



Evaluation of Exudative Pleural Effusions: A Multicenter, Prospective, Observational Study

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Abstract

Purpose The aim of this study is to determine the diagnostic performances of pleural procedures in undiagnosed exudative pleural effusions and to evaluate factors suggestive of benign or malignant pleural effusions in tertiary care centers.

Methods This was a multicenter prospective observational study conducted between January 1 and December 31, 2018. A total of 777 patients with undiagnosed exudative pleural effusion after the initial work-up were evaluated. The results of diagnostic procedures and the patients' diagnoses were prospectively recorded. Sensitivity, specificity, and accuracy estimates with 95% confidence intervals were used to examine the performance of pleural procedures to detect malignancy.

Results The mean age $\pm$ SD of the 777 patients was 62.0 ± 16.0 years, and 68.3% of them were male. The most common cause was malignancy (38.3%). Lung cancer was the leading cause of malignant pleural effusions (20.2%). The diagnostic sensitivity and accuracy of cytology were 59.5% and 84.3%, respectively. The diagnostic sensitivity of image-guided pleural biopsy was 86.4%. The addition of image-guided pleural biopsy to cytology increased diagnostic sensitivity to more than 90%. Thoracoscopic biopsy provided the highest diagnostic sensitivity (94.3%). The highest diagnostic sensitivity of cytology was determined in metastatic pleural effusion from breast cancer (86.7%).

Conclusion The diagnostic performance increases considerably when cytology is combined with image-guided pleural biopsy in malignant pleural effusions. However, to avoid unnecessary interventions and complications, the development of criteria to distinguish patients with benign pleural effusions is as important as the identification of patients with malignant pleural effusions.

Keywords Exudative pleural effusion · Cytological diagnostic sensitivity · Image-guided pleural biopsy · Malignant pleural effusion · Benign pleural effusion

Introduction

Pleural effusion is one of the clinical problems that are becoming more common in chest diseases clinics. Although pleural effusion may develop because of primary respiratory system problems, the effects of other systems on the pleura represent an important part of the causes of pleural effusion. The most common causes of pleural effusion are heart failure, infections and malignancies [1]. Clinical, laboratory,

and radiologic examinations performed during the initial evaluation of patients with pleural effusion are of great importance. Transudative pleural effusions and infectious pleural effusions are easily distinguished by clinical evaluation and initial analysis of the pleural effusion, including biochemical analysis, cell count, and microbiologic examination, allowing diagnosis of more than half of patients [1, 2]. In the remaining patients, the majority of whom have malignancies, diagnostic work-up is initiated with cytology, which is the simplest procedure. If necessary, image-guided and thoracoscopic pleural biopsies are performed with a stepwise approach [3–5].

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Despite improvements in imaging, biopsy techniques, and cytopathologic examination over the years, a specific diagnosis still cannot be made in a certain number of patients by initial diagnostic work-up. While some of these patients remain benign at the end of follow-up, some are diagnosed as malignant [6–8]. It is useful to document the characteristics of patients with pleural effusion well and even to develop standards or algorithms by considering possible regional differences in diagnosis [9, 10]. In order to successfully manage the process and achieve diagnostic results in a patient with pleural effusion, it is important to know the malignant effusions that can be easily diagnosed by cytology and to perform pleural biopsy promptly in those that cannot be diagnosed. On the other hand, recognizing benign pleural effusion and avoiding unnecessary interventions and their complications is as important as recognizing the malignant pleural effusion.

The aim of this prospective observational study is to determine the pleural fluid characteristics, diagnostic performance of procedures (including sensitivity of cytology in malignant subgroups), and final diagnoses besides identifying factors favoring benign or malignant pleural effusion in patients with undiagnosed exudative pleural effusions in tertiary care centers.

Materials and Methods

Study Design and Participants

The study was a multicenter prospective observational study conducted by the Turkish Respiratory Society Pleura Study Group between January 1 and December 31, 2018 in Turkey. A total of 826 undiagnosed patients with exudative pleural effusion as per the criteria of Light et al. [2] were included in the study after the initial analysis in 14 tertiary care centers that were able to perform pleural biopsies, cytoblock, and immunohistochemical staining. The study was approved by the Clinical Research Ethics Committee of the University of Health Sciences Sıreyyapasa Pulmonary Diseases and Thoracic Surgery Training and Research Hospital (No: 116.2017.016). Participants were included in the study using an opt-out approach.

Forty-nine patients who could not be adequately examined for a benign or malignant diagnosis and whose benign results could not be followed for at least one year and patients who withdrew consent were excluded from the analysis (Fig. 1). Age, sex, amount of pleural effusion, side of pleural effusion, appearance of pleural effusion, diagnostic procedures and their success and final diagnosis were prospectively recorded.

The amount of pleural effusion was classified as mild, moderate, or massive based on the chest radiograph. The

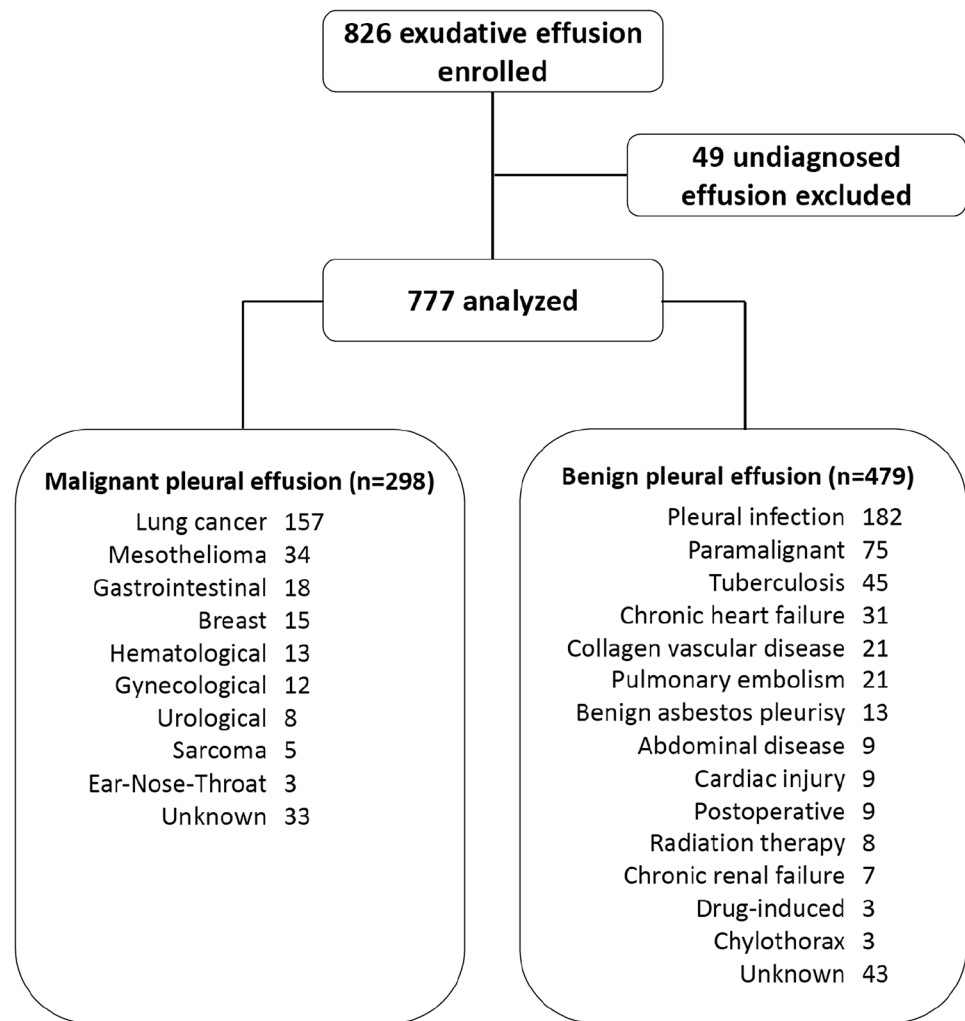
side of pleural effusion was recorded as right, left, or bilateral. The appearance of pleural effusion was recorded as serous, serosanguineous, hemorrhagic, whitish (purulent, or milky) at the first pleural puncture. The diagnosis was made according to national and international guidelines, taking into account clinical findings, pleural effusion findings, and chest computed tomography [10, 11]. When necessary, pleural biopsy procedures and/or thoracoscopic biopsies were performed after pleural puncture. Cytological workup was performed in all centers in at least two 30–50 ml materials using cytoblock and immunohistochemical staining. Immunohistochemical staining of pleural tissue samples was also performed in all centers for diagnosis and differential diagnosis.

For the diagnosis of malignancy, patients were accepted if they were classified as ‘definitely malignant’ by the cyto/histopathologist. Procedures reported as ‘suspicious for malignancy’ or ‘atypia of undetermined significance’ or ‘negative for malignancy’ were not considered diagnostic. Patients in whom a diagnosis could not be made on the basis of diagnostic workup were followed up for at least 1 year [7]. Patients whose pleural effusion did not resolve or who had pleural thickening were reexamined for malignancy during follow-up. Patients in whom a specific diagnosis could not be made and who survived the 1-year period without problems were classified as benign after joint evaluation by the two consultants.

The diagnosis of tuberculous pleurisy among benign effusions was based on clinical findings, evidence of tuberculosis bacilli in the pleural effusion or culture of sputum/bronchoalveolar lavage fluid, and/or a histopathologic diagnosis. For the other benign effusions, the benign diagnosis was based on clinical findings, pleural effusion findings, microbiological analysis, radiological findings, and, if necessary, cytology of the pleural effusion and histology of the pleural tissue, and malignancy was ruled out after one year of follow-up in the required patients.

Statistical Analysis

SPSS (version 15.0) and MedCalc Statistical Software (version 19.1.16, Medcalc Software Ltd, Ostend, Belgium) were used to analyze the data. Categorical variables were expressed as frequency and percentage, and continuous variables were expressed as mean $\pm$ SD and min–max values in the study. Chi-square and independent samples *t*-test were used to compare the data. Sensitivity, specificity, and accuracy estimates with 95% confidence intervals were used to investigate the ability of pleural procedures to detect malignancy. Multivariate logistic regression analysis was performed to distinguish between malignant and benign pleural effusions. Odds ratio and 95% confidence interval were

Fig. 1 Flowchart of the study population

determined by building a model with variables with $p < 0.10$ in the univariate analysis.

Results

The characteristics of the patients included in the study are shown in Table 1. The mean age $\pm$ SD of the patients was 62.0 ± 16.0 years, and 68.3% of them were male. Among the 777 patients with exudative pleural effusion analyzed in the study, the most common cause was malignancy (38.3%), and the second most common cause was pleural infection (23.4%). Among malignant pleural effusions, the most common cause was lung cancer (20.2%) (Fig. 2A and B).

Table 2 shows the comparison of the characteristics of malignant and benign pleural effusion. Young patients, men, patients with mild pleural effusion, and serous pleural effusion were more likely to have benign pleural effusion (Table 2). Multivariate logistic regression analysis revealed that the probability of benign pleural effusion was higher in

men than in women, in patients aged < 65 years compared with patients aged ≥ 65 years, in patients with mild effusion compared with those with moderate and massive effusion, and in patients with serous pleural effusion compared with those with serohemorrhagic and hemorrhagic effusion (Fig. 3).

Of 777 patients, cytology was performed in 751, blind closed pleural biopsy in 51, image-guided pleural biopsy in 58, medical thoracoscopy or video-assisted thoracoscopic surgery in 95. While a sufficient amount of biopsy was obtained in all patients who underwent image-guided and thoracoscopic biopsy, insufficient tissue was obtained in 9.8% of patients who underwent blind closed pleural biopsy.

The sensitivity, specificity, and accuracy of the diagnostic procedures are shown in Table 3. The diagnostic sensitivity of cytology was 59.5% and its accuracy was 84.3%. The diagnostic sensitivity of blind closed pleural biopsy was 50.0%, and that of image-guided pleural biopsy was 86.4%. The addition of blind closed pleural biopsy to cytology did not increase diagnostic sensitivity, whereas the addition of

Table 1 Characteristics of patients

Variables	<i>n</i> = 777
Age, year ($X \pm SD$) (min–max)	62.0 $\pm$ 16.0 (18–92)
Sex, <i>n</i> (%)	
Male	531 (68.3)
Female	246 (31.7)
Size, <i>n</i> (%)	
Mild	291 (37.5)
Moderate	325 (41.8)
Massive	161 (20.7)
Laterality, <i>n</i> (%)	
Right	432 (55.6)
Left	300 (38.6)
Bilateral	45 (5.8)
Macroscopic appearance, <i>n</i> (%)	
Serous	435 (56.0)
Serosanguineous	207 (26.6)
Hemorrhagic	93 (12.0)
Whitish (pus or milky)	42 (5.4)

SD standard deviation

image-guided pleural biopsy to cytology increased diagnostic sensitivity to more than 90%. Thoracoscopic biopsies had the highest diagnostic sensitivity at 94.3%.

Table 4 shows the diagnostic sensitivity of cytology in patients with malignant pleural effusion in whom two samples of at least 30–50 ml can be examined by the cytoblock method and immunohistochemistry. The highest diagnostic sensitivity was found in breast cancer with 86.7%, followed by gynecological malignancies. Diagnostic sensitivity in lung cancer, which constitutes the majority of the malignant group, was 62.1%. The diagnostic sensitivity in mesothelioma was 18.2%. Cytology was able to diagnose one of the 5 patients with sarcoma, whereas it was unable to diagnose any of the 3 patients with ear, nose, and throat cancer. In patients with malignancy of unknown primary origin, the diagnostic sensitivity was 83.9%.

Discussion

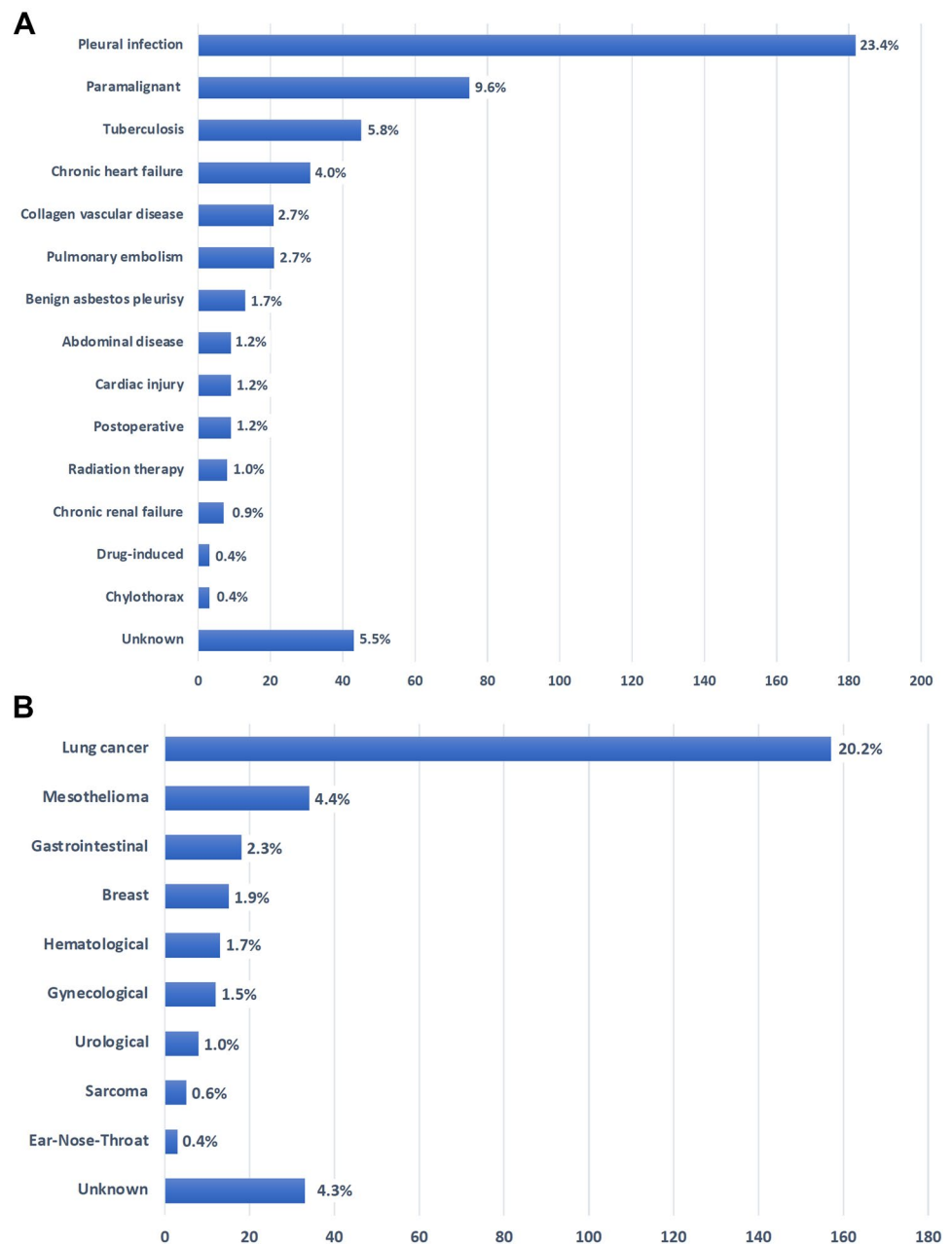
In our multicenter study, we examined patients admitted for undiagnosed exudative pleural effusion in 14 tertiary care hospitals that have a standard of care for pleural effusion. We found that malignant pleural effusions were the most common cause and that the diagnostic sensitivity of cytology for malignant pleural effusions was 59.5%. Diagnostic sensitivity reached 90% when cytology was combined with image-guided pleural biopsy. Our prospective study is the first multi-institutional large study from Turkey. Moreover, since it is a recent cross-sectional study in clinics where

the use of cytoblock and immunohistochemical staining is standardized, the results provide insights that will contribute to the literature on etiology, diagnostic sensitivity of cytology, and cytology plus image-guided pleural biopsy.

To our knowledge, heart failure is the most frequent cause of pleural effusions, followed by infectious effusions and malignant pleural effusions [12], although this order varies by clinic, region, and even country. One of the largest series investigating the causes of pleural effusions in previous years was published by Porcel et al. [13]. Porcel et al. reported that in their study, which evaluated more than 3000 patients admitted to surgical and medical facilities over a period of approximately 20 years, malignancies (27%), heart failure (21%), and pleural infections (19%) were among the three most common causes. In the study conducted by Arnold et al. in the United Kingdom, in which they included 921 patients over an 8-year period, it was found that more than half of the patients (56%) were malignant [3]. In both series, lung cancer was the main cause of malignant pleural effusion. While breast cancer was the second most common cause in the Spanish study, mesothelioma was the second most common cause in the UK-based study. Contrary to the results of the above-mentioned studies, in a South Korean study investigating idiopathic pleural effusions, 25% of 2470 patients evaluated at a university hospital over an 8-year period were due to pleural infection, 22% to transudative and 16% to tuberculosis [14]. Porcel et al. reported the tuberculous pleural effusion rate as 9% [13].

Most of the centers from which we recruited cases of exudative pleural effusions for this study were pulmonary departments. Consistent with the literature, the most common causes of exudative pleural effusions in our study were malignant pleural effusions and infectious effusions [3, 13]. In our study, paramalignant effusions (~ 10%) were the third most common pathology, followed by tuberculous pleurisy with a rate of about 6%. Among malignant effusions, lung carcinoma ranked first in agreement with the literature. The second most common cause of malignant pleural effusion was mesothelioma which is in line with data published by Arnold et al. [3]. In a recent study that examined geographic patterns and temporal trends in the incidence of lung cancer between 1978 and 2012 in 43 countries, Turkey was reported as the country with the highest incidence of lung cancer in men, with an incidence of ~ 70/100,000 [15]. In our country, environmental asbestos exposure in rural areas is also a well-known problem, and the standardized incidence rate of mesothelioma in exposed areas was found to be 79/100,000 [16]. It is therefore to be expected that lung cancer accounted for one-fifth of all effusions in our study, paramalignant effusions ranked fourth among all effusions, and mesothelioma ranked second among malignant effusions. It is encouraging that TB pleurisy is not as common as expected in our country.

Fig. 2 **A** Etiology of benign pleural effusion. **B** Etiology of malignant pleural effusion



In our study, the criteria of Light et al. were used to distinguish transudate from exudate pleural effusion [2]. It is well-known that these criteria may lead to false exudate results, especially in patients with heart failure and on diuretic therapy [17, 18]. Also, the protein and/or albumin gradient often does not solve the problem. Despite the use of the albumin and protein gradient in addition to the criteria of Light et al. in our study, the cause of pleural effusion was found to be chronic heart failure and renal insufficiency in about 5% of patients as a result of the examinations and follow-up. The number of these patients is indeed considerable. Distinguishing patients with benign pleural effusions who should not be investigated further is as important as

diagnosing patients with malignant pleural effusions without delay. Further investigation of pleural effusion may lead to unfavorable results in patients who are elderly, have many comorbidities, and are on multiple medications, including antiaggregant and anticoagulants. Indeed, Walker et al. have shown that this group of patients had a mortality rate similar to malignant pleural effusions. The 1-year mortality rates of patients with pleural effusion due to heart failure and renal failure are 50% and 46%, respectively [19].

We demonstrated that younger patients, men, patients with mild pleural effusion, and serous pleural effusion had a higher probability of benign pleural effusion in multivariate logistic regression analysis. The proportion of pleural

Table 2 Comparison of the characteristics of malignant and benign pleural effusions

Variables	Malignant pleural effusions	Benign pleural effusions	<i>p</i>
Age, year ($X \pm SD$)	66.2 $\pm$ 12.4	59.4 $\pm$ 17.4	< 0.001
Sex, <i>n</i> (%)			
Male	190 (35.8)	341 (64.2)	0.030
Female	108 (43.9)	138 (56.1)	
Size, <i>n</i> (%)			
Mild	82 (28.2)	209 (71.8)	< 0.001
Moderate	129 (39.7)	196 (60.3)	
Massive	87 (54.0)	74 (46.0)	
Laterality, <i>n</i> (%)			
Right	174 (40.3)	258 (59.7)	0.271
Left	111 (37.0)	189 (63.0)	
Bilateral	13 (28.9)	32 (71.1)	
Macroscopic appearance, <i>n</i> (%)			
Serous	140 (32.2)	295 (67.8)	< 0.001
Serosanguineous	106 (51.2)	101 (48.8)	
Hemorrhagic	47 (50.5)	46 (49.5)	
Whitish (pus or milky)	5 (11.9)	37 (88.1)	

SD standard deviation

effusions with no specific diagnosis, not recurring and classified as benign after 1-year follow-up was 5.5% in the current study. Detection of a malignant diagnosis, particularly mesothelioma, after the initial diagnostic workup is important to improve the outcome of the patient. It is recommended that further diagnostic procedures be performed immediately in patients with risk factors such as a history of asbestos exposure and pain [6, 7].

Previous studies have shown that the diagnostic sensitivity of cytology was about 60% [10, 11]. However, in the recent study by Arnold et al. the overall diagnostic sensitivity of pleural effusion cytology in diagnosing malignant disease was reported to be 46% [3]. Despite improvements in laboratory testing and the use of immunohistochemical staining, the primary origin of malignant pleural effusion

appears to be the most important factor affecting the diagnostic sensitivity of cytology. Gynecological malignancies, breast cancer, cancers of the gastrointestinal tract, and lung cancer are malignancies that are most likely to be diagnosed by cytology [3, 13]. The diagnostic sensitivity of pleural effusion cytology in these tumors is more than 60%. On the other hand, mesothelioma, hematologic malignancies, and sarcomas in particular are among the malignancies that are difficult to diagnose with cytology. Although the diagnostic sensitivity of cytology for mesothelioma was considered high in some centers [20], it is usually less than 30%. Arnold et al. reported that the low diagnostic sensitivity of cytology was due to the fact that approximately 30% of patients in their series were diagnosed with mesothelioma. They speculated that the sensitivity of cytology in their series could have been increased to 55% if they had artificially lowered the prevalence of mesothelioma to a level equivalent to that of a typical European center (~ 10% of all malignant effusions) [3].

The performance of cytologic analysis of pleural effusion in the current study was consistent with previous studies. In our study, the diagnostic sensitivity of cytology in patients with malignant pleural effusions was 59.5%. When considering the underlying malignant diseases, it was found that the highest diagnostic sensitivity was for breast cancer (87%), followed by gynecological malignancies (83%), cancers of the gastrointestinal tract (67%), and lung cancer (62%). This rate was 54% in patients with hematological malignancies and 18% in mesothelioma. This low diagnostic rate in mesothelioma may be due in part to the fact that pathologists still want to see the pleural invasion. The diagnostic sensitivity of cytology was 84% for malignancies whose primary site could not be determined. Molecular analysis with next generation sequencing may be helpful in patients with malignant pleural effusion of unknown etiology.

As expected, the diagnostic sensitivity of image-guided pleural biopsy and thoracoscopic biopsies was quite high in our study. When image-guided pleural biopsy was combined with cytology, the diagnostic sensitivity reached 90%. Similarly, the diagnostic sensitivity of thoracoscopic biopsy was more than 90%. In contrast, the diagnostic sensitivity

Table 3 Sensitivity, specificity and accuracy of diagnostic procedures to detect malignant pleural effusion

Procedures	Sensitivity, % (CI)	Specificity, % (CI)	Accuracy, % (CI)
Cytology	59.5 (53.6–65.1)	100.0 (99.2–100.0)	84.3 (81.5–86.8)
Blind closed pleural biopsy	50.0 (27.2–72.8)	100.0 (86.8–100.0)	78.3 (63.6–89.1)
Image-guided pleural biopsy	86.4 (72.6–94.8)	100.0 (76.8–100.0)	89.7 (78.8–96.1)
Cytology <i>plus</i> Blind closed pleural biopsy	54.5 (32.2–75.6)	100.0 (88.1–100.0)	80.4 (66.9–90.2)
Cytology <i>plus</i> Image-guided pleural biopsy	90.9 (78.3–97.5)	100.0 (76.8–100.0)	93.1 (83.3–98.1)
Medical thoracoscopy or video-assisted thoracoscopic surgery	94.3 (80.8–99.3)	100.0 (93.9–100.0)	97.9 (92.5–99.7)

CI confidence interval

Fig. 3 Forest plot showing the results of multivariate logistic regression analysis to distinguish between malignant and benign pleural effusions. *Mild versus moderate; **Mild versus massive

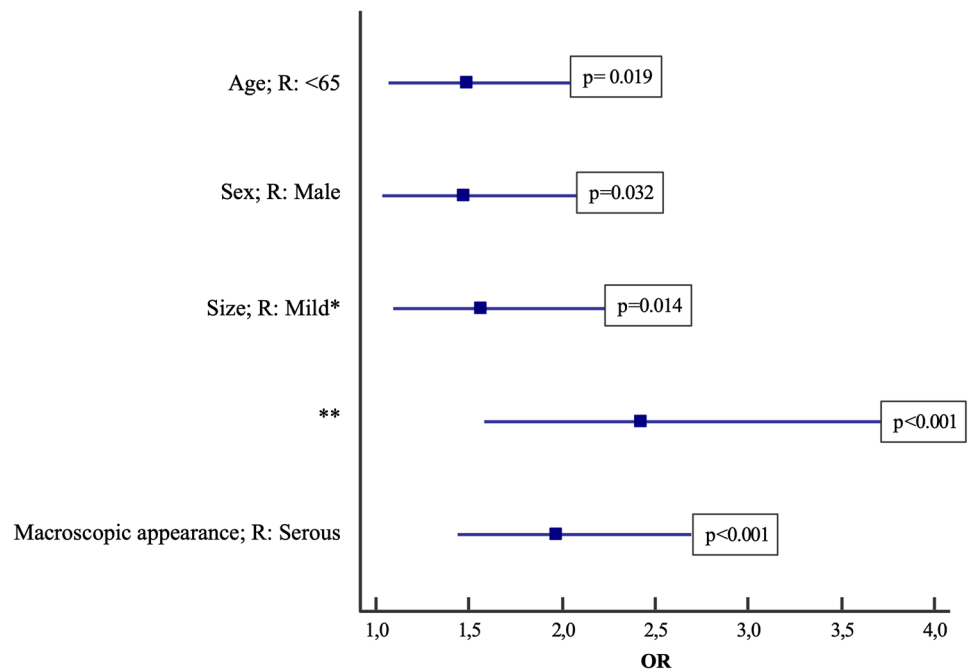


Table 4 Diagnostic sensitivity of cytology in patients with malignant pleural effusion

Diagnosis	Diagnostic cytology/n*	Diagnostic sensitivity, %
Mesothelioma	6/33	18.2
Lung cancer	95/153	62.1
Gastrointestinal	12/18	66.7
Breast	13/15	86.7
Hematological	7/13	53.8
Gynecological	10/12	83.3
Urological	3/8	37.5
Sarcoma	1/5	20.0
Ear–nose–throat	0/3	0
Unknown malignancy	26/31	83.9

*Cytology performed

of blind closed pleural biopsy was only 50%. On the other hand, blind pleural biopsy failed to obtain adequate tissue in 10% of patients. Clearly, sufficient tissue is needed to perform molecular testing for targeted therapies in lung cancer and many other cancers. Therefore, we would like to reiterate that blind closed pleural biopsies should not be performed unless there is a strong suspicion of tuberculosis in centers with limited resources. This is the first study to combine the diagnostic sensitivity of image-guided pleural biopsy with cytology. In patients with undiagnosed pleural effusion, the majority of patients can be diagnosed by following the algorithms and guidelines in the diagnostic approach [9–11].

The strengths of this multicenter study are that it was conducted in the 14 tertiary care centers and that the final diagnosis was made by diagnostic workup and close follow-up of patients for at least one year. We think that after the first guideline on pleural diseases published in 2016 [10], a standard of care for patients with pleural effusion has been achieved in our country. The results of our study are important as they show the distribution and management of patients with undiagnosed pleural effusion in routine practice of pulmonary departments.

The main limitation of the study was the limited number of variables in the database. If a larger database with more variables had been recorded, suggestions could have been made regarding which patients should undergo further invasive procedures after cytological workup. Differentiation of benign disease is as important as detection of malignant disease to avoid unnecessary interventions and their complications.

Conclusion

This study, which included patients with exudative pleural effusion managed according to the guidelines, showed that malignant pleural effusions ranked first, followed by infections and paramalignant effusions, and that the diagnostic success of cytology in patients with malignant pleural effusions could reach 60%. Diagnostic success reached 90% when cytology and image-guided pleural biopsy were combined. To avoid unnecessary interventions and the risk of complications, the development of criteria to distinguish

patients with benign pleural effusions is at least as important as the determination of malignant ones. Further studies on this topic are required.

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Declarations

Conflict of interest Authors declare that they have no conflict of interest.

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