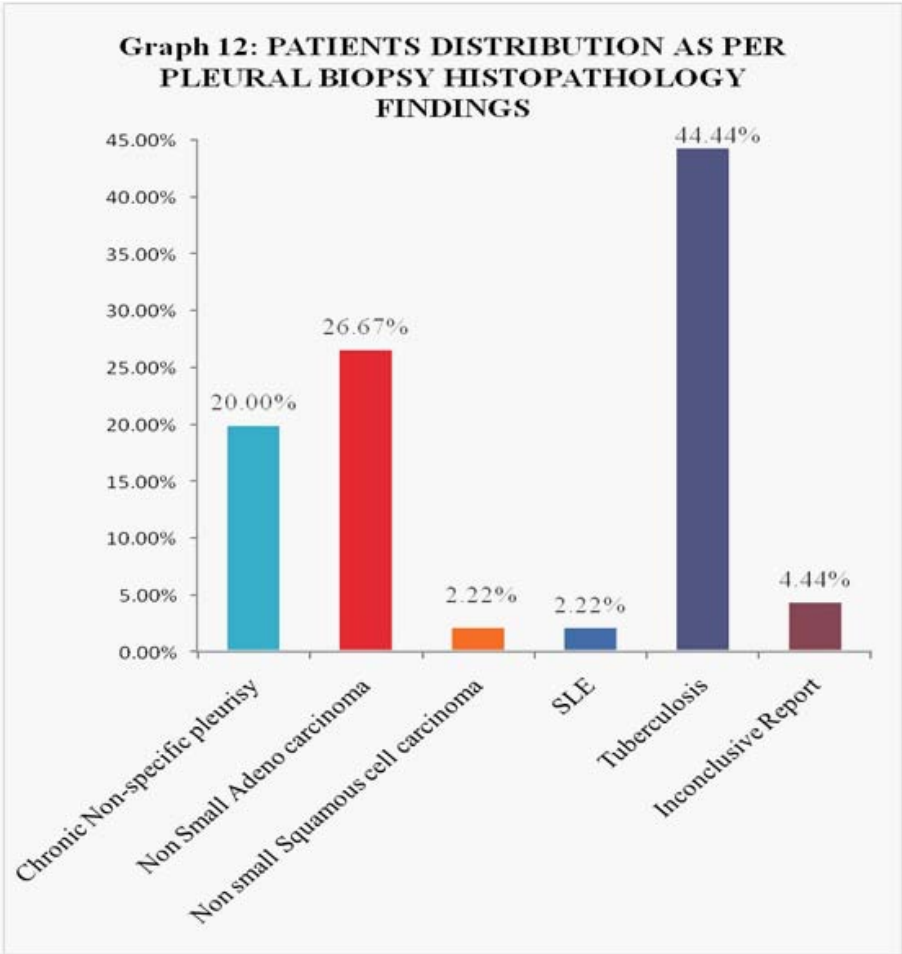
Table 12: The histopathological results obtained by thoracoscopic pleural biopsy in the studied group.

Pleural Biopsy Histopathology Findings	Frequency	Percentage
Chronic Non-specific pleurisy	9	20.00%
Non Small cell Adenocarcinoma	12	26.67%
Non small Squamous cell carcinoma	1	2.22%
SLE	1	2.22%
Tuberculosis (TB)	20	44.44%
Inconclusive Report	2	4.44%
Total	45	100.00%

In this study out of total 45 patients, 2 patients (4.44%) had inconclusive report on pleural biopsy histopathology.

Total 43 (95.56%) patients were diagnosed. Among them 12 patients (26.67%) showed Non small cell adenocarcinoma, 1 patient (2.22%) had Non-small squamous cell carcinoma, 20 patients (44.44%) were diagnosed TB, 9 patients (20.00%) had chronic non-specific pleurisy and 1 patient (2.22%) was diagnosed as systemic lupus erythematosus (SLE).

This is shown in Graph 12.

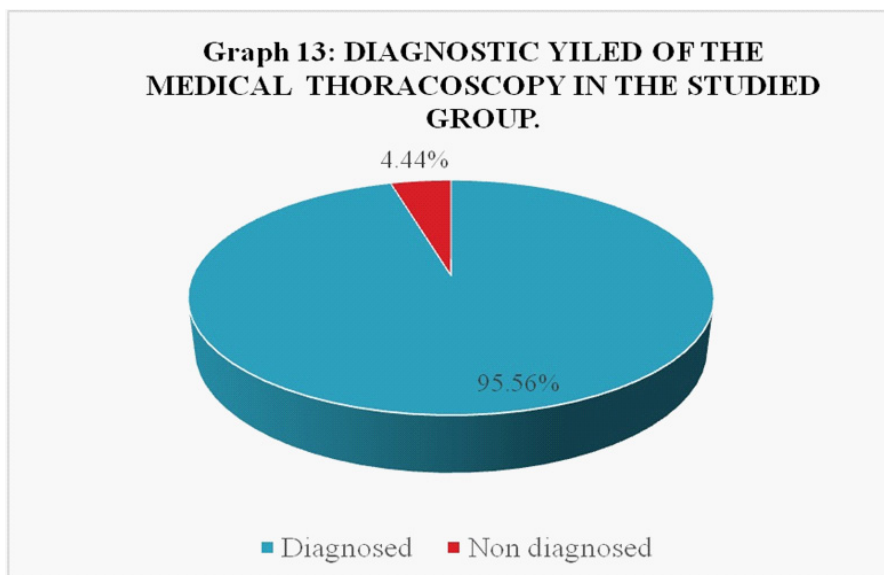


Diagnostic yield of the medical thoracoscopy in the studied group is shown in **Table 13**.

Table 13: Diagnostic yield of the medical thoracoscopy in the studied group.

Patients	Frequency	Percentage
Diagnosed	43	95.56%
Undiagnosed	2	4.44%
Total	45	100.00%

In this study, 43 patients out of 45 patients were diagnosed. Diagnostic yield of thoracoscopic pleural biopsy was 95.56%. This is shown in graph 13.



Correlation of thoracoscopic findings with pleural biopsy findings was as shown in **Table 14**.

In this study, 3 patients had pleural thickening on thoracoscopic findings. Among them, 1 patient (33.33%) was diagnosed TB, 1 patient (33.33%) had SLE and 1 patient (33.33%) showed chronic non-specific pleurisy.

One patient showed mass lesion over costal pleural on thoracoscopy. Patient was diagnosed TB on histopathology report (100.00%).

5 patients had sago grain appearance on thoracoscopy and all patients (100%) were diagnosed as TB.

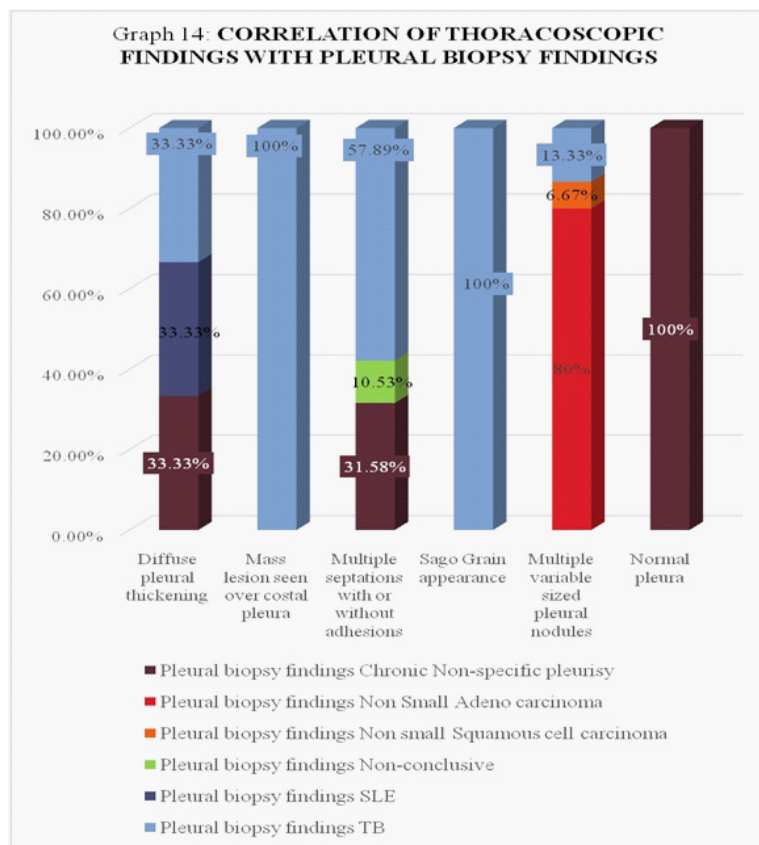
19 patients had multiple septations with or without adhesions on thoracoscopy. Out of 19 patients, 11 patients (57.89%) were diagnosed TB, 6 patients (31.58%) had chronic non-specific pleurisy and 2 patients (10.53%) had in-conclusive findings on histopathology.

15 patients showed multiple variable sized pleural nodules. Of these, 12 patients (80.00%) were diagnosed non-small cell adeno carcinoma, 1 patient (6.67%) had non-small squamous cell carcinoma and 2 (13.33%) patients were diagnosed TB on histopathology.

2 patients had normal pleura on thoracoscopy findings and both patients (100.00%) showed chronic non specific pleurisy on pleural biopsy histopathology. This is shown in graph 14.

Table 14: Correlation of thoracoscopic findings with pleural biopsy finding.

Thoracoscopic findings	Pleural biopsy findings						Total
	Chronic Non-specific pleurisy	Non Small Adeno carcinoma	Non small Squamous cell carcinoma	Non-conclusive	SLE	TB	
Diffuse pleural thickening	1 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1(33.33%)	1 (33.33%)	3 (100.00%)
Mass lesion seen over costal pleura	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (100.00%)	1 (100.00%)
Sago grain appearance	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5(100.00%)	5(100.00%)
Multiple septations with or without adhesions	6 (31.58%)	0 (0.00%)	0 (0.00%)	2 (10.53%)	0 (0.00%)	11 (57.89%)	19 (100.00%)
Multiple variable sized pleural nodules	0 (0.00%)	12 (80.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	2 (13.33%)	15 (100.00%)
Normal pleura	2 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (100.00%)
Total	9 (20.00%)	12 (26.67%)	1 (2.22%)	2 (4.44%)	1 (2.22%)	20 (44.44%)	45 (100.00%)



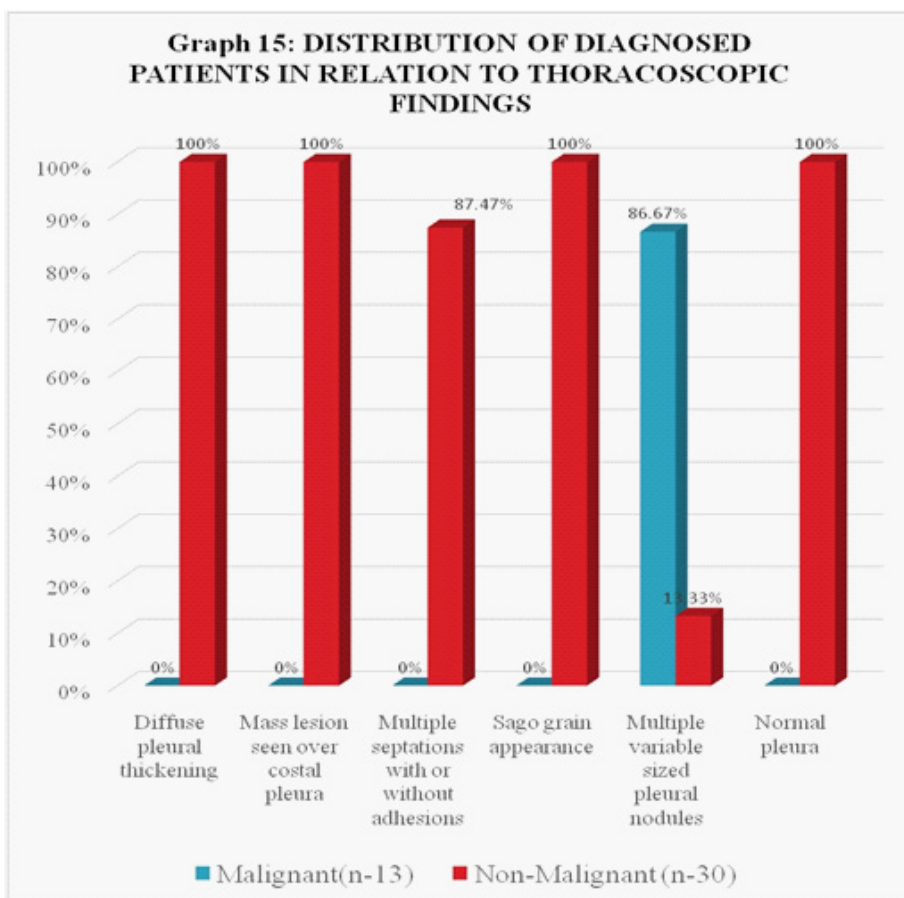
Distribution of the diagnosed patients in the studied group in relation to the thoracoscopic findings was as shown in **Table 15**.

Table 15: Distribution of the diagnosed patients in the studied group in relation to the thorascopic findings.

Thorascopic findings	Malignant (n-13)	Non-Malignant (n-30)	Fisher exact P value
Diffuse pleural thickening	0	3 (100.00%)	0.542
Mass lesion seen over costal pleura	0	1 (100.00%)	1
Multiple septations with or without adhesions	0	17 (100.00%)	0.0004
Sago grain appearance	0	5 (100.00%)	0.301
Multiple variable sized pleural nodules	13 (86.67%)	2 (13.33%)	<.0001
Normal pleura	0	2 (100.00%)	1

Out of 45 patients, 13 patients were diagnosed malignant and 30 patients were non-malignant. 2 patients were remained undiagnosed.

86.67% of patients with nodules were malignant, while only 13.33% were non-malignant and this difference was statistically highly significant. 100% patients with mutiple septations with or without adhesions were non malignant. It was statistically significant. All patients (100%) with sago grain appearance were diagnosed TB. This is shown in figure 15.



Correlation of pleural effusion on the basis of gross appearance of pleural fluid with pleural biopsy findings was as shown in **Table 16 and 17**.

In this study, out of 15 patients with hemorrhagic pleural effusion, 12 patients (80.00%) were diagnosed malignancy, 2 patients (13.33%) had chronic non-specific pleurisy and 1 patient (6.67%) was diagnosed TB on pleural biopsy histopathology reports.

30 patients had non-hemorrhagic pleural effusion. Of these, 19 patients (63.33%) were diagnosed TB, 7 patients (23.33%) had chronic non-specific pleurisy, 1 (3.33%) patient had malignancy, 1 (3.33%) patient was diagnosed SLE. 2 (6.67%) patients remained undiagnosed due in-conclusive reporting.

In hemorrhagic pleural effusion 80% patients were malignant whereas in non-hemorrhagic pleural effusion 63.33% patients were tuberculosis and only 3.33% patients were malignant.

Taking non-hemorrhagic Pleural effusion as reference, risk of malignancy in hemorrhagic Pleural effusion is significantly high with odd ratio of 116 and p value 0.0001. P value < .0001 which means Pleural biopsy result is significantly different for Hemorrhagic pleural effusion as compared to Non-Hemorrhagic pleural effusion.

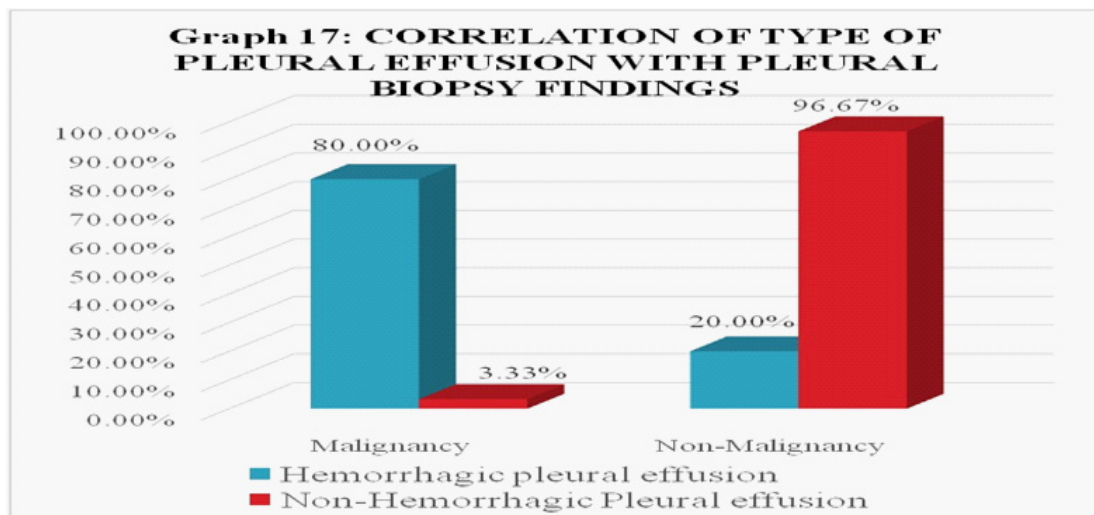
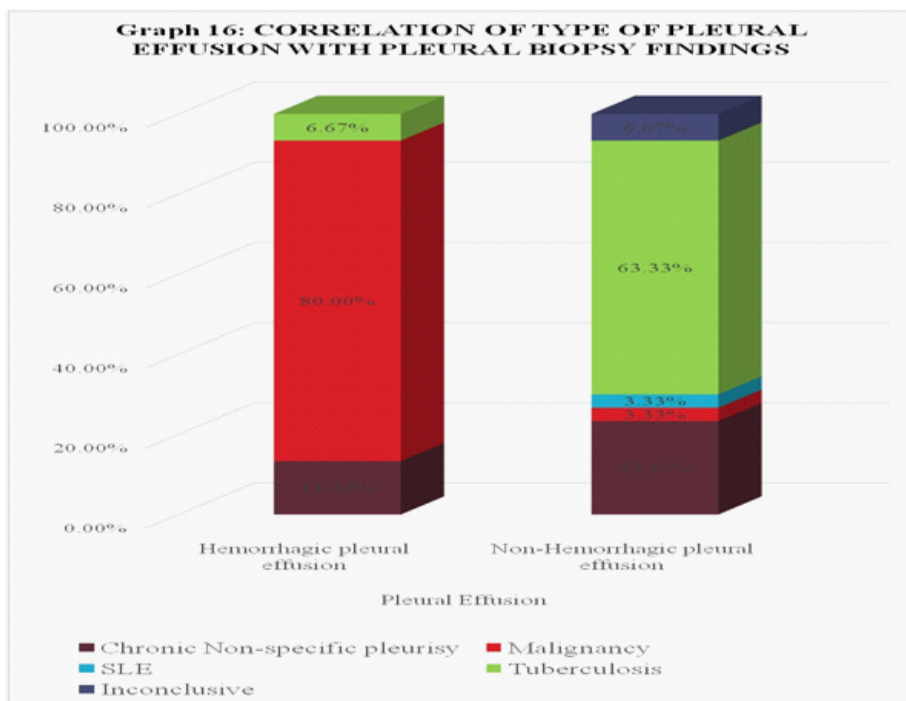
These are shown in graph 16 and 17.

Table 16: Correlation of type of pleural effusion with pleural biopsy findings.

Type of Pleural effusion	Pleural biopsy					Total	P value
	Chronic Non-specific pleurisy	Malignancy	SLE	Tuberculosis	Inconclusive		
Hemorrhagic pleural effusion	2 (13.33%)	12 (80.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	15 (100.00%)	<.0001
Non-Hemorrhagic pleural effusion	7 (23.33%)	1 (3.33%)	1 (3.33%)	19 (63.33%)	2 (6.67%)	30 (100.00%)	
Total	9 (20.00%)	13 (28.89%)	1 (2.22%)	20 (44.44%)	2 (4.44%)	45 (100.00%)	

Table 17: Correlation of type of pleural effusion with pleural biopsy findings type of Pleural effusion.

Type of Pleural effusion	Pleural Biopsy Findings		Total	P Value	Odd ratio
	Malignancy	Non-Malignancy			
Hemorrhagic pleural effusion	12 (80.00%)	3 (20.00%)	15 (100.00%)	0.0001	116
Non-Hemorrhagic Pleural effusion	1 (3.33%)	29 (96.67%)	30 (100.00%)		
Total	13 (28.89%)	32 (71.11%)	45 (100.00%)		

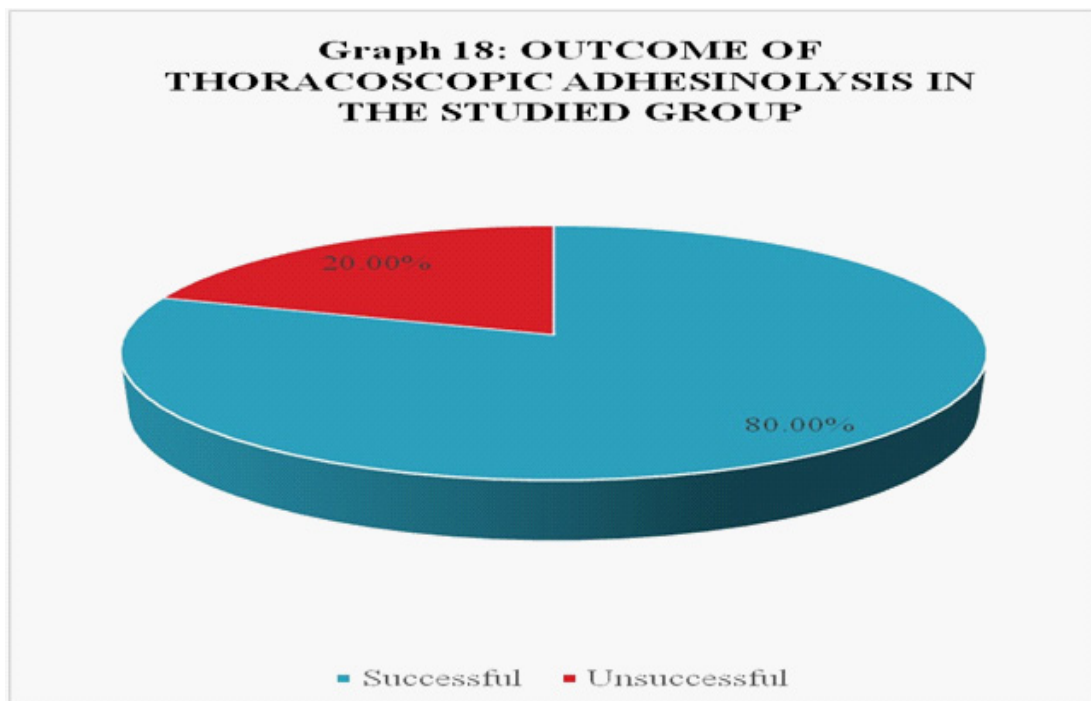


Outcome of thoracoscopic adhesinolysis in the studied group is as shown in **Table 18**.

Table 18: Outcome of thoracoscopic adhesinolysis in the studied group.

Adhesinolysis	Frequency	Percentage
Successful	8	80.00%
Unsuccessful	2	20.00%
Total	10	100%

22 patients had undergone thoroscopic procedure. 24 patients had thin or thick septations (loculations). Out of them, 10 patients showed adhesions preventing lung expansion completely. Adhesinolysis was done among 10 patients. Procedure was successful in 8 patients (80.00%). Lung did not expand fully due to trapped lung in 2 patients (20.00%). This is depicted in table and graph 18.

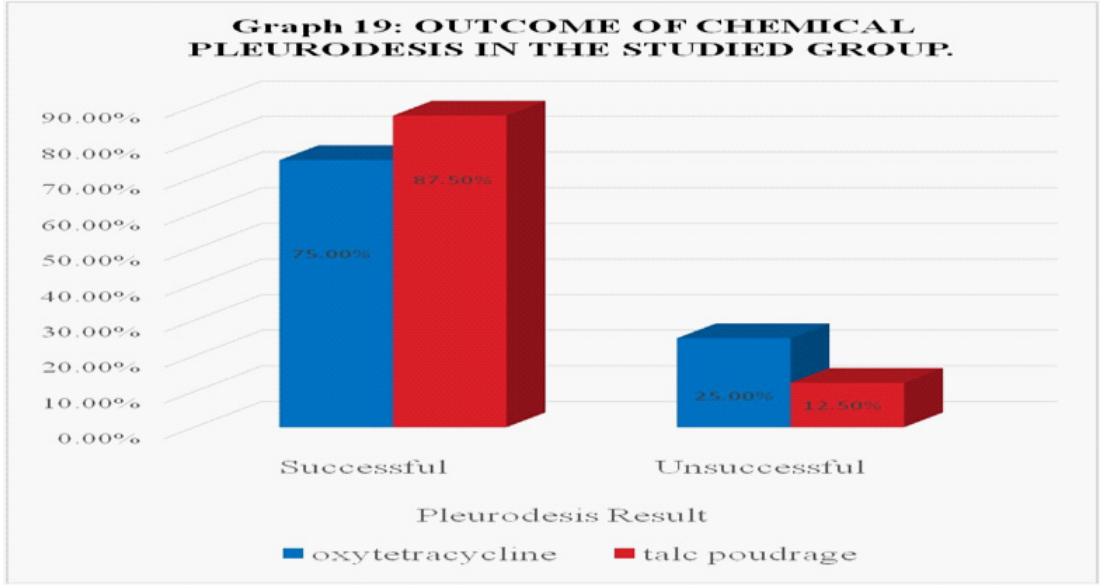


Outcome of thoracoscopic pleurodesis in the studied group is as shown in **Table 19**.

Table 19: Outcome of chemical pleurodesis in the studied group.

Chemical pleurodesis in malignant pleural effusion		Pleurodesis Result		Total	P value
		Successful	Unsuccessful		
Sclerosing agent	oxytetracycline	3 (75.00%)	1 (25.00%)	4 (100.00%)	1
	talc poudrage	7 (87.50%)	1 (12.50%)	8 (100.00%)	
Total		10 (83.33%)	2 (16.67%)	12 (100.00%)	

Chemical pleurodesis was done among 12 patients diagnosed with malignant pleural effusion. Oxytetracycline and talc were used as sclerosing agent. Oxytetracycline was used in 4 patients. 3 out 4 patients (75.00%) did not have recurrence of pleural effusion over 2 month follow up. One patient (25.00%) had early failure of pleurodesis. Talc poudrage was used as sclerosant agent in 8 patients. Patients were followed up over 2 months. Talc pleurodesis was successful in 7 out of 8 patients (87.50%). One patient lost to follow up after discharge. So, this was considered as failed pleurodesis. Successful chemical pleurodsis was achieved in 10 patients out of 12 (83.33%). Chemical pleurodesis failed in 2 patients (16.67%). p value is 1 means there is no significant difference between success of oxytetracycline pleurodesis and talc poudrage pleurodesis. This is shown in graph 19.



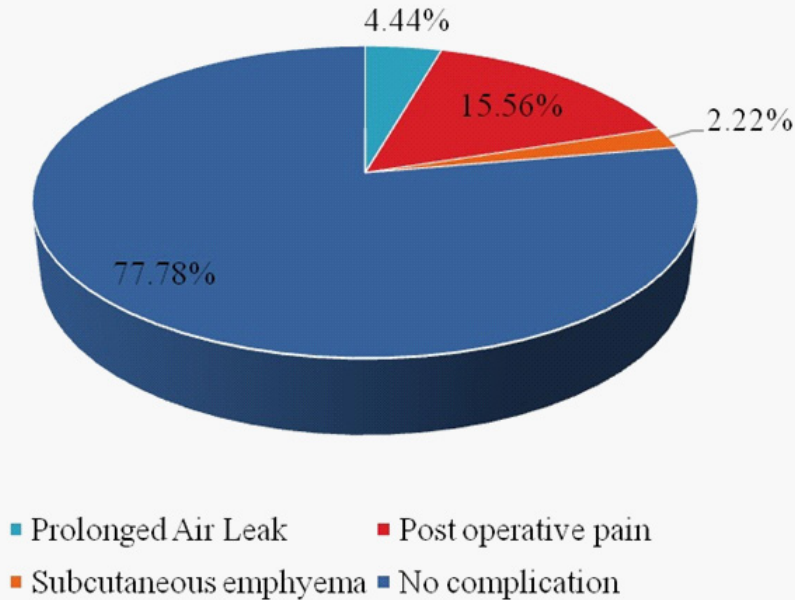
Post-thorascopic complications in the studied group are as shown in **Table 20**.

Table 20: Post-thorascopic complications in the studied group.

Post-thorascopic complication	Frequency	Percentage
Prolonged Air Leak	2	4.44%
Post operative pain	7	15.56%
Subcutaneous emphysema	1	2.22%
No complication	35	77.78%
Total	45	100.00%

The post-thorascopic complications in the studied group were occurred in 10 patients (22.22%). The complications were prolonged air leak (>7 days) in two patients (4.44%), surgical emphysema in 1 patient (2.22%), post-operative pain in 7 patients (15.56%). There was no complication in 35 patients (77.78%). This is depicted in graph 20.

Graph 20-POST THORACOSCOPIC COMPLICATIONS IN STUDIED GROUP



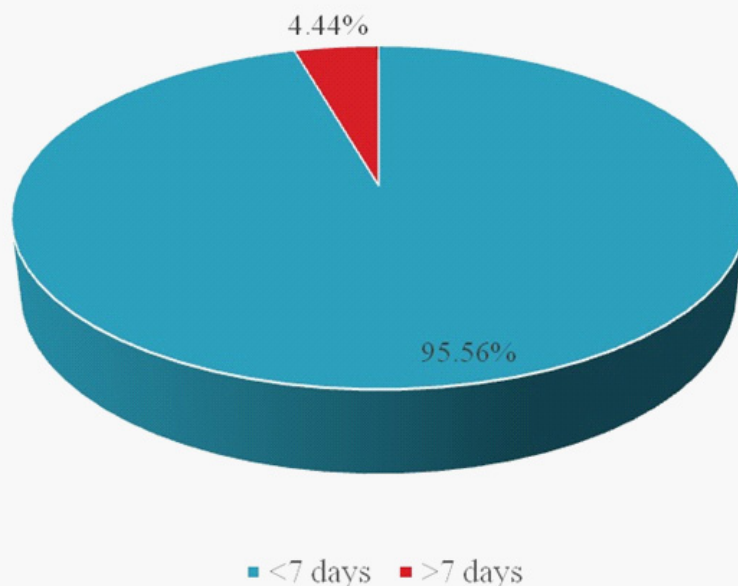
Distributions of patients according to post thoracoscopic intercostal drain (ICD) duration in days are as shown in **Table 21**.

Table 21: Distribution of patients according to post thoracoscopic ICD duration.

ICD Duration	Frequency	Percentage
<7 days	43	95.56%
>7 days	2	4.44%
Total	45	100.00%
Mean $\pm$ SD	4.44 $\pm$ 2.27	

In the present study, 43 out of 45 patients (95.56%) had ICD duration <7 days, while 2 patients (4.44%) had ICD duration > 7 days (Prolonged air leak). Duration of ICD ranged from 1-13 days. The mean ICD duration was 4.44 days. The median ICD duration was 4 days. This is depicted in Graph 21.

Graph 21-DISTRIBUTION OF PATIENTS ACCORDING TO POST-THORACOSCOPIC ICD DURATION



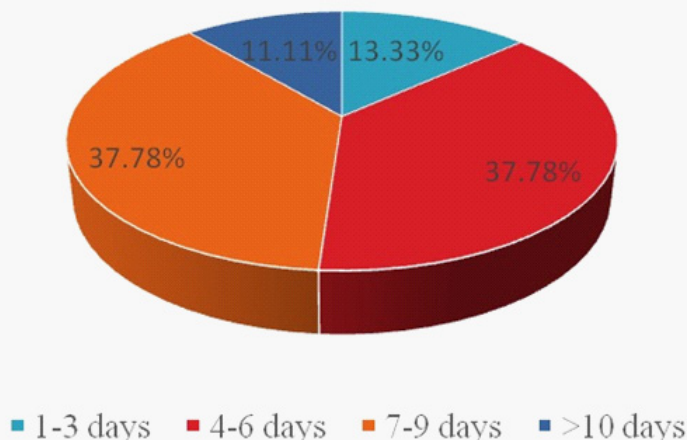
Distributions of patients according to hospital stay are as shown in **Table 22**.

Table 22: Distributions of patients according to hospital stay.

Hospital stay	Frequency	Percentage
1-3 days	6	13.33%
4-6 days	17	37.78%
7-9 days	17	37.78%
>10 days	5	11.11%
Total	45	100.00%
Mean $\pm$ SD	6.67 $\pm$ 2.72	

In the present study, 6 patients (13.33%) had hospital stay of 1-3 days. 17 patients (37.78%) had hospital stay of 4-6 days. 17 patients (37.78%) had hospital stay of 7-9 days and 5 patients (11.11%) had hospital stay of >10 days. Duration of hospital stay ranged from 3-15 days. The mean hospital stay was 6.67 days. The median hospital stay was 6 days. This is depicted in Graph 22.

Graph 22- DISTRIBUTION OF PATIENTS ACCORDING TO HOSPITAL STAY



Overall results of diagnostic test of the study as shown in **Table 23**.

Table 23: Overall results of diagnostic test of the study.

Diagnostic test	Percentage	95% Confidence Interval
Sensitivity	92.31%	63.97% to 99.81%
Specificity	90.62%	74.98% to 98.02%
Positive Predictive Value	80.00%	51.91% to 95.67%
Negative Predictive Value	96.67%	82.78% to 99.92%
Positive Likelihood Ratio	9.85	3.31 to 29.24
Negative Likelihood Ratio	0.08	0.01 to 0.56
Diagnostic accuracy	91.11%	

Overall diagnostic accuracy, sensitivity and specificity were 91.11%, 92.31% and 90.62% respectively. Overall positive and negative predictive value of study was 80.00% and 96.67% respectively. Positive and negative likely hood ratio was 9.85 and 0.08 respectively.

DISCUSSION

Patients with pleural effusions are commonly seen in the pulmonary practice and can be caused by benign or malignant etiologies [5]. In areas of high incidence of TB, the commonest causes of pleural effusion include - TB (25%), malignancy (22.9%), congestive heart failure (17.9%) and pneumonia (14%) [48]. While dealing with patients with pleural effusion, initial approach include clinical history, physical examination followed by chest radiography and pleural fluid analysis for microbiology, biochemistry and cytology. If findings of pleural fluid analysis are inconclusive,

in this case additional procedure is required to obtain pleural biopsy for histopathology [49]. 25-40% of pleural effusions remain undiagnosed even after thoracentesis and CPB [4-5]. The relatively low yield of closed pleural biopsy was caused by several factors, including minimal and non uniform pleural involvement in early disease, especially diaphragmatic and visceral pleura. These limitations can be overcome by semirigid thoracoscopy because the biopsy was taken directly under vision [47]. Medical thoracoscopy also known as pleuroscopy is a safe and valuable tool for diagnosis of pleural effusion of unexplained origin because it allows obtaining pleural biopsy under direct vision [50].

The utility of semirigid thoracoscopy in undiagnosed pleural effusion has been evaluated both prospectively and retrospectively. The aim of this study was to establish diagnostic yield of medical thoracoscopy in cases of undiagnosed pleural effusion in our setup. In our study, medical thoracoscopy was done in consecutive 45 patients with pleural effusion of undetermined etiology.

Pleural effusion of undetermined etiology has been noted in all age groups. In the present study, the age of the patients ranged from 21-64 years. The mean age was 43.49 years. The median age was 45 years. The youngest patient's age was 21 and the oldest patient's age was 64 years. This is similar to studies by Shaheen et al [44] where mean age was 53 year and youngest and oldest patient was 26 and 72 year old respectively. The maximum numbers of patients were from age group 51-60 years. Mean age was found to be 48.68 year, 49 year, 51.3 year by Mootha et al, [10] Prabhu and Narasimhan [38] and Helala et al [43] respectively in their studies.

In this study, 29 (64.44%) were males and 16 (35.56%) were females. Similar observations were seen in studies by Mootha et al [10], Law et al [29], Mehta et al [35] and Helala et al. [43].

In this study maximum patients belonged to age group 51-60 years (31.11%) and 57.14% patients were male. Maximum males and females were from age group 51-60 years. No significant observations on age sex relationship have been encountered in this study or other studies.

Out of total 45 patients, 33 (73.33%) patients had complaints of fever, 42 (93.33%) patients had cough with or without expectoration, 30 (66.67%) patients had dyspnea, 24 (53.33%) patients had complaints of chest pain, 28 (62.22%) patients had associated anorexia, 23 (51.11%) patients had weight loss, and 1 patient (2.22%) had hemoptysis. Similar observations were seen in a study by Prabhu and Narasimhan [38].

In our study out of total 45 patients, 2 patients (4.44%) had normal thoracoscopic findings. Total 43 patients (95.56%) had abnormal findings. Among them 3 patients (6.67%) showed diffuse pleural thickening, 1 patient (2.22%) had mass lesion over costal pleura, 19 patients (42.22%) showed multiple septations with or without adhesions, 5 patients (11.11%) had sago grain appearance, 15 (33.33%) had multiple variable sized pleural nodules.

Prabhu and Narasimhan [38] reported a study in which nodules were found in 33 patients, 26 patients had adhesions, 8 patients had sago grain appearance, and 1 patient had normal pleura.

A study by Helala et al [43] in Egypt, out of 40 patients nodules were found in 28 patients (70%), sago-grain nodules were found in 5 patients (12.5%), adhesions were found in 3 patients (7.5%), collection of pus in one patient (2.5%), and mass was found in one patient (2.5%), Violaceous lesions were found in one patient (2.5%) and there were no specific findings in only one patient (2.5%).

In our study, diagnostic yield of medical thoracoscopy was 95.56% (43/45 patients). Malignancy was diagnosed in 13 patients (28.89%), 20 patients (44.44%) were diagnosed TB, 9 patients (20.00%) had chronic non-specific pleurisy and 1 patient (2.22%) was diagnosed SLE. Pleural metastasis is most common cause of malignancy. 12 patients were diagnosed Non-small cell adenocarcinoma and 1 patient was diagnosed Non-small cell squamous cell carcinoma. We couldn't diagnose any case of mesothelioma. Our study outcomes were comparative with other studies.

Similar observations were seen in a study by Saifullah and Rizvi [40] Yield of pleuroscopic biopsy in the diagnosis of exudative pleural effusion is 96.7%. Specific diagnosis through pleuroscopic biopsy have shown 45% cases of tuberculosis, 41.7% cases of adenocarcinoma, 8.3% cases of chronic non specific inflammation, 1.7% cases of lymphoma and one case of hemagioendothelioma was also diagnosed.

In 2012 in a study by Prabhu and Narasimhan [38] diagnostic yield of pleuroscopy was 97% (66/68 patients). Compared to our study findings were same. Malignancy was diagnosed in 24 patients, 22 patients had non-specific inflammation, tuberculosis was found in 16 patients, empyema was found in 2 patients, 1 patient had sarcoidosis, 1 patient had normal pleura and it was non-diagnostic in 2 patients. In 24 patients who had malignancy, 15 patients had Metastatic adenocarcinoma, three patients had Mesothelioma, three patients had undifferentiated carcinoma, one patient had lymphoma, one patient had Metastatic clear cell carcinoma and one patient had Metastatic squamous cell carcinoma.

A study was carried out by Tscheikuna et al [32] in Thailand, The diagnostic yield was 95.2%. The malignancy was diagnosed by thoracoscopy in 45.35% patients.

Similar observations were seen in a comparative retrospective study in China by Wang et al [30], diagnostic efficiency of medical thoracoscopy was 93% (25/27). Thoracoscopic pleural biopsy revealed tuberculous pleurisy in 6 patients, adenocarcinoma in 7, squamous-cell carcinoma in 2, metastatic carcinoma in 3, mesothelioma in 2, non-hodgkin's lymphoma in 1, and others in 4. Only 2 patients could not get definite diagnosis.

In 2014, a study by Helala et al, [43] gave a definitive diagnosis in 38 out of 40 patients with diagnostic yield 95%. Malignancy was diagnosed in 28 patients (70%), one patient was diagnosed as empyema (2.5%), tuberculosis was found in 9 patients (22.5%), and it was non diagnostic in 2 patients (5%). The results of our study contradict with the results of Helala et al. [43] where

the most common malignancy obtained by thorascopic pleural biopsy in the studied group was malignant mesothelioma which was found in 15 patients (53.6%).

In contrast, Law et al, [29] Ng et al [31] and Thangakunam et al [34] reported low diagnostic yield of medical thoracoscopy 66.7% (12/18 patients), 79% (11/14 patients) and 45.5% (10/22 patients) respectively.

In current study, 86.67% of patients with nodules were malignant, while only 13.33% were non-malignant and this difference was statistically highly significant. 100% patients with multiple septations with or without adhesions were non malignant. It was statistically significant. All patients (100%) with sago grain appearance were diagnosed TB. Similar observations were seen in studies by Prabhu and Narasimhan [38] and Helala et al. [43].

In our study, in hemorrhagic pleural effusion, 80% patients were malignant whereas in non-hemorrhagic pleural effusion 63.33% patients were diagnosed TB and only 3.33% patients were malignant. Taking non-hemorrhagic Pleural effusion as reference, risk of malignancy in hemorrhagic Pleural effusion is significantly high with odd ratio of 116 and p value 0.0001. P value < 0.0001 means Pleural biopsy result is significantly different for hemorrhagic pleural effusion as compared to non-hemorrhagic pleural effusion.

Our findings were similar to in a study by Shaheen et al [44] in which 19 patients presented with hemorrhagic pleural effusion (47.5%), 20 (50%) presented with straw colored and one (2.5%) presented with green colored pleural effusion. The majority (79%) of patients with hemorrhagic effusions were finally diagnosed as malignant, other diagnoses were tuberculous and parapneumonic effusions.

In present study, Chemical pleurodesis was done among 12 patients diagnosed with malignant pleural effusion. Oxytetracycline was used in 4 patients. 3 out of 4 patients (75.00%) did not have recurrence of pleural effusion over 2 month follow up. One patient (25.00%) had early failure of pleurodesis. Talc poudrage was used as sclerosant agent in 8 patients. Patients were followed up over 2 months. Talc pleurodesis was successful in 7 out of 8 patients (87.50%). One patient lost follow up after discharge. So, this was considered as failed pleurodesis. There were no any major complications noted after pleurodesis. Successful chemical pleurodesis was achieved in 10 patients out of 12 (83.33%). Chemical pleurodesis was failed in 2 patients (16.67%). p value of 1 meaning no significant difference between success of oxytetracycline pleurodesis and talc poudrage pleurodesis.

A study by Viallat et al, [21] of the 327 patients whose response could be evaluated, 90.2% had a successful talc poudrage pleurodesis at 1 month. A retrospective study was done by Tettey et al [27] to establish the effectiveness of tetracycline pleurodesis in 38 patients with malignant pleural effusion. 61% of patients achieved complete symphysis of the pleura with no recurrence. A study by Lee et al, [28] success rates with pleuroscopic talc pleurodesis for malignant pleural

effusions was 94% after 3 month of follow up. The 3-month success rate for the six patients undergoing pleurodesis was 83% (five patients) in a study by Law et al. [29]. Rozman et al [46] performed pleurodesis in 34 patients; in 32 (94.1%) it was assessed as successful after 1 month.

There were no major complications reported during our study. The post-thoracoscopic complications in the studied group were occurred in 10 patients (22.22%). The complications were prolonged air leak (>7 days) in two patients (4.44%), surgical emphysema in 1 patient (2.22%), post-operative pain in 7 patients (15.56%). There was no complication in 35 patients (77.78%).

Colt [19] reported prospective study in which minor adverse events, however, were noted in ten instances (19%). These included fever after talc pleurodesis, asymptomatic pneumothorax after chest tube removal, and minor wound infection in a patient with empyema.

Wang et al [30] reported following post thoracoscopic complications. The most common complication was transient chest pain (20 of 27 patients) from the indwelling chest tube, which could be managed with conventional analgesics. One case of subcutaneous emphysema and 2 cases of postoperative fever were self-limiting. No severe complications occurred.

Prabhu and Narasimhan [38] reported that there were no major complications post thoracoscopy, only four patients had minor complication like subcutaneous emphysema (three patients) and prolonged air leak (one patient).

Minor complications related to the pleuroscopy procedure were bleeding, surgical emphysema and infection with overall incidence rate of <1 % in a study by Mehta et al. [39] Procedure related mortality was zero.

In the present study, the mean hospital stay was 6.67 days. de Groot and Walther [23] and Tscheikuna et al [32] and reported mean hospital stay was 6.7 days and 9.1 days after thoracoscopy respectively.

In our study the median ICD duration was 4 days. Brims et al [41] reported median time with chest drain post-procedure was 3 days.

In our study, overall diagnostic accuracy, sensitivity and specificity were 91.11%, 92.31% and 90.61% respectively. Overall positive and negative predictive value of study was 80.00% and 96.67% respectively. Positive and negative likely hood ratio was 9.85 and 0.08 respectively. Our study compared well with these findings.

Menzies and Charbonneau [17] reported a study in which overall, thoracoscopy was 96% accurate with a sensitivity of 91%, a specificity of 100% and a negative predictive value of 93% for the diagnosis of pleural malignancy. Boutin et al [18] suggested that thoracoscopy is useful for diagnosis of a number of lung diseases. For pleural effusion, the sensitivity of thoracoscopy is 92-97% and its specificity is 99%. A thoracoscopic study by Mohan et al [33] provided a diagnostic accuracy of 91.3%, sensitivity of 87%, and specificity of 100%.

With our experience, we suggest medical thoracoscopy should be performed in all patients with undiagnosed pleural effusion because it has high diagnostic yield. It is very simple and safe procedure with low complication rate.

LIMITATIONS

1. The limitation in this study was that no investigative method other than semirigid thoracoscopy was used for undiagnosed pleural effusion. Therefore, no comparative study was possible.
2. The present study is an observational study and does not have a control group and is non-randomized.
3. Our study is limited by a relative small number of patients. For future studies, larger study populations are needed.
4. This study cannot be generalized as it was conducted in a tertiary care hospital setup.
5. As a part of study design data may have recall bias from patient's side, though each patient's medical records and available investigation were searched thoroughly to provide valid documentations.

CONCLUSION

1. In our study, diagnostic yield of medical thoracoscopy was 95.56% (43/45 patients). Malignancy was diagnosed in 13 patients (28.89%), 20 patients (44.44%) were diagnosed TB, 9 patients (20.00%) had chronic non-specific pleurisy and 1 patient (2.22%) was diagnosed as SLE.
2. In current study, 86.67% of patients with nodules were malignant, while only 13.33% were non-malignant and this difference was statistically highly significant. 100% patients with multiple septations with or without adhesions were non malignant. It was statistically significant. All patients (100%) with sago grain appearance were diagnosed TB.
3. In our study, in hemorrhagic pleural effusion, 80% patients were malignant whereas in non-hemorrhagic pleural effusion 63.33% patients were diagnosed TB and only 3.33% patients were malignant. Risk of malignancy in hemorrhagic Pleural effusion is significantly high with odd ratio of 116 and p value 0.0001.
4. Chemical pleurodesis was successful in 10 patients out of 12 (83.33%) over 2 month follow up.
5. There were no any major procedure related complications noted.
6. Medical thoracoscopy is a safe and effective tool for diagnosis in patients with undiagnosed pleural effusion with high diagnostic yield and low complication rate.

RECOMMENDATIONS

1. Medical thoracoscopy should be performed as soon as possible in all patients with undiagnosed pleural effusion after initial pleural fluid reports were inconclusive.
2. It is very easy to learn for those who handle bronchoscope routinely.
3. Medical thoracoscopy is safe method with high diagnostic yield, low complication rate.
4. Medical thoracoscopy with semirigid thoracoscope has made the procedure more convenient to use as routine procedure.
5. Single port medical thoracoscopy thus is sufficient for diagnostic purpose in all pleural effusion with indeterminate etiology

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