

Pleural Effusion in Adults: an Updated and Integrated Diagnostic Approach

Derrame pleural en el adulto: enfoque diagnóstico integrado y actualizado

Alejandro E. Chale-de la Cruz^{1,✉}, Lenin D. Valencia-Pérez^{1,✉}, Josmar S. Hernández-Montero^{1,✉}, Sergio Quiroz-Gómez^{1,✉}

¹Academic Division of Health Sciences, Universidad Juárez Autónoma de Tabasco, Tabasco, Villahermosa, Mexico

Received: 06/25/2026

Accepted: 09/10/2026

Correspondence

Alejandro Ernesto Chale-de la Cruz. E-mail:
ernestochalecc@gmail.com

ABSTRACT

Pleural effusion is the pathological accumulation of fluid in the pleural space secondary to multiple etiologies. The diagnostic approach has evolved toward an integrated strategy combining clinical evaluation, imaging studies, and pleural fluid analysis. Light's criteria remain the standard for differentiating transudates from exudates, although they present limitations in conditions such as heart failure treated with diuretics, where false exudates may occur, requiring the use of gradients or biomarkers such as NT-proBNP. Thoracic ultrasound has assumed a central role by improving diagnostic accuracy and the safety of thoracentesis. Following initial classification, the evaluation of exudates involves differentiating infectious, tuberculous, and malignant etiologies, guiding diagnostic escalation to molecular testing or pleural biopsy in complex cases. This review provides a practical and structured evidence-based update for clinicians

Keywords: pleural effusion thoracentesis diagnostic criteria treatment
pleural exudate

RESUMEN

El derrame pleural es la acumulación patológica de líquido en el espacio pleural secundaria a múltiples etiologías. Su abordaje diagnóstico ha evolucionado hacia un enfoque integrado que combina la evaluación clínica, los estudios de imagen y el análisis del líquido pleural. Los criterios de Light continúan siendo el estándar para diferenciar trasudados de exudados, aunque presentan limitaciones en contextos como la insuficiencia cardíaca tratada con diuréticos, donde pueden generarse falsos exudados que requieren el uso de gradientes o marcadores, como el NT-proBNP. La ecografía torácica ha adquirido un papel central al mejorar la precisión diagnóstica y la seguridad de la toracocentesis. Tras la clasificación inicial, el estudio de exudados abarca la diferenciación de etiologías infecciosas,

Rev Am Med Resp 2026;26:122-134. <https://doi.org/10.56538/ramr.IEHE2929>



<https://creativecommons.org/licenses/by-nc-sa/4.0/>

tuberculosas y neoplásicas, y guía la escalación diagnóstica hacia pruebas moleculares o biopsia pleural en casos complejos. Esta revisión proporciona una actualización práctica y estructurada basada en la evidencia para el clínico.

Palabras clave: derrame pleura toracocentesis criterios diagnósticos tratamiento exudado pleural

INTRODUCTION

Pleural effusion (PE) is a common clinical manifestation characterized by the pathological accumulation of fluid in the pleural space, resulting from an imbalance between its formation and reabsorption. This condition reflects a wide spectrum of underlying processes and may impair respiratory mechanics and gas exchange. Clinically, PE poses a diagnostic challenge due to its multifactorial etiology; classification as transudates or exudates is fundamental to guiding the diagnostic approach. Its high incidence makes it a frequent reason for evaluation in internal medicine and pulmonology. Accordingly, this review aims to synthesize current evidence on the diagnostic and therapeutic management of PE, with emphasis on aspects of greatest relevance to clinical practice.

DEFINITION AND PATHOPHYSIOLOGY

PE is defined as the pathological accumulation of fluid in the pleural space resulting from an imbalance between its formation and reabsorption.^{1,2} Under physiological conditions, the pleural space contains a minimal volume of low-protein fluid, maintained by a dynamic equilibrium between capillary filtration and lymphatic drainage, regulated by Starling forces. The parietal pleura is the primary site of fluid production owing to its higher hydrostatic pressure derived from systemic circulation.^{3,4} The pleural mesothelium is a metabolically active structure involved in transcellular transport, immune response, and inflammation, playing a central role in pleural homeostasis.^{4,5}

PE develops when this equilibrium is disrupted, whether due to increased hydrostatic pressure, decreased oncotic pressure, increased vascular permeability, or impaired lymphatic drainage. From a pathophysiological standpoint, transudates arise from systemic alterations without direct pleural involvement, whereas exudates reflect inflamma-

tory, infectious, or neoplastic processes associated with increased vascular permeability. In the latter, activation of mesothelial and inflammatory cells induces the release of cytokines and mediators that perpetuate pleural barrier dysfunction. Impairment of lymphatic drainage, particularly in neoplastic processes, further contributes to fluid accumulation.¹ Functionally speaking, PE alters respiratory mechanics by restricting lung expansion and impairing diaphragmatic function, thereby increasing the work of breathing and leading to dyspnea, irrespective of the effusion volume.⁶ Thus, PE should be understood as the manifestation of an integrated disruption of pleural homeostasis, in which hemodynamic, inflammatory, and lymphatic mechanisms converge with direct impact on the respiratory function.

EPIDEMIOLOGY AND ETIOLOGY

PE is a common entity with significant clinical impact, particularly among hospitalized patients and those with chronic diseases. Its annual incidence is estimated at approximately 350-360 cases per 100,000 inhabitants, with nearly 1.5 million cases occurring annually in the United States. Its clinical relevance stems from its association with increased morbidity and mortality, particularly in patients with heart failure (HF), neoplasms, and pulmonary infections.^{1,6,7}

From an etiologic standpoint, PE is multifactorial, although a limited number of conditions account for most cases. HF, malignancies, pneumonia, and tuberculosis account for approximately 75% of etiologies.⁸ The classification of pleural effusions as transudates or exudates reflects both the underlying pathophysiologic mechanism and the biochemical characteristics of pleural fluid (PF). Transudative effusions are associated with systemic alterations in hydrostatic or oncotic pressure, with HF being the most common cause.^{9,10} In contrast, exudative effusions result from local processes that induce pleural inflammation

or tissue damage, including infection, neoplasms, pulmonary embolism, and autoimmune diseases. Less common etiologies include rheumatologic diseases, chylothorax, pseudochylothorax, pancreatitis, and drug-induced reactions, which should be considered in specific clinical contexts.¹¹

The coexistence of multiple etiologies may complicate diagnostic interpretation. In this context, the Contarini syndrome illustrates the etiologic complexity, with effusions of distinct origins occurring in each hemithorax.¹²

CLASSIFICATION OF PLEURAL EFFUSION: LIGHT CRITERIA AND THEIR LIMITATIONS

Differentiating between a transudate and an exudate is the first step in the diagnostic evaluation of PE. The criteria introduced by Richard W. Light in 1972 remain the standard approach for this distinction because of their high sensitivity (98%) and adequate specificity (83%).¹³ These criteria are based on comparisons of protein and lactate dehydrogenase (LDH) levels in PF and serum.

A PE is classified as an exudate if at least 1 of the following criteria is met: a pleural fluid-to-serum protein ratio ≥ 0.5 , a pleural fluid-to-serum LDH ratio ≥ 0.6 , or a pleural fluid LDH level $\geq$ two-thirds the upper limit of normal for serum LDH. If none of these criteria is met, the effusion is classified as a transudate.

Limitations of the Light criteria

Despite their high sensitivity, the Light criteria have limitations in certain clinical settings. Up to 29% of patients with HF and approximately 18% of those with hepatic hydrothorax may be misclassified as exudates, when their effusions are actually transudative. These cases are referred to as “pseudo-exudates,” that is, transudates that meet the criteria for an exudate, as a result of diuretic therapy.¹⁴⁻¹⁶ Diuretic therapy is an important contributor to this discrepancy because it can increase the concentrations of protein and LDH in PF, thereby altering its biochemical profile and resulting in misclassification.

Strategies to improve classification

To reduce these diagnostic errors, several complementary approaches have been proposed:

- **Absolute protein concentration in PF:** Values > 3.1 g/dL suggest an exudate, whereas values < 3.1 g/dL are more consistent with a transuda-

te. This criterion allows correct reclassification of approximately 55% of cases in HF and 61% in hepatic hydrothorax.¹⁷

- **Serum-pleural fluid albumin gradient:** A gradient > 1.2 g/dL indicates a transudate, whereas values < 1.2 g/dL suggest an exudate. This method has been shown to improve diagnostic classification, correctly reclassifying approximately 78% of patients with HF and 77% of those with hepatic hydrothorax.¹⁸

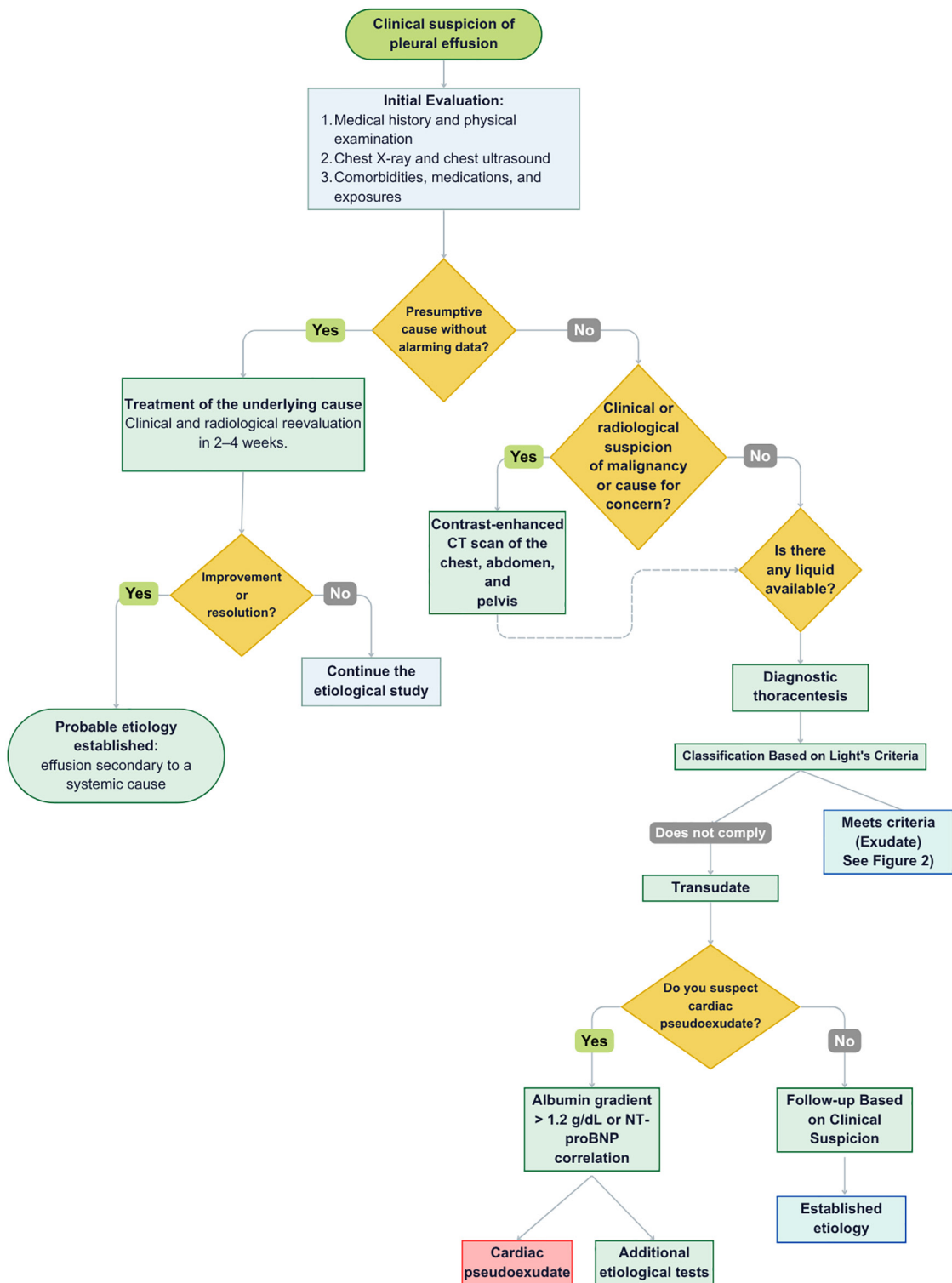
CLINICAL ASSESSMENT

A detailed medical history and physical examination constitute the initial cornerstone for guiding the diagnostic evaluation of PE. It is essential to assess the patient's general condition and perform a focused anamnesis aimed at identifying: prior diseases, medication use (particularly methotrexate, amiodarone, phenytoin, and nitrofurantoin), smoking history, and occupational exposures (notably current or past asbestos exposure).^{12,13} Clinical presentation is variable. Some patients present with manifestations derived from the underlying disease; others develop symptoms directly attributable to the PE; and some patients are asymptomatic, with the effusion being an incidental finding on imaging studies. The most frequent symptoms of PE include dyspnea, pleuritic chest pain, and dry cough. In the setting of malignant involvement, pain may be dull.⁵ On physical examination, PE is associated with characteristic signs, such as decreased or absent tactile fremitus, percussion dullness, egophony, and whispered pectoriloquy. A pleural friction rub may be present in early stages of the inflammatory process, before fluid accumulation separates the pleural surfaces.¹⁹ Additionally, findings attributable to the underlying disease may be identified, such as signs of heart failure, chronic liver disease, or neoplasms.¹⁶ (Figures 1 and 2)

DIAGNOSIS

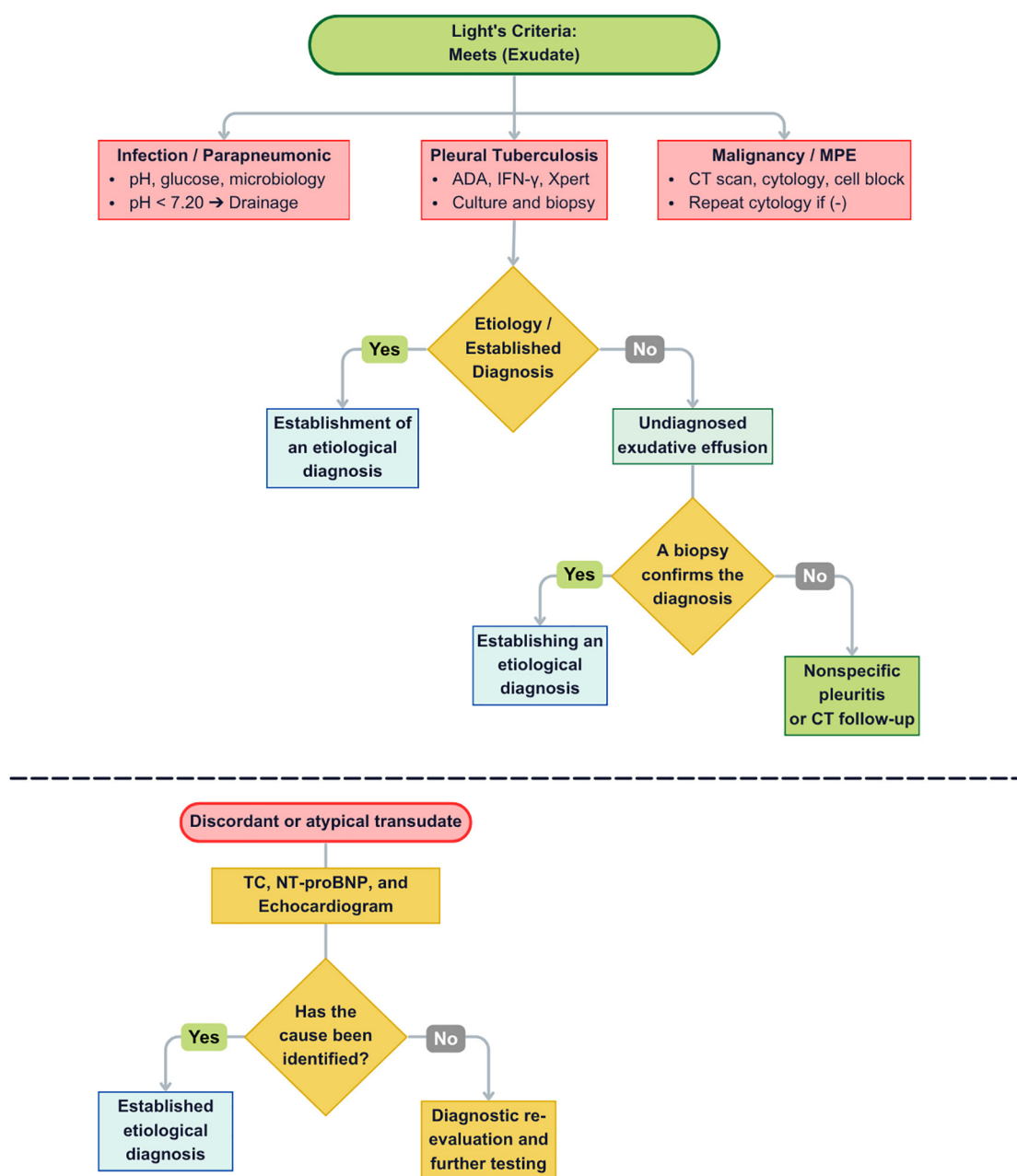
Chest radiograph: Chest radiography is the initial imaging test for detecting pleural effusion because of its widespread availability and rapid acquisition. In the posteroanterior view, effusion can be detected when at least 200 mL of pleural fluid are present, a volume sufficient to blunt the lateral costophrenic angle. On the lateral view, approximately 50 mL of fluid can blunt the posterior

Figure 1. Algorithm for initial evaluation, treatment response, and differentiation of transudates and pseudoexudates in adults with pleural effusion



CT: computed tomography; HF: heart failure; NT-proBNP: N-terminal pro-B-type natriuretic peptide; TUS: thoracic ultrasound

Figure 2. Algorithm for the etiologic characterization of pleural exudates, evaluation of discordant transudates, and escalation to invasive procedures.



ADA: adenosine deaminase; CT: computed tomography; IFN-γ: interferon gamma; MPE: malignant pleural effusion; ; NT-proBNP: N-terminal pro-B-type natriuretic peptide

costophrenic angle.^{20,21} The effusion may be free or loculated, typical or atypical, unilateral or bilateral, and may be located within the fissures, which can sometimes simulate a pulmonary mass.^{22,23}

Thoracic ultrasound (TUS): This is the most sensitive noninvasive method for detecting PE; it is widely available, and does not use ionizing

radiation. The literature reports an overall sensitivity of 94.5% and a specificity of 97.9% for its detection.⁵ Ultrasound can visualize as little as 5 mL of fluid¹⁶, and is useful for identifying and confirming the presence of PF, differentiating it from other lesions such as pleural thickening or masses, estimating its volume, detecting septations, and

guiding procedures such as thoracentesis. In free PE, typical ultrasound findings include a subcostal echogenic line corresponding to the parietal pleura, followed by an anechoic zone corresponding to the fluid and a deeper hyperechoic line corresponding to the visceral pleura and lung; these findings constitute the “quad sign” or grid sign.²⁴ Ultrasound is recommended before any thoracentesis.

Chest CT scan: CT provides a comprehensive assessment of the pleural space, lung parenchyma, and mediastinum, and is essential for characterizing PE and planning image-guided procedures. CT should preferably be performed before complete drainage of the pleural effusion, as the presence of pleural fluid facilitates the identification of pleural and parenchymal abnormalities. Contrast-enhanced CT improves the detection of pleural thickening, nodularity, and mediastinal pleural involvement, which raise suspicion for malignant pleural effusion (MPE). According to the British Thoracic Society, follow-up CT should be considered in patients with pleural infection who have concerning signs, to exclude an underlying neoplasm.²³ Although CT findings have high specificity for the diagnosis of MPE, their sensitivity is limited, and a negative CT does not definitively exclude malignancy. In this context, scoring systems based on CT findings have been proposed to improve the differentiation between benign and malignant pleural etiologies (Table I).

Positron Emission Tomography/Computed Tomography (PET-CT): PET-CT has been proposed as an imaging technique for differentiating benign from malignant pleural disease, with reported sensitivity ranging from 86% to 95% and specificity ranging from 61% to 82%.¹⁶ However, false-positive results may occur in inflammatory or infectious conditions, including pleural infection, uremic pleuritis, previous pleurodesis, and even epithelial mesothelioma. PET-CT enables visualization of metabolically active tissue through uptake of 18F-fluorodeoxyglucose.

Thoracentesis: Thoracentesis is the procedure of choice for the initial diagnosis and treatment of PE. Currently, image-guided thoracentesis is recommended because it improves procedural accuracy and substantially reduces the risk of complications. It is indicated for effusions of undetermined etiology, particularly when they are unilateral, newly diagnosed, or unresponsive to

treatment of the underlying condition. In patients with a clear suspicion of transudative effusion, such as those with HF and bilateral effusions that respond to treatment, thoracentesis may initially be deferred.²³

In addition to its diagnostic utility, thoracentesis has a therapeutic role in relieving dyspnea in patients with large pleural effusions. The volume drained should be limited to approximately 1.5 L per procedure to reduce the risk of re-expansion pulmonary edema. Complications are uncommon when thoracentesis is performed with ultrasound guidance, with pneumothorax being the most common. Other complications include bleeding, pain at the puncture site, and vasovagal reactions.²⁵ Routine postprocedure chest radiography is not recommended, except in symptomatic patients or when a complication is suspected.

Pleural fluid analysis: PF analysis includes macroscopic, biochemical, cytologic, and microbiologic evaluation, and is a cornerstone of the etiologic assessment of PE.^{18,19,23} Macroscopic examination provides an initial diagnostic indication based on characteristics such as fluid color, clarity, and consistency, whose correlation with specific etiologies is summarized in Table 2.

Biochemical analysis is essential for clinical decision-making.

- **Glucose:** Pleural fluid glucose generally reflects serum glucose levels. Values <55 mg/dL are associated with empyema, tuberculosis, neoplasms, and rheumatoid arthritis.
- **LDH:** Elevated pleural fluid LDH levels are characteristic of exudates, and levels >1,000 IU/L suggest marked pleural inflammation.¹⁸
- **pH:** Pleural fluid pH is a key parameter. In the setting of a parapneumonic effusion, a pleural fluid pH <7.20 indicates the need for pleural drainage and is associated with greater clinical severity.
- **Amylase:** Pleural fluid amylase may be elevated in pancreatitis, esophageal rupture, and certain neoplasms, and can be useful in selected clinical settings.

Microbiologic evaluation: This includes Gram staining and culture, and is essential for confirming an infectious etiology.^{10,26,27}

Cytologic study: Pleural fluid cytology is the initial diagnostic test when MPE is suspected, with an overall reported sensitivity ranging from 49% to 91%, whereas specificity is approximately 99% to

Table 1. Chest CT Evaluation of Pleural Effusion

Parameter	Score
Unilateral pleural effusion	1
Pleural lesions > 1 cm	1
Hepatic metastasis	1
Lung mass > 1 cm	1
Pericardial effusion	1
Absence of loculations	1
Absence of cardiomegaly	1
Mediastinal lymphadenopathy	1
Pleural thickening > 1 cm	1
Abdominal disease or mass	1

Note: A score of ≥ 7 out of 10 on this scale indicates malignancy, with a sensitivity of 88% and specificity of 94%.²⁷

Table 2. Gross Appearance of Pleural Fluid and Probable Etiology

Parameter	Finding	Probable etiology
Color	Clear yellow (straw-colored)	Transudate
	Yellow-green	Rheumatoid pleural effusion
	Bloody (reddish)	Neoplasm, trauma, pulmonary embolism, traumatic thoracentesis
	Milky white	Chylothorax, empyema
	Green	Bilopleural fistula, <i>Pseudomonas aeruginosa</i> infection
	Black	<i>Aspergillus niger</i> infection
	Reddish-brown ("chocolate")	Pleuropulmonary amebiasis
Transparency / Consistency	Turbid	Infection, increased cellularity, elevated lipid content
	Viscous	Mesothelioma (high hyaluronic acid content)
Gross Content	Purulent	Empyema
	Chylous	Elevated triglyceride level (≥ 110 mg/dL)
	Pseudochylous	Elevated cholesterol level (chronic effusion)
Odor	Foul-smelling	Anaerobic empyema
Coagulability	Spontaneous clotting	Presence of fibrin (inflammatory exudate)

Note: Adapted from multiple sources, including Oyonarte W. Enfoque diagnóstico en el paciente con derrame pleural. Rev Med Clin Las Condes. 2024;35(3-4), and Ruiz Reyes G, Ruiz Argüelles A. Fundamentos de interpretación clínica de los exámenes de laboratorio. 3rd ed. 2017.

100%. Thus, a positive result is virtually diagnostic, whereas a negative result does not exclude malignancy.^{6,28,29} The diagnostic yield of cytology varies considerably according to tumor histology, being highest for adenocarcinoma (79%-91%), intermediate for hematologic neoplasms (approximately

40%), and substantially lower for squamous cell carcinoma (approximately 24%) and mesothelioma (6%-33%). In the latter settings, early progression to definitive diagnostic methods is recommended.²⁸⁻³⁰ Pleural thickening on CT is associated with a higher likelihood of false-negative cytology

results.³¹ Combining cytology with biochemical markers, such as carcinoembryonic antigen (CEA) or C-reactive protein (CRP) may improve overall diagnostic yield.³² Regarding the number of samples, the first thoracentesis has a diagnostic yield of approximately 65%; a second sample provides an additional yield of 25% to 28%, whereas a third one provides only marginal additional benefit (<5%). Therefore, examination of more than 2 specimens is generally not recommended when the initial cytologic examinations are negative.^{15,21,33,34} Increasing the volume of pleural fluid submitted for cytologic examination beyond 50 mL does not appear to improve diagnostic yield. Pleural fluid should be processed by both direct smear and cell block preparation to optimize diagnostic sensitivity.

Cellular analysis may also provide clues to the underlying etiology: a neutrophil-predominant effusion suggests acute processes (e.g., infection, pancreatitis, or pulmonary embolism), whereas a lymphocyte-predominant effusion is associated with chronic processes such as tuberculosis, neoplasms, or autoimmune disease.^{14,15}

Pleural biopsy: When pleural fluid cytology is negative after 1 or 2 thoracenteses and clinical or radiologic suspicion of malignancy persists, pleural biopsy is indicated.^{6,15,21,33} The choice of the method depends on the findings on chest CT:

- When pleural thickening or nodules/masses are present, image-guided percutaneous biopsy (CT or ultrasonography) may be the initial approach, with a diagnostic yield of 88% to 94%.
- In the absence of pleural thickening, thoracoscopy (medical or surgical) is preferred, with a higher diagnostic yield of 94% to 100%.⁴³ Thoracoscopy, particularly video-assisted thoracoscopic surgery (VATS), is considered the reference standard for the diagnosis of DPM and also allows pleurodesis to be performed during the same procedure.³⁰

When mesothelioma is specifically suspected, given the low sensitivity of cytology, earlier progression to definitive diagnostic procedures is recommended.^{29,30}

Pleural tuberculosis

The diagnosis of pleural tuberculosis requires an integrated approach combining biochemical, immunologic, microbiologic, and histopatholo-

gic tests, because no single diagnostic method achieves optimal yield. Clinical suspicion and epidemiologic context are essential for the correct interpretation of results.

- **Biochemical and immunologic tests:** Pleural fluid adenosine deaminase (ADA) and interferon- γ (IFN- γ) are among the most useful tools in clinical practice because of their high diagnostic accuracy and relative availability. At a cutoff point of approximately 40 IU/L, ADA has demonstrated good diagnostic accuracy in meta-analyses, although its positive predictive value depends strongly on the local prevalence of tuberculosis; therefore, results should be interpreted within the appropriate epidemiologic context.^{35,36} The accuracy of unstimulated IFN- γ is slightly higher than that of ADA and, when available, the 2 tests may be used in combination to increase diagnostic confidence, particularly in cases in which the diagnosis remains uncertain or in settings with a low prevalence of disease.³⁷
- **Microbiologic and molecular tests:** Pleural fluid culture has limited sensitivity because tuberculous pleural effusions are typically paucibacillary, but it remains useful for microbiologic confirmation and antituberculous drug-susceptibility testing.³⁸ The molecular assay Xpert MTB/RIF Ultra has greater sensitivity than its predecessor, conventional Xpert MTB/RIF, and enables rapid detection of rifampicin resistance. However, its moderate sensitivity precludes its use as a rule-out test: a negative result does not exclude pleural tuberculosis. Therefore, Xpert MTB/RIF Ultra should be used as an adjunct to, rather than a substitute for, biochemical testing and culture.³⁹
- **Pleural biopsy and a practical approach:** Pleural biopsy, preferably image-guided or performed by medical thoracoscopy, remains indicated when diagnostic uncertainty persists after conventional pleural fluid studies have been completed.^{36,37} From a practical standpoint, in settings with a high prevalence of tuberculosis or when the pretest probability is high, an elevated pleural fluid ADA level combined with lymphocyte predominance may provide strong support for the diagnosis and, in selected clinical contexts, may allow antituberculous treatment to be initiated without

immediate biopsy.^{35,36} This approach should be individualized according to the epidemiologic setting, clinical presentation, pretest probability, and availability of microbiologic or histopathologic testing. IFN- γ and Xpert MTB/RIF Ultra may be used as adjunctive tests to increase diagnostic confidence, whereas pleural biopsy should be considered when diagnostic uncertainty persists, the pretest probability is low, or histopathologic or microbiologic confirmation is required.

TREATMENT

Treatment of pleural effusion is directed at identifying and managing the underlying cause. Pleural drainage is indicated in symptomatic patients, whereas in asymptomatic patients it is performed primarily for diagnostic purposes, except when infection or hemorrhage is suspected.¹ For pleural infections, management includes antibiotic therapy, pleural drainage, and, in selected cases, fibrinolytic therapy or surgery. Empiric antibiotic therapy should be initiated promptly, and it should subsequently be tailored according to microbiologic results and the clinical context.⁴⁰ In community-acquired infections, antibiotic therapy should provide coverage for aerobic and anaerobic bacteria, generally with a β -lactam/ β -lactamase inhibitor combination or a regimen that includes metronidazole. In hospital-acquired infections, broader-spectrum coverage is required, including coverage for resistant organisms such as methicillin-resistant *Staphylococcus aureus*.⁴¹ Pleural drainage is a cornerstone of treatment for complicated infection and empyema and is preferably performed using a small-bore chest tube. It can be supplemented with intrapleural fibrinolytic therapy to improve drainage, particularly in the presence of loculations.^{42,43} Repeated therapeutic thoracentesis may be considered in selected cases, whereas surgery is generally reserved for patients with refractory disease or complications. For transudative pleural effusions, treatment is directed at the underlying disease, with diuretics commonly used when appropriate.

FOLLOW-UP

Follow-up of PE depends on its underlying etiology and clinical course. Transudative effusions that respond to treatment of the underlying disease do not require invasive evaluation; however, failure to resolve despite optimal management should prompt reconsideration of the diagnosis and referral to a specialist. Simple parapneumonic effusions can be managed with antibiotic therapy and clinical surveillance, whereas complicated effusions and empyema generally require urgent pleural drainage and, in selected cases, an advanced intervention strategy.^{8,18,19,23} MPE require an approach focused on symptom control and management of recurrence. Therapeutic thoracentesis can be used to assess symptomatic response, and in patients with recurrent effusions, strategies such as pleurodesis or placement of an indwelling pleural catheter should be considered.^{18,27,44} Routine chest radiography after thoracentesis is not recommended unless the patient develops symptoms or if there is clinical suspicion of complications.^{20,23} Referral to a specialist is indicated when an exudate is suspected, the diagnosis remains uncertain, the effusion is complicated or malignant, or assistance with diagnostic procedures is required.

DISCUSSION

The diagnostic approach to PE has evolved from a rigid algorithm-based model toward a more comprehensive, context-driven approach. Although Light criteria are still considered the cornerstone of the initial classification of pleural effusions, their isolated interpretation has limitations, particularly in patients with HF receiving diuretic therapy, in whom the presence of “pseudoexudates” may lead to diagnostic errors. The incorporation of additional parameters and their clinical integration can improve diagnostic accuracy in these settings. TUS has assumed a central role in the evaluation of PE and in the safe performance of thoracentesis. Image-guided thoracentesis has progressively replaced blind procedures and is associated with a lower risk of

complications. This represents one of the major recent changes in clinical practice.

Similarly, PF analysis has shifted toward a targeted approach in which the selection of tests is guided by clinical suspicion, thereby optimizing diagnostic yield. Nevertheless, important limitations remain, including the limited sensitivity of cytology and the lack of biomarkers with sufficiently high diagnostic accuracy. Imaging techniques, including CT and PET/CT, provide complementary information for the characterization of PEs; however, they cannot definitively exclude malignancies. Cytologic or histologic evaluation therefore remains essential for standard diagnosis. The present analysis highlights the transition toward an integrated diagnostic approach in which the combination of clinical assessment, PF analysis, and imaging tools improves diagnostic accuracy,

facilitates clinical decision-making, and reduces unnecessary invasive procedures. (Table 3)

CONCLUSION

PE is a common clinical condition with various etiologies that requires a systematic diagnostic approach. Integration of clinical, biochemical, and imaging findings is essential to identify the underlying cause and guide treatment. A structured approach can optimize management and reduce associated morbidity and mortality.

Conflict of interest

Authors have no conflicts of interest to declare.

Funding

This study received no external funding.

Table 3. Comparison of Major International Guidelines for the Diagnostic and Therapeutic Management of Pleural Effusion

Appearance	BTS 2023	SEPAR 2022/2023	ERS	ATS/STS/STR 2018
Initial evaluation, imaging, and thoracentesis	Medical history and physical examination plus TUS at presentation. If aspiration is not considered safe → CT; if malignancy is suspected → CT of the chest, abdomen, and pelvis. Image-guided pleural procedures.	TUS to detect small effusions and guide the thoracentesis site; contrast-enhanced CT if malignancy is suspected.	ERS statement on benign pleural effusions in adults (2024): Integrates clinical, biochemical, and imaging findings; CT is generally used when the etiology remains undetermined.	Management of Malignant Pleural Effusions (2018): Recommends ultrasound guidance for pleural interventions; in symptomatic MPE, large-volume thoracentesis may be considered to assess the relationship between the effusion and symptoms and to evaluate lung re-expansion.
Transudate, exudate, and pseudoexudate	Light's criteria; serum NT-proBNP as an adjunct when heart failure is suspected.	Light's criteria (GRADE A1). Cardiac false exudates may be reclassified using serum-pleural fluid albumin gradients or ratios, or NT-proBNP.	ERS statement on benign pleural effusions in adults (2024): Maintains Light's criteria as the reference standard; in patients with a high probability of HF, a serum-pleural fluid albumin gradient > 1.2 g/dL and NT-proBNP may support reclassification.	Not within the scope of the guideline, which focuses specifically on MPE.
Pleural infection	If there's no pus, measure pleural fluid pH immediately. A pH ≤ 7.20 indicates high risk; pH 7.20–7.40 warrants consideration of LDH and other findings; pH ≥ 7.40 indicates a low likelihood of requiring immediate drainage.	pH is the principal marker; drainage is recommended for empyema or complicated infectious effusion with pH < 7.20, septations, or microorganisms.	ERS/ESTS statement on the management of pleural infection in adults (2023): Emphasizes a pleural fluid pH < 7.20, pus, and/or positive microbiology; glucose and LDH may support decision-making when pH is unavailable	No specific recommendations in this guideline, which focuses on MPE.

(continue)

(continuation)

Appearance	BTS 2023	SEPAR 2022/2023	ERS	ATS/STS/STR 2018
Pleural tuberculosis	ADA $\pm$ IFN- γ depending on prevalence; tissue sampling for culture and susceptibility testing is preferred..	Routine ADA testing; IFN- γ has high diagnostic accuracy but limited availability. Microbiologic or molecular identification in PF or tissue provides etiologic confirmation.	EERS/ESTS statement on pleural infection (2023): Tuberculous pleuritis is explicitly excluded from its scope, as it is considered a distinct entity from nontuberculous pleural infection.	Pleural tuberculosis is outside the scope of the ATS/STS/STR guideline on malignant pleural effusion.
Malignancy: cytology and biopsy	Cytology as the initial diagnostic test, with cell block preparation; a negative cytology result should prompt further investigation. Image-guided or thorascopic pleural biopsy; blind biopsy is not recommended.	Contrast-enhanced CT as the imaging modality of choice. Cytologic yield depends on tumor type; repeating cytology more than twice does not increase diagnostic yield. If clinical suspicion persists, pleural biopsy should be performed; thoracoscopy is the diagnostic reference standard.	ERS/EACTS statement on the management of malignant pleural effusions (2018): Cytology has variable diagnostic yield (49%–91%), with maximal yield achieved with approximately two samples; pleural biopsy remains the diagnostic standard, and thorascopic	Management of malignant pleural effusions (2018): Primarily focuses on the management of known or suspected MPE; recommends TUS for pleural procedures and large-volume thoracentesis when assessment of symptoms or lung re-expansion is needed.
Persistent undiagnosed pleural effusion	Reconsider TB, pulmonary embolism, lymphoma, IgG4-related disease, and heart failure; consider serial CT follow-up.	Proceed to image-guided pleural biopsy or thorascopy based on the suspected etiology, particularly when malignancy or TB is suspected.	ERS Statement on Benign Pleural Effusions in Adults (2024): Thorascopic biopsy represents the final diagnostic step for an unexplained exudate; following a diagnosis of nonspecific pleuritis, repeat biopsy or follow-up may be required, as no single consensus strategy has been established.	Does not provide a specific algorithm for undiagnosed pleural effusion; the guideline focuses on known or suspected MPE.

Note: The guidelines differ in scope: BTS (2023), SEPAR (2022), and ERS (2024) address pleural disease broadly, whereas ATS/STS/STR (2018) focuses exclusively on malignant pleural effusion. There is broad consensus regarding the use of TUS, Light's criteria, and pleural biopsy when suspicion persists. The main differences relate to the reclassification of pseudoexudates, biochemical criteria for pleural infection, and etiologic scope.

Abbreviations: ADA, adenosine deaminase; BTS, British Thoracic Society; MPE, malignant pleural effusion; ERS, European Respiratory Society; IFN- γ , interferon-gamma; LDH, lactate dehydrogenase; PF, pleural fluid; SEPAR, Spanish Society of Pulmonology and Thoracic Surgery; TB, tuberculosis; CT, computed tomography; TUS, thoracic ultrasonography.

REFERENCES

1. Ferreiro L, Toubes ME, Riveiro Blanco V, Valdés L. Pathophysiology of dyspnoea in pleural effusion. *Breathe*. 2025;21:250238. <https://doi.org/10.1183/20734735.0238-2025>
2. Botana Rial M, Pérez Pallarés J, Cases Viedma E, et al. Diagnosis and treatment of pleural effusion. Recommendations of the Spanish Society of Pulmonology and Thoracic Surgery. Update 2022. *Arch Bronconeumol*. 2023;59:27-35. <https://doi.org/10.1016/j.arbres.2022.09.017>
3. Sandeesh V, Ravi Kiran CV, Ushakiran P, Sulemani MD, Lakshmanakumar N. A comparative study of serum effusion albumin gradient and Light's criteria to differentiate exudative and transudative pleural effusion. *J Family Med Prim Care*. 2020;9:4847-52. https://doi.org/10.4103/jfmpc.jfmpc_321_20
4. Ferreiro L, Toubes ME, Suárez-Antelo J, Rodríguez-Núñez N, Valdés L. Clinical overview of the physiology and pathophysiology of pleural fluid movement: a narrative review. *ERJ Open Res*. 2024;10:00050-2024. <https://doi.org/10.1183/23120541.00050-2024>
5. Zaki HA, Albaroudi B, Shaban EE, Shaban A, Elgassim M, Almarri ND, et al. Advancement in pleural effusion diagnosis: a systematic review and meta-analysis of point-of-care ultrasound versus radiographic thoracic imaging. *Ultrasound J*. 2024;16: 3. <https://doi.org/10.1186/s13089-023-00356-z>

6. Feller-Kopman D, Light R. Pleural disease. *N Engl J Med*. 2018; 378:740-51. <https://doi.org/10.1056/NEJMra1403503>
7. Boddiger U, Hallifax RJ. Epidemiology: why is pleural disease becoming more common? *ERS Monogr*. 2020;2020:1-12. <https://doi.org/10.1183/2312508X.10022819>
8. Sundaralingam A, Grabczak EM, Burra P, Costa MI, George V, Harriss E, et al. ERS statement on benign pleural effusions in adults. *Eur Respir J*. 2024;64:2302307. <https://doi.org/10.1183/13993003.02307-2023>
9. Shen-Wagner J, Gamble C, MacGilvray P. Pleural effusion: diagnostic approach in adults. *Am Fam Physician*. 2023;108:464-75.
10. Ruan SY, Chuang YC, Wang JY, Lin JW, Chien JY, Huang CT, et al. Revisiting tuberculous pleurisy: pleural fluid characteristics and diagnostic yield of mycobacterial culture in an endemic area. *Thorax*. 2012;67:822-7. <https://doi.org/10.1136/thoraxjnl-2011-201363>
11. Ahmed A, Moursy A, Shoman A, Said A. Diagnostic role of lung ultrasound for pneumonia and parapneumonic pleural effusion in Respiratory Intensive Care Unit, Zagazig University Hospitals. *Zagazig Univ Med J*. 2022;28:1025-32. <https://doi.org/10.21608/zumj.2022.164100.2647>
12. Cragun WH. Pleural effusion prediction failures. *Chest*. 2002;122:1505-6. <https://doi.org/10.1378/chest.122.5.1505>
13. Light RW, MacGregor MI, Luchsinger PC, Ball WC Jr. Pleural effusions: the diagnostic separation of transudates and exudates. *Ann Intern Med*. 1972;77:507-13. <https://doi.org/10.7326/0003-4819-77-4-507>
14. Jankovicova K, Kondelkova K, Habal P, Andrys C, Krejsek J, Mandak J. TLR2 in pleural fluid is modulated by talc particles during pleurodesis. *Clin Dev Immunol*. 2012;2012:158287. <https://doi.org/10.1155/2012/158287>
15. Matuchova I, Kelbich P, Kubalik J, Hanuljakova E, Stanek I, Maly V, et al. Cytological-energy analysis of pleural effusions with predominance of neutrophils. *Ther Adv Respir Dis*. 2020;14:1753466620935772. <https://doi.org/10.1177/1753466620935772>
16. Oyonarte WM. Enfoque diagnóstico en el paciente con derrame pleural. *Rev Med Clin Las Condes*. 2024;35:299-308. <https://doi.org/10.1016/j.rmcl.2024.05.010>
17. Porcel JM. Biomarkers in the diagnosis of pleural diseases: a 2018 update. *Ther Adv Respir Dis*. 2018;12:1753466618808660. <https://doi.org/10.1177/1753466618808660>
18. Romero-Candeira S, Hernández L, Romero-Brufao S, Orts D, Fernández C, Martín C. Is it meaningful to use biochemical parameters to discriminate between transudative and exudative pleural effusions? *Chest*. 2002;122:1524-9. <https://doi.org/10.1378/chest.122.5.1524>
19. Adderley N, Goldin J, Sharma S. Pleural friction rub. En: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.
20. Sureka B, Thukral BB, Mittal MK, Mittal A, Sinha M. Radiological review of pleural tumors. *Indian J Radiol Imaging*. 2013; 23:313-20. <https://doi.org/10.4103/0971-3026.125577>
21. Feller-Kopman DJ, Reddy CB, Gould MK, Balekian AA, DeCamp MM, Diekemper RL, et al. Management of malignant pleural effusions: An official ATS/STS/STR clinical practice guideline. *Am J Respir Crit Care Med*. 2018;198:839-49. <https://doi.org/10.1164/rccm.201807-1415ST>
22. Gayen S. Malignant pleural effusion: presentation, diagnosis, and management. *Am J Med*. 2022;135:1188-92. <https://doi.org/10.1016/j.amjmed.2022.04.017>
23. Roberts ME, Rahman NM, Maskell NA, Bibby AC, Blyth KG, Corcoran JP, et al. British Thoracic Society Guideline for pleural disease. *Thorax*. 2023;78(Suppl 3): s1-42. <https://doi.org/10.1136/thorax-2022-219784>
24. Volpicelli G, Elbarbary M, Blaivas M, Lichtenstein DA, Mathis G, Kirkpatrick AW, et al. International evidence-based recommendations for point-of-care lung ultrasound. *Intensive Care Med*. 2012;38:577-91. <https://doi.org/10.1007/s00134-012-2513-4>
25. Wilcox ME, Chong CAKY, Stanbrook MB, Tricco AC, Wong C, Straus SE. Does this patient have an exudative pleural effusion?: The rational clinical examination systematic review. *JAMA*. 2014;311:2422-31. <https://doi.org/10.1001/jama.2014.5552>
26. Zhang X, Duan H, Yu Y, Ma C, Ren Z, Lei Y, et al. Differential diagnosis between benign and malignant pleural effusion with dual-energy spectral CT. *PLoS One*. 2018;13:e0193714. <https://doi.org/10.1371/journal.pone.0193714>
27. Mercer RM, Varatharajah R, Shepherd G, Lu Q, Castro-Añón O, McCracken DJ, et al. Critical analysis of the utility of initial pleural aspiration in the diagnosis and management of suspected malignant pleural effusion. *BMJ Open Respir Res*. 2020;7(1):e000701. <https://doi.org/10.1136/bmjresp-2020-000701>
28. 40. Elsheikh A, Bhatnagar M, Rahman NM. Diagnosis and management of pleural infection. *Breathe*. 2023;19:230146. <https://doi.org/10.1183/20734735.0146-2023>
29. 41. Hassan M, Gad-Allah M, El-Shaarawy B, El-Shazly AM, Daneshvar C, Sadaka AS. The Short versus Long Antibiotic Course for Pleural Infection Management (SLIM) randomised controlled open-label trial. *ERJ Open Res*. 2023;9:00635-2022. <https://doi.org/10.1183/23120541.00635-2022>

30. 42. Adhikari S, Marwah V, Choudhary R, Pandey I, Kumar TA, Malik V, et al. Intrapleural fibrinolysis with urokinase versus alteplase in complicated pleural effusions and empyema: A prospective randomized controlled trial. *Tuberc Respir Dis (Seoul)*. 2024;87:378-85. <https://doi.org/10.4046/trd.2022.0168>
31. 31. Paz DL, Bayeh B, Chauvin P, Poizeau F, Lederlin M, Kerjouan M, et al. Intrapleural use of urokinase and DNase in pleural infections managed with repeated thoracentesis: A comparative cohort study. *PLoS One*. 2021;16: e0257339. <https://doi.org/10.1371/journal.pone.0257339>
32. 44. Sharma S, Arora RD, Boster J. Malignant pleural effusion. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024-.
33. 35. Aggarwal AN, Agarwal R, Sehgal IS, Dhooria S, Prasad KT, Vaishya R. Adenosine deaminase for diagnosis of tuberculous pleural effusion: A systematic review and meta-analysis. *PLoS One*. 2019;14:e0213728. <https://doi.org/10.1371/journal.pone.0213728>
34. 36. Blakiston M, Chirila M, Morpeth S, Ristic N, Freeman JT. Diagnostic Performance of Pleural Fluid Adenosine Deaminase for Tuberculous Pleural Effusion in a Low-Incidence Setting. *J Clin Microbiol*. 2018;56:e00258-18. <https://doi.org/10.1128/JCM.00258-18>
35. 37. Aggarwal AN, Agarwal R, Sehgal IS, Dhooria S, Prasad KT, Vaishya R. Comparative accuracy of pleural fluid unstimulated interferon-gamma and adenosine deaminase for diagnosing pleural tuberculosis: A systematic review and meta-analysis. *PLoS One*. 2021;16:e0253525. <https://doi.org/10.1371/journal.pone.0253525>
36. 38. Wang G, Wang S, Yang X, et al. Accuracy of Xpert MTB/RIF Ultra for the Diagnosis of Pleural TB in a Multicenter Cohort Study. *Chest*. 2020;157:268-75. <https://doi.org/10.1016/j.chest.2019.07.027>
37. 39. Aggarwal AN, Agarwal R, Dhooria S, Prasad KT, Sehgal IS, Muthu V. Xpert MTB/RIF Ultra versus Xpert MTB/RIF for diagnosis of tuberculous pleural effusion: A systematic review and comparative meta-analysis. *PLoS One*. 2022;17:e0268483.
38. 28. Kassirian S, Allen MB, Sharma A, et al. Diagnostic sensitivity of pleural fluid cytology in malignant pleural effusions: systematic review and meta-analysis. *Thorax*. 2023;78:32-40. <https://doi.org/10.1136/thoraxjnl-2021-217959>
39. 29. Arnold DT, De Fonseca D, Perry S, Morley A, Harvey JE, Medford A, et al. Investigating unilateral pleural effusions: the role of cytology. *Eur Respir J*. 2018;52:1801254. <https://doi.org/10.1183/13993003.01254-2018>
40. 30. Shaker N, Wu D, Abid AM. Cytology of malignant pleural mesothelioma: Diagnostic criteria, WHO classification updates, and immunohistochemical staining markers diagnostic value. *Diagn Cytopathol*. 2022;50:532-37. <https://doi.org/10.1002/dc.25053>
41. 31. Pairman L, Arnold DT, Morley A, Medford ARL, Maskell NA. Evaluation of pleural fluid cytology for the diagnosis of malignant pleural effusion: a retrospective cohort study. *Intern Med J*. 2022;52:1154-9. <https://doi.org/10.1111/imj.15725>
42. 32. Basso SMM, Lumachi F, Mazza F, Chiara GB, Del Conte A, Ermani M, et al. Diagnostic Accuracy of Pleural Fluid Cytology, Carcinoembryonic Antigen and C-Reactive Protein Together in Patients With Pulmonary Metastases and Malignant Pleural Effusion. *Anticancer Res*. 2020;40:5877-81. <https://doi.org/10.21873/anticancer.14607>
43. 33. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143:e142S-e165S. <https://doi.org/10.1378/chest.12-2353>
44. 34. Fox AH, Jett JR, Roy UB, Arenberg DA, Beattie J, Bonta D, et al. Acquiring tissue for advanced lung cancer diagnosis and comprehensive biomarker testing: A National Lung Cancer Roundtable best-practice guide. *CA Cancer J Clin*. 2023;73:358-75. <https://doi.org/10.3322/caac.21774>