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Diagnostic accuracy of semirigid thoracoscopy in exudative pleural effusions and relationship of thoracoscopic findings with probability of malignant diagnosis

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Abstract

Semirigid thoracoscopy is increasingly becoming the procedure of choice for evaluation of undiagnosed exudative pleural effusions. Few studies have reported relationship of thoracoscopic appearances of pleural abnormalities and etiological diagnoses. We aimed our study to assess the diagnostic utility and safety of semirigid thoracoscopy for evaluation of patients with undiagnosed exudative pleural effusion. Further, we also pursued to find any relation of various thoracoscopic findings with the final diagnosis. We prospectively enrolled
hospitalized patients with undiagnosed exudative pleural effusion who underwent semirigid thoracoscopy. Demographic, clinical and laboratory data along with data on thoracoscopic appearance of various pleural abnormalities and histopathological diagnosis of pleural biopsy specimens were collected and analysed. Semirigid thoracoscopy was diagnostic in 46 (N=55) patients (83.64%). Malignancy was diagnosed in 31 patients (56.36%), of which adenocarcinoma was the most common histopathological diagnosis (45.16%). Sensitivity, specificity, PPV, NPV LR+ and LR- of thoracoscopy were 93.87%, 100%, 100%, 66.67%, 40.30 and 0.06, respectively. Pleural nodules, masses and hemorrhagic pleural fluid significantly increased the diagnostic yield of malignancy [OR= 37.16 (95%CI = 3.61-382.65), =0.002]. The procedure-related complications were mild and transient. Post-procedural pain (20%) was most commonly reported followed by dry cough (18.18%), subcutaneous emphysema (7.27%) and anesthesia related complication (1.82%). Semirigid thoracoscopy is a simple, safe and effective procedure in diagnosing exudative pleural effusion of unknown etiology with high diagnostic accuracy and minor procedure-related complications. The likelihood of diagnosing malignancy is high if the combination of pleural nodules, masses and hemorrhagic pleural fluid is present.

**Keywords:** Thoracoscopy, pleural effusion, exudative, malignant.

**Introduction**

Semirigid thoracoscopy is an endoscopic procedure that allows clinicians to inspect the entire pleural cavity. This procedure was firstly introduced by Hans Christian Jacobus for the treatment of pulmonary tuberculosis by removal of adhesions to obtain collapse of the lung (1). It is a safe and effective procedure for the diagnosis of various pleural disorders and also has limited therapeutic value. Nowadays, this procedure is increasingly being used by pulmonologists for evaluation of various pleural pathologies, most commonly exudative pleural effusion.

The precise diagnosis of the pleural pathology can present a significant challenge to the clinicians. Approximately in one-fourth patients with the pleural pathology, clinicians are unable to diagnose a specific etiology even after substantial work up that includes pleural fluid analysis (cyto-biochemical and microbiological) and closed pleural biopsy (2–5). More than half of these patients are eventually diagnosed as malignant (6). Semirigid thoracoscopy
permits direct visualization of pleural abnormalities and to take biopsies from the affected area that significantly increases its diagnostic utility over closed pleural biopsy. Studies has reported various thoracoscopic findings and their association with the etiological diagnosis (2,7). They are described as nodules, masses, pleural infiltration, pleural thickening, polypoid lesions and “candle wax drops” pattern (8). Present study evaluates the diagnostic utility and safety of semirigid thoracoscopy among the patients with undiagnosed exudative pleural effusion and relationship of thoracoscopic appearance with etiological diagnosis with emphasis on malignancy.

Materials and Methods
This was a prospective, interventional study conducted at our institute, a tertiary care centre in southern Rajasthan, from July 2017 to December 2019. Semirigid thoracoscopy was performed in the cases of exudative pleural effusion whose microbiological and cytological diagnosis was either inconclusive or suspicious of malignancy. Informed and written consent was obtained from all the patients. The study protocols were approved by institutional ethics committee. All the patients with undiagnosed exudative pleural effusion underwent semirigid thoracoscopy. We excluded the patients having history of pleurodesis or if there was an inability to create space between the lung and the thorax because of some prior insult. We also excluded the patients who are not able to tolerate lateral decubitus position, having severe respiratory distress, intractable cough, oxyhemoglobin desaturation even with supplemental oxygen, bleeding disorders and lack of informed consent. Patients underwent for all the relevant routine investigations; thoracic ultrasound to quantify the amount of fluid, presence of loculations and to select the optimal site of entry; and Contrast Enhanced Computed Tomography (CECT) scan of the thorax up to adrenals if there was suspicion of malignancy. Semirigid thoracoscopy was performed in an endoscopy suite with the patient under conscious sedation and local anaesthesia. Patients were monitored for heart rate, respiratory rate, percentage peripheral oxygen saturation and continuous electrocardiography throughout the procedure and for two hours after the procedure. The site for trocar insertion was always selected based on ultrasonographic guidance. Patients were positioned in lateral decubitus position with affected side up. Chest wall was cleaned with povidone iodine and spirit. 10 ml to 15 ml of 2% lignocaine was used for infiltrating the intercostal space from skin to the parietal pleura. A skin incision of about 1 cm was made followed by blunt dissection to enter the pleural
cavity. Trocar and canula were inserted into the pleural cavity. The instrument used was a semi-rigid thoracoscope (Olympus EVIS EXERA LTF-160) to perform the procedure.

After entering into the pleural cavity, all the pleural fluid was aspirated out slowly to achieve maximum visualization. The entire pleural cavity was inspected carefully to visualize costal, diaphragmatic and the visceral pleura. We had noted pleural abnormalities in the form of nodules over pleura as well as on the lung surface, pleural thickening, pleural masses, pigmentation and adhesions. Multiple pleural biopsies (3 to 5 in number) were taken from abnormal lesions over parietal pleura (sometimes from visceral pleura also) by “lift and peel” method. Pleural biopsy specimens were collected in formalin for histopathological diagnosis. Adhesiolysis was additionally done whenever required. After completion of the procedure, intercostal chest drain (24 to 28 F) was inserted and secured in position by suture. Drain was removed after complete expansion of the lung if pleural fluid drainage was less than 100 ml/day. Pleurodesis was done in patients with recurrent pleural effusion only after evidence of complete expansion of the lung post-thoracoscopy.

Statistics

Analysis was done using SPSS version 21 (IBM Corp. Ltd, Newark, USA). Categorical variables were expressed as frequency (percentage) and quantitative variables were expressed as mean (SD). Univariate or linear regression was applied for analysing the correlation between different parameters and diagnosis of pleural malignancy. Binary logistic regression was applied for the parameters which have significant relation in diagnosing malignancy in univariate analysis. Parameters have significant correlation on univariate analysis were clubbed in a fashion to increase the diagnostic accuracy for pleural malignancy. Diagnostic accuracy parameters were expressed as sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio positive and likelihood ratio negative.

Results

A total of 55 patients with exudative pleural effusion of unknown etiology underwent semirigid thoracoscopy during the study period. The mean age of the patients was 56.90 ± 15.94 years. There were 37 males (67.27%) and 18 females (32.73). The majority of male patients were farmer (27/37; 72.97%) and females were housewife (16/18; 88.89%). Thirty-five patients (63.64%) were non-smoker.

In the study population, 11 patients (20%) had associated comorbid illness (Table 1). Thirty-three patients (60%) had right sided, 21 (38.18%) had left sided and one patient (1.81%) had
bilateral pleural effusion. Pleural fluid appearance was hemorrhagic in 32 (58.18%) patients and cytology suspicious of malignancy was present in 12 (21.82%) patients. Pleural fluid examination revealed exudative effusion with protein level of 4.56 ± 0.95 gm/dL. Pleural fluid examination for acid fast bacilli (AFB) and Cartridge based nucleic acid amplification (CBNAAT) was negative in all the patients.

The findings observed during thoracoscopy are summarized in Table 2. The most common findings were pleural nodules (38 patients; 69.09%) and adhesions (26 patients; 47.27%) (Figure 1-3). Of the 55 patients, a diagnosis was obtained in 46 patients (83.64%). Of these, 31 patients were found to be positive for malignancy (56.36%) and 15 patients had tuberculosis (40%). Seven patients (12.73%) had non-specific pleuritis and two patients (3.63%) had normal pleura.

The most common histopathological diagnosis was adenocarcinoma [14 patients, (45.16%)] followed by squamous cell carcinoma [8 patients, (25.81%)] and mesothelioma [5 patients (16.13%)] in the present study. Bronchogenic carcinoma [16 patients (51.61%)] was the most common primary malignancy followed by mesothelioma [5 patients (16.13%)] and metastatic carcinoma (2 patients with colon carcinoma and one each for breast and bone carcinoma). The primary could not be identified in six patients (19.35%).

All the thoracoscopic procedures were performed safely without any major complications (Table 2). Minor complications reported were post-procedural pain (20%), dry cough (18.18%), sub-cutaneous emphysema (7.27%) and anaesthesia related complication (1.82%).

We carried out univariate regression analysis of the various parameters to find out their probability of diagnosing pleural malignancy (Table 3). Nodules, pleural masses, hemorrhagic pleural fluid and cytology suggestive of malignancy were significantly associated with the diagnosis of pleural malignancy whereas presence of adhesions favoured non-malignant etiology (p= 0.002).

Binary logistic regression was applied for the thoracoscopic parameters which have significant relation in diagnosing malignancy in univariate analysis (Table 4). It revealed that presence of pleural nodules, hemorrhagic fluid and pleural masses was significantly associated with diagnosis of pleural malignancy and it increases the likelihood of diagnosing malignancy around 37 times.

Sensitivity, Specificity, Positive predictive value (PPV), Negative predictive value (NPV), Likelihood ratio positive (LR+) and likelihood ratio negative (LR-) for malignancy of two or more combined thoracoscopy findings is shown in table 5. The post-test odds (“rule in” disease) of positive test for having disease are increased by 5 times with the use of either criteria 1 or 2
or 3 whereas presence of malignant cytology and nodules (criteria 4) increase the post-test odd by 6 times. Similarly, post-test odds of negative test (“rule out” disease) for having disease with criteria 1 and 2 decrease by 0.4 and 0.87, respectively.

The overall Sensitivity, Specificity, Positive predictive value (PPV), Negative predictive value (NPV), Likelihood ratio positive (LR+) and likelihood ratio negative (LR-) of semirigid thoracoscopy in present study is 93.88%, 100%, 100%, 66.67%, 40.30 and 0.06 respectively.

**Discussion**

Undiagnosed exudative pleural effusion is among the common respiratory ailments frequently encountered in clinical practise. Thoracentesis and closed-needle pleural biopsy are used to perform to identify the etiology but they have low yield particularly in malignant pleural effusion. Closed-needle pleural biopsy has good diagnostic yield in diffuse pleural involvement like in tuberculosis but in malignancy, there is patchy involvement of pleura, it is diagnostic only in half of the cases (9). Furthermore, it has limited value if there is involvement of diaphragmatic, mediastinal or visceral pleura. Also, negative closed-needle pleural biopsy substantially delays the diagnosis hence initiation of effective treatment.

Semirigid thoracoscopy has now become the standard diagnostic modality for undiagnosed exudative pleural effusion. It not only allows pleural biopsies from abnormal looking pleura but also provides opportunity to take biopsies from visceral pleura, breaking off the adhesions and simultaneously to carry out pleurodesis. British thoracic society also recommends semirigid thoracoscopy as next investigation of choice in patients with exudative pleural effusion where a diagnostic pleural aspiration is negative or inconclusive, and malignancy is suspected (10).

In the present study, 55 consecutive patients with undiagnosed exudative pleural effusion underwent semirigid thoracoscopy. The diagnostic yield of the study was 83.64% (95% CI – 73.88 - 93.40). Various studies across the globe have reported similar diagnostic yield (4,11–16). Studies from Indian subcontinent reported diagnostic yield ranging from 66% to 97% (17–22). Some of the studies included non-specific pleuritis as a final diagnosis that has increased their diagnostic yield (23–25).

The most common causes of undiagnosed pleural effusion are malignancy and tuberculosis though that varies across regions. In our study, the most common etiology was pleural malignancy that was found in 31 (56.36%) patients. Another 15 (40%) patients had tuberculosis, seven patients (12.73%) had non-specific pleuritis and two patients (3.63%) had normal pleura. Similar observations have been made in the other studies also. Munavver et al.
performed semirigid thoracoscopy in 56 patients and were able to obtain biopsy in 54 patients. Among them, 32 patients (59.26%) were diagnosed with malignancy (11). Nattusamy et al. reported malignant etiology in 30 patients (62.5%) out of 42 patients (18). Similarly, in a retrospective study of 150 patients, thoracoscopy detected malignancy in 92 patients (61.33%) (8).

Further, in our study, bronchogenic carcinoma was the most common primary malignancy among the patients diagnosed with pleural malignancy (16 patients; 51.61%). Mesothelioma and metastatic carcinoma secondary to colon, breast and bone was observed in 16.13% and 12.90% cases, respectively. In the six patients (19.35%), the primary tumour could not be identified. Histologically, adenocarcinoma [14 patients, 45.16%] was the most common subtype followed by squamous cell carcinoma [8 patients, 25.81%]. Mesothelioma was seen in five patients (16.13%). Prabhu et al reported adenocarcinoma, mesothelioma and metastatic carcinoma in 62.5%, 12.5% and 8.33% patients, respectively (25). Another study of 42 patients reported malignant etiology in 30 patients. It observed adenocarcinoma in 60%, squamous cell carcinoma in 3.33% and metastatic carcinoma in 13.33% of the patients (18).

Thoracoscopic appearance of pleural abnormalities helps in predicting the diagnosis of malignancy. Various studies have reported association of macroscopic appearances of pleural pathologies and the likelihood of the malignancy (2, 8, 25, 26). In our study, presence of nodules alone has the 13 times odds of predicting the malignancy, while presence of hemorrhagic effusion along with nodules increase the odds to 17 and combining pleural mass with the nodules and haemorrhage increase the odd to 37. Presence of pleural mass has resulted in definitive diagnosis of malignancy as there were no cases of presence of mass without malignancy. Hence, the odds of presence of mass alone can’t be calculated. However, the diagnostic accuracy of presence of mass for malignancy is found to be only 25.80%.

Apart from malignant pleural effusion, semirigid thoracoscopy has excellent diagnostic accuracy in benign disorders including Tuberculosis. Loddenkemper et al. described combined role of closed pleural biopsy, pleural fluid culture and semirigid thoracoscopy (5). They reported diagnostic yield of closed pleural biopsy of 51% which could be increased up to 61% by adding pleural fluid culture. Semirigid thoracoscopy alone had diagnostic yield of 99%. All the three procedures combined had 100% diagnostic yield.

In our study, 15 patients (27.27%) had tuberculosis and seven patients (12.73%) had non-specific pleuritis on histopathology. Among seven patients of non-specific pleuritis, four were treated with anti-tuberculous treatment based on clinical profile and responded well with resolution of the pleural effusion. Two patients were diagnosed as empyema based on
thoracoscopic appearance and inflammatory changes on pleural biopsy. One patient remained undiagnosed and denied for repeat procedure. So, apparently, we failed to diagnose four patients (7.27%) of tuberculosis even with the semirigid thoracoscopy. The failure to diagnose tuberculosis could be due to both thick adhesions and not performing pleural biopsy culture for mycobacteria which would double the diagnostic yield (5).

Among the patients with non-specific pleuritis, tuberculous pleuritis has been frequently reported on long term follow up. A retrospective study of 75 patients with thoracoscopic pleural biopsy diagnosis of non-specific pleuritis reported that 91.7% patients followed a benign process and only 8.3% eventually developed malignancy (27).

Semirigid thoracoscopy has good diagnostic accuracy with reported sensitivity of 81%-100% and specificity 100% across various studies (20). A systematic review and meta-analysis has reported the pooled sensitivity (95% CI) of 97% (92%-99%), specificity of (95% CI) 100% (69%-100%), positive likelihood ratio (95% CI) 5.47 (1.11-16.86) and negative likelihood ratio (95% CI) 0.08 (0.04-0.18) (20). Another meta-analysis on diagnostic accuracy and safety of semirigid thoracoscopy in undiagnosed pleural effusion observed sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio of 91%, 100%, 4.92, 0.08, and 102.28, respectively (28). In our study, we observed sensitivity, specificity, positive likelihood ratio and negative likelihood ratio of semirigid thoracoscopy 93.88%, 100%, 100%, 66.67%, 40.30 and 0.06 respectively. Thus, our data further confirms the high diagnostic potential of semirigid thoracoscopy.

Complications related to the procedure were mostly mild and self-limiting with no mortality among the study population. One female patient developed midazolam related respiratory depression requiring immediate intubation and bag and mask ventilation. She was recovered in endoscopy suite during next half an hour and was extubated there only. We did not observe any episode of hypotension, bradycardia, post-procedural fever and prolonged air leak.

In conclusion, semirigid thoracoscopy is a useful diagnostic tool for evaluation of undiagnosed exudative pleural effusions. It is safe, easy to perform and have excellent diagnostic yield and accuracy. Presence of hemorrhagic pleural effusion, nodules and masses altogether significantly increases the likelihood of diagnosing malignancy.

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Figure 1. Thoracoscopic and histopathological appearance of malignant pleural effusion. A) **Squamous cell carcinoma**; Left: Thoracoscopy - Multiple nodular lesions along with pleural masses are seen with hyperemic pleura; Right: Histopathology - Section studied reveals clusters of malignant neoplastic cells having high N:C ratio, pleomorphism, eosinophilic cytoplasm with no evidence of keratin pearl formation suggestive of non-keratinizing squamous cell carcinoma. B) **Mesothelioma**; Left: Thoracoscopy - Diffuse pleural thickening with pigmentation; Right: Histopathology - Section (40X) reveals sheets of spindle shaped cells with high N:C ratio with intervening lymphocytic infiltration suggestive of sarcomatoid type malignant mesothelioma. C) **Adenocarcinoma**; Left: Thoracoscopy - Focal pleural plaques with scatter nodules with hemorrhagic effusion; Right: Histopathology - section (40X) reveals sheets of malignant cells forming adenoid pattern, having pleomorphism with high N:C ratio and signet ring appearance suggestive of adenocarcinoma.
Figure 2. Thoracoscopic and histopathological appearance of metastatic malignant pleural effusion. A) Patient with carcinoma colon; Left: Thoracoscopy - Multiple tiny nodular lesions uniformly distributed with large nodular mass; Right: Histopathology - section studied reveals neoplastic cells arranged in papillary pattern with clear cytoplasm having mucinous differentiation suggestive of metastatic well differentiated adenocarcinoma. B) Patient with infiltrating duct carcinoma breast; Left: Thoracoscopy - Nodules of varying size are aggregated over parietal pleura with flimsy adhesion; Right: Histopathology - Section studied reveals sheets of neoplastic cells arranged in acinic pattern, having pleomorphism suggestive of adenocarcinoma. C) Patient with undifferentiated carcinoma; Left: Thoracoscopy - Multiple nodules over parietal pleura with hemorrhagic pleural effusion; Right: Histopathology - Section studied reveals sheets of neoplastic cells with few foci shows cells having eosinophilic cytoplasm as well; however, anaplasia seen suggestive of Undifferentiated carcinoma.
Figure 3. Thoracoscopic appearance and their histopathological diagnosis in patient with benign pleural diseases. A) Tuberculosis; Left: Thoracoscopy - Multiple nodular lesions over parietal pleura and lung surface resembling “sago-like appearance”; Right: Histopathology - section (40X) studied reveals sheets of epitheloid cells forming granuloma, areas of caseous necrosis with Langhans type giant cells seen, consistent with tuberculosis. B) Empyema; Left: Thoracoscopy - Presence of pus and adhesions with cheesy material and mild parietal pleural thickening; Right: Histopathology - Section (40X) studied reveals alveoli with chronic inflammatory cell infiltrates consisting of cyst macrophage and lymphocytes features consistent with empyema. C) Patient of pulmonary embolism; Left: Thoracoscopy - Band of adhesion with pigmentation; Right: Histopathology - Section (40X) studied reveals only fibro-collagenous tissue with flattened columnar epithelium (normal pleura).
Table 1. Baseline characteristics of the patients.

| Characteristic                      | Value     |
|-------------------------------------|-----------|
| Total number of patients, n         | 55        |
| Age, years (mean ± SD)              | 56.90 ± 15.94 |
| Sex, n (%)                          |           |
| Male                                | 37 (67.27) |
| Female                              | 18 (32.73) |
| Occupation                          |           |
| Farmer                              | 27 (49.09) |
| Labourer                            | 4 (7.27)  |
| Office work                         | 6 (10.90) |
| Stone worker                        | 1 (1.81)  |
| Housewife                           | 16 (29.09)|
| Shop keeper                         | 1 (1.81)  |
| Smoking status, n (%)               |           |
| Current smoker                      | 5 (9.09)  |
| Ex-smoker                           | 15 (27.27)|
| Non-smoker                          | 35 (63.64)|
| Comorbid conditions, n (%)          |           |
| Hypertension                        | 3 (5.45)  |
| Diabetes Mellitus                   | 4 (7.27)  |
| Ischemic heart disease              | 1 (1.81)  |
| Fracture humerus                    | 1 (1.81)  |
| Non-Hodgkin’s Lymphoma              | 1 (1.81)  |
| Carcinoma Breast                    | 1 (1.81)  |
| Side of pleural effusion, n (%)     |           |
| Right                               | 33 (60)   |
| Left                                | 21 (38.18)|
| Bilateral                           | 1 (1.81)  |
| Pleural fluid characteristics       |           |
| Appearance, n (%)                  |           |
| Serosanguinous                      | 23 (41.82)|
| Hemorrhagic                         | 32 (58.18)|
| Protein (gm/dl), (mean ± SD)        | 4.56 ± 0.95|
| Glucose (mg/dl), (mean ± SD) | 90.33 ± 59.45 |
|-----------------------------|---------------|
| ADA (U/L), (mean ± SD)      | 31.66 ± 16.66 |
| Cytology, n (%)             |               |
| Malignant                   | 12 (21.82)    |
| Non-malignant               | 43 (78.18)    |
**Table 2.** Performance characteristics of thoracoscopy in patients with undiagnosed pleural effusion.

| Thoracoscopic appearance, n (%) |       |
|-------------------------------|-------|
| Nodules                       | 38 (69.09) |
| Adhesions                     | 26 (47.27) |
| Diffuse pleural thickening    | 21 (38.18) |
| Pigmentation                  | 11 (20) |
| Mass lesions                  | 8 (14.55) |
| Lung nodules                  | 19 (34.55) |
| Pus                           | 7 (12.73) |

| Histopathological diagnosis, n (%) |       |
|-----------------------------------|-------|
| Malignancy                        | 31 (56.36) |
| Tuberculosis                      | 15 (27.27) |
| Non-specific inflammation         | 7 (12.73) |
| Normal pleura                     | 2 (3.63) |

| Pathological subtypes of malignant pleural effusion, n (%) |       |
|------------------------------------------------------------|-------|
| Adenocarcinoma                                             | 14 (45.16) |
| Squamous cell carcinoma                                    | 8 (25.81) |
| Small cell carcinoma                                       | 1 (3.23) |
| Mesothelioma                                                | 5 (16.13) |
| Poorly differentiated carcinoma                             | 3 (9.68) |

| Primary malignancy                                          |       |
|-------------------------------------------------------------|-------|
| Bronchogenic Carcinoma                                      | 16 (51.61) |
| Mesothelioma                                                | 5 (16.13) |
| Metastatic carcinoma                                        |       |
| Breast                                                      | 1 (3.23) |
| Colon                                                       | 2 (6.45) |
| Bone                                                        | 1 (3.23) |
| Unknown primary                                             | 6 (19.35) |

| Procedure related complications, mild and transient, n (%) |       |
|------------------------------------------------------------|-------|
| Condition                        | Count (Percentage) |
|--------------------------------|--------------------|
| Post-operative pain             | 11 (20)            |
| Cough                           | 10 (18.18)         |
| Subcutaneous emphysema          | 4 (7.27)           |
| Anaesthesia related             | 1 (1.82)           |
Table 3. Thoracoscopic findings and other factors and their relation with the probability of malignant etiology.

| Thoracoscopic findings          | Malignancy | p       | Diagnostic odds ratio (95% CI) |
|---------------------------------|------------|---------|--------------------------------|
|                                 | Yes | No    |      |                                |
| Nodules                         |     |       |      |                                |
| Yes                             | 28  | 10    | <0.001 | 13.1 (3.09-55.20)              |
| No                              | 3   | 14    |       |                                |
| Adhesions                       |     |       |      |                                |
| Yes                             | 9   | 17    | 0.002  | 0.17 (0.05-0.54)               |
| No                              | 22  | 7     |       |                                |
| Mass                            |     |       |      |                                |
| Yes                             | 8   | 0     | 0.007  | 0.511 (0.150-0.872)*           |
| No                              | 23  | 24    |       |                                |
| Diffuse pleural thickening      |     |       |      |                                |
| Yes                             | 11  | 10    | 0.640  | 0.77 (0.25-2.30)               |
| No                              | 20  | 14    |       |                                |
| Pigmentation                    |     |       |      |                                |
| Yes                             | 7   | 4     | 0.587  | 1.5 (0.37-5.70)                |
| No                              | 24  | 20    |       |                                |
| Lung nodules                    |     |       |      |                                |
| Yes                             | 14  | 5     | 0.06   | 3.1 (0.93-10.52)               |
| No                              | 17  | 19    |       |                                |
| Hemorrhagic pleural fluid       |     |       |      |                                |
| Yes                             | 24  | 8     | 0.001  | 6.9 (2.07-22.66)               |
| No                              | 7   | 16    |       |                                |
| Malignant cytology              |     |       |      |                                |
| Yes                             | 10  | 2     | 0.033  | 5.2 (1.02-26.78)               |
| No                              | 21  | 22    |       |                                |
| ADA ≤ 32.8 IU/L                 |     |       |      |                                |
| Yes                             | 24  | 10    | 0.007  | 4.8 (1.49-15.45)               |
| No                              | 7   | 14    |       |                                |

*One of the values is zero, therefore OR is not calculated and data is provided as beta coefficient. # Data has been provided as supplementary material.
Table 4. Binary logistic regression (forward conditional) of thoracoscopic findings with the probability of diagnosing malignancy.

| Parameters                                      | Diagnostic odds ratio (95% CI) | p       |
|-------------------------------------------------|--------------------------------|---------|
| Only nodules present                            | 13.07 [3.09-55.20]             | <0.001  |
| Only hemorrhagic fluid present                  | 9.43 [2.11-42.11]              | 0.003   |
| Nodules and hemorrhagic fluid both present      | 17.61 [3.27-94.75]             | 0.001   |
| Nodules, hemorrhagic fluid and pleural mass present | 37.16 [3.61-382.65]           | 0.002   |

Table 5. Sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio positive and likelihood ratio negative for malignancy of two or more combined thoracoscopy findings.

| Diagnostic criteria | Three out of ADA ≤32.8 mg/dl or nodules or mass or hemorrhage present together (criteria 1) | Nodules, mass plus hemorrhagic effusion present (criteria 2) | Hemorrhagic effusion plus nodules present (criteria 3) | Malignant cytology plus nodules (criteria 4) | Pleural biopsy |
|---------------------|--------------------------------------------------------------------------------------------------|-------------------------------------------------------------|-------------------------------------------------------|---------------------------------------------|---------------|
| Test Positive/ Test Negative in malignant        | 20/11                                                                                           | 4/27                                                        | 21/10                                                 | 8/23                                        | 46/3 M=31     |
| Test positive / Test Negative in non-malignant   | 3/21                                                                                           | 0/24                                                        | 3/21                                                  | 1/23                                        | 0/6 NM=24     |
| Sensitivity        | 64.51                                                                                            | 12.90                                                       | 67.74                                                 | 25.80                                       | 93.87         |
| Specificity        | 87.5                                                                                             | 100                                                         | 87.5                                                  | 95.83                                       | 100           |
| PPV                | 86.95                                                                                            | 100                                                         | 87.5                                                  | 88.88                                       | 100           |
| NPV                | 65.62                                                                                            | 47.05                                                       | 67.74                                                 | 50                                          | 66.67         |
| LR+                | 5.16                                                                                             | 4.83                                                        | 5.42                                                  | 6.19                                        | 40.30#        |
| LR-                | 0.40                                                                                             | 0.87                                                        | 0.37                                                  | 0.77                                        | 0.06          |

PPV- Positive predictive value, NPV-Negative predictive value, LR+ = Likelihood ratio positive and LR- = likelihood ratio negative M= Malignant, NM-Non-malignant; #For calculation of LR+ in biopsy group, continuity correction of 1 was applied as false test positive is zero.