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## Review Article

# Diagnostic approach to pleural effusion based on pathogenesis and radiological findings: A narrative review

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## ABSTRACT

Pleural effusion (PE) is a common feature of various diseases. The most common causes of PEs are infection, pulmonary embolism, and heart failure. Other diseases include rheumatological diseases, ovarian hyperstimulation syndrome, liver cirrhosis, hypoalbuminemia, and nephrotic syndrome. The principle of PE pathogenesis is either increased fluid production or decreased fluid removal from the pleural cavity, mainly by the parietal pleural layer. According to the underlying cause, the pathogenesis could be due to increased permeability, decreased oncotic pressure or increased hydrostatic pressure of parietal pleural capillaries, increased fluid oncotic pressure, tumor invasion to the pleura, increased lymphatic vessel hydrostatic pressure, lung inflammation, and increased lung interstitial fluid content. Exploring the underlying cause and pathogenic mechanism is the best approach and is immensely helpful in planning the treatment of PE. Treating the underlying cause is the primary approach in treating PEs; thoracocentesis, pleurodesis, pleurectomy, and other possible modalities are applied when indicated, mainly to relieve symptoms. Hence, this review article will discuss the conceivable pathophysiological mechanisms of PEs, common etiologies, radiological diagnostic modalities, and the available therapeutic options.

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## 1. Introduction

Pleural effusion (PE) may occur due to several illnesses, including heart disease, renal failure, liver cirrhosis, pneumonia, and malignancy.<sup>1</sup> PE prevalence is not constant and varies between nations depending on factors, such as socioeconomic status, ethnicity, residency, age, and underlying cause. Approximately 1.5 million PEs are reported in the US annually<sup>2</sup>, and in China, it was

estimated that PEs were 4684/one million Chinese adults, and tuberculosis was the abundant cause.<sup>3</sup> There are four common causes of PEs, which include heart failure (HF), pulmonary embolism, pneumonia, and malignancy, although more than 50 underlying causes have been reported<sup>4–6</sup>. PEs often occur in individuals with pulmonary diseases and are associated with increased death rates and extended hospitalization time.<sup>7</sup> The underlying pathophysiological process determines fluid properties. The fluid may be transudate or exudate (purulent, nonpurulent, bloody exudate, or chyle). Imaging investigations help

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identify the PE but are nonreliable for determining the fluid's biochemical composition, and the specific underlying cause.<sup>5,8</sup>

In healthy adults, a small amount of low-protein fluid (1–20 mL) is present in the pleural space, which creates a thin lubricating film (approximately 10 m thickness) between the visceral and parietal pleural surfaces.<sup>9</sup> Typically, the pleural fluid is exchanged routinely and the exchange rate ranges from 0.1 mL/kg to 0.3 mL/kg.<sup>10</sup> The outer layer of the pleura (parietal pleura) generates pleural fluid. It is absorbed by lymphatic vessels in specific areas of the outer layer of the pleura at the mediastinal and diaphragmatic parietal pleural surface.<sup>11</sup> It is believed that interstitial fluid pours into the pleural space due to hydrostatic pressure from systemic arteries supplying the parietal pleura is higher, inducing PE fluid with decreased protein content compared to serum. Fluid accumulation may occur due to excessive production, insufficient absorption, or a combination of both beyond normal homeostatic regulation. The main reason for PE may be attributed to alterations in the balance between hydrostatic and oncotic pressures, leading to transudates, increased mesothelial and capillary permeability, or decreased lymphatic drainage causing exudates.<sup>12</sup>

Various imaging techniques may be used for diagnosing and treating pleural illness, including chest X-ray, ultrasound (US), Computed tomography (CT), magnetic resonance imaging (MRI), and Fluorodeoxyglucose positron emission tomography/CT (FDG PET/CT).<sup>1,13</sup> Updates on the pathogenesis of PEs and the abilities of radiological diagnostic tools to diagnose and distinguish between the types of PEs will be reviewed. We searched EMBASE, Google Scholar, Google, and PubMed for review articles and original articles about PEs' pathogenesis and the ability of the different radiological modalities to diagnose and differentiate between the PE types. Various phrases and texts, such as pleural effusion pathogenesis, chylous pleural effusion, malignant pleural effusion, types of pleural effusion, CT findings in normal pleura and malignancy, ultrasound features of pleural effusions, best radiological tool for differentiation between pleural effusion types, were utilized.

## 2. Pleural Effusion Classification

PE can occur alone or in conjunction with infection, inflammation, heart or renal failure, hypoalbuminemia, liver cirrhosis, nephrotic syndrome, protein malabsorption and malnutrition, or malignancy. PE is a determined cause that increases death risk and morbidity.<sup>10</sup> Depending on the PE fluid content of the protein, the lactate dehydrogenase (LDH) enzyme, and PE fluid LDH/serum LDH ratio, the modified Light's criteria classify pleural fluid as transudate or exudate. The exudative PE fluid criteria were A) pleural fluid and serum protein ratio of  $> 0.5$ . B) Pleural fluid

LDH/serum LDH ratio  $> 0.6$ . C) Pleural fluid LDH exceeded two-thirds of normal blood LDH readings.

Increased hydrostatic or decreased oncotic pleural pressure conditions, including congestive HF, nephrotic syndrome, liver cirrhosis, nutritional or malabsorptive hypoalbuminemia, and peritoneal dialysis often cause transudates. Infection and malignancy are the principal causes of exudative PEs. However, less common etiologies of exudate PE include pulmonary embolism, drug-induced (methotrexate, phenytoin, amiodarone, and dasatinib), which generally causes exudate PE, esophageal rupture, ovarian hyperstimulation syndrome, and post-radiotherapy.<sup>14</sup> Some PE fluids might have a mixed picture of exudative and transudate fluid features, such as chylous, pulmonary embolism, and drug-induced PEs. Furthermore, Eosinophilic pleural effusion is usually seen with drugs like nitrofurantoin, angiotensin-converting enzyme inhibitors, bromocriptine, valproic acid, propylthiouracil, isotretinoin, and dantrolene.<sup>15</sup> On the other hand, some kinds of PEs are difficult to differentiate. Tuberculous PE and parapneumonic PE share clinical characteristics, making diagnosis challenging. Both PEs have high LDH and adenosine deaminase Ratio (ADA). It was observed by some observational studies that tuberculosis PE has a lower LDH/ADA ratio than parapneumonic PE. LDH/ADA ratio may distinguish TPE from parapneumonic PE if the LDH/ADA ratio cutoff value of  $<15$  based on limited evidence was suggested.<sup>16</sup>

## 3. Pathogenesis of Pleural Effusion

Various pathophysiological processes underlie PE. Visceral and parietal pleura are physiologically important in maintaining fluid balance within the pleural layers. The average rate of generation and pleural fluid reabsorption is approximately 0.2 mL/kg/hour, indicating that the entire pleural fluid volume is usually replaced within one hour.<sup>14,17</sup> In normal individuals, pleural fluid absorption and production rates are balanced. PE occurs because of an imbalance in this equilibrium, likely caused by heightened production and reduced resorption; however, the opposite can happen. The parietal pleura is primarily responsible for pleural fluid generation and removal. Exceptionally, the visceral pleura produces PE due to left HF, and the difference between the hydrostatic and oncotic hydrostatic pressure of the pulmonary, systemic circulation, and pleural space influences the pleural fluid volume.<sup>14,15</sup>

There are almost 500,000 instances of PE in HF reported annually in the US. PE in HF suggests an acute deterioration or patient poor compliance. These effusions often occur bilaterally but may sometimes be unilateral. The development of this condition includes an increase in fluid movement from blood vessels in the parietal pleura into the intra-pleural space and perhaps a reduction in

the absorption of pleural fluid into lymphatic vessels via the parietal pleura. Heightened fluid oozing occurs due to increased capillary pressure caused by increased venous outflow pressure and reduced lymphatic flow into the central circulation due to HF. Approximately 20–25% of PE cases in HF are exudative PEs, while the majority are transudative.<sup>18</sup> Further testing is needed to provide clear evidence, including measuring pleural fluid albumin to serum albumin gradient or measuring pleural fluid N-terminal pro-brain natriuretic peptide. An albumin gradient of 1.2 g/dL indicates that the fluid was a transudate. PE in a patient with HF at the time of discharge is linked to a higher chance of being re-admitted and experiencing death in the following year.<sup>18</sup>

The lymphatic veins in the parietal pleura absorb the fluid between the pleura layers. The absorptive ability of the flow in lymphatic channels and the parietal pleura may increase 20 times when more pleural fluid is generated, indicating a significant reserve capacity in the lymphatic reabsorbing system of the pleura. Increased lymphatic duct pressure due to compression, stenosis, accidental or therapeutic surgical intervention, and tumor infiltration leads to poor drainage and PE.<sup>5</sup>

Parapneumonic pleural effusion (PPE) refers to the buildup of fluid between plural caused by viral or bacterial pneumonia or a lung abscess. PPE develops due to lung inflammation, causing PE caused by direct bacterial invasion, which triggers a cascade of inflammatory reactions. This results in inflammation of the visceral pleura, increasing the permeability and leading to exudative fluid leakage and accumulation into the pleural cavity. Patient characteristics and other existing medical conditions can play a role in developing parapneumonic effusion.<sup>19</sup>

Empyema is characterized by the accumulation of purulent (pus) in the pleural space, resulting often from pneumonia. Lung abscesses, bronchopleural fistula, esophageal perforation, postsurgical complications, or trauma are known causes of empyema.<sup>20</sup> The potential mechanism of empyemic PE may be attributed to reduced pleural pressure, which may lead to the buildup of pleural fluid, especially in severe empyema, once the visceral pleura is covered with a collagenous layer, leading to lung entrapment. Enhanced capillary permeability, especially during pleural inflammation, also plays a role in the development of PE.<sup>19</sup>

The worldwide incidence of malignant PE (MPE) is predicted to be 70/100,000<sup>21</sup>. MPE is prevalent, with an annual incidence of 150,000 new cases globally. MPE is a frequent consequence of cancer, with over 500,000 new cases appearing in Europe and the US.<sup>22</sup> MPE may develop in 20% of cancer cases and is linked to several types of cancer, including primary (mesothelioma) and metastatic pleural lesions from the lung, ovaries, and breast neoplasms. MPE is a frequent consequence of thoracic

and extrathoracic cancers, leading to high death rates and increased healthcare expenses. MPE is an exudative and protein-rich fluid containing growth factors, tumor necrosis factor, oncogenic cytokines, and molecules with pro-inflammatory and angiogenic features like vascular endothelial growth factor, as well as immunosuppressive substances such as interleukins<sup>23</sup>.

Tumor cells primarily travel to the pleura via the circulation, first infiltrating the visceral pleura rather than by lymphangitic dissemination or infiltration from surrounding organs like the diaphragm, pericardium, or chest wall, as shown by postmortem investigations. Thus, secondary spread to the parietal pleura happens when tumors spread via adhesions or when malignant cells are released into the fluid. Once tumor cells are trapped in the mesothelium, they reach the parietal pleura, bypassing pleural immune defenses, infiltrating the pleural tissue, and obtaining nutrition and growth factors. Patients with MPE have a complicated interplay between tumor and host cells, leading to an immunosuppressive environment in the pleura. Dysfunctional macrophages and lymphocytes, plus an excessive release of pro-inflammatory and tumor-promoting substances cause this immunosuppressive environment. Interestingly, A recent study found that tumor cell cultures grow faster when seeded in pleural effusion, indicating a growth-promoting characteristic of pleural fluid independent of its source<sup>24</sup>. Thus, it might be debated whether PE fluid may not only be a feature of malignancy but could also be a feature of cancer progression.

The etiology of MPEs in certain tumors is unknown. Tumor invasion of the drainage system decreases the absorption ability of the parietal pleura and the drainage of the fluid to the thorax duct and lymphatic system<sup>22,25</sup>. Blockage of fluid clearance alone is insufficient to account for MPE development for the following reasons: In most individuals with MPE, there is a discrepancy between the PE fluid volume and the severity of invasion and the tumor's original site. MPE may arise in individuals with no parietal pleura involvement<sup>22,26</sup>. It is now considered that both increased fluid synthesis triggers MPE development due to leakage from blood vessels in the pleura or tumor vasculature and reduced drainage via the lymphatic system. Communication between tumor and host cells, such as mesothelial, endothelial, lymphoid, and myeloid cells leads to the production of vasoactive mediators. The equilibrium between molecules that promote permeability (e.g., tumor necrosis factor, osteopontin, and vascular endothelial growth factor) and those that prevent MPE development (e.g., endostatin) is important<sup>27</sup>.

Tuberculosis (TB) without suggestive chest radiological changes may cause pleural effusion<sup>28</sup>. The effusion may be a sequela following a 6–12-week infection or TB reactivation<sup>28</sup>. In industrialized nations, elderly individuals had greater TB pleural effusions, and its occurrence at the

median age of 56 years indicates disease reactivation as per a North American study<sup>29</sup>. According to the San Francisco research, most individuals had postprimary infections and TB-related PE<sup>30</sup>. In contrast, studies in Houston, Baltimore, and sub-Saharan Africa, where pleural TB was 63.2% reported in primary TB.<sup>29,31</sup>

Lung subpleural caseous focus rupture into the pleural space may cause TB PE<sup>32,33</sup>. This was because 12 out of 15 individuals with TB pleuritis had a contiguous caseous TB focus in the lung, infecting the pleura<sup>33,34</sup>. Moreover, tuberculous empyema is a persistent and ongoing infection in the pleural space. TB PE is characterized by thick, dense, and uneven calcification in the pleura layers. This layer generally surrounds a localized collection of fluid in the pleural space, which includes a higher amount of tubercle bacilli. TB empyema is distinct from the more common tuberculous pleural effusion, which is an inflammatory response to a limited pleural infection due to a low number of bacteria in TB<sup>35</sup>.

Tuberculous EFs may occur from delayed sensitization to mycobacteria and antigens between the pleura layers. Inflammation causes lymphocytic pleuritis, diminishing the pleural fluid reabsorption. Pleural fluid accumulates due to inflammation-induced fluid production and reduced lymphatic clearance<sup>29,31</sup>.

Pulmonary embolism ranks as the fourth cause of PE worldwide. All individuals with undiagnosed PE should be assessed for the potential presence of pulmonary embolism<sup>36</sup>. Most PEs caused by pulmonary embolism are exudates, exhibit significant mesothelial hyperplasia, and are often bloody. Patients with PE and pulmonary embolism may have an embolus in the central, lobar, segmental, or subsegmental pulmonary arteries, which may be detected by spiral computed tomography pulmonary angiography (CTPA) in those locations<sup>37</sup>. Pulmonary embolism often leads to PE by causing elevated interstitial fluid in the lungs due to ischemia or the production of vasoactive cytokines<sup>36</sup>.

Chylous pleural effusion is often linked to malignant conditions<sup>5</sup>. Typically, it is an exudative PE, distinguished by high lipid content, mainly consisting of chylomicrons, cholesterol esters, long-chain triglycerides, and phospholipids. The substance has a high concentration of lymphocytes, particularly T lymphocytes, with counts ranging from 400 to 6800 cells. Chyle has a comparable electrolyte content to plasma but contains high levels of immunoglobulins and fat-soluble vitamins. The root cause is elevated lymphatic pressure caused by tumor cells presence inside the lymphatic vessels, blockage of lymphatic ducts, heightened pressure within the thoracic cavity, fibrosis in the mediastinum after radiation therapy, metastasis, large aneurysm in the mediastinal aorta, and primary tumors in the mediastinum.

Post-traumatic PE is usually eosinophilic. It is mainly attributed to immune complex reactions, which are

suggestively related to blood or air presence between the pleural layers.<sup>38,39</sup> The eosinophil in the PE fluid recruitment is stimulated by cytokines and interleukins (ILs). IL-3, IL-5, regulated upon activation normal T-cell expressed and secreted (RANTES), and granulocyte-macrophage colony-stimulating factor (GM-CSF) precipitate proliferation of eosinophils in the bone marrow, movement into the circulation, and adhesion and migration across endothelial barriers into the pleura layers.<sup>38</sup>

In cases of renal failure and CKD, PE occurs primarily because of increased parietal pleural layer permeability due to increased hydrostatic blood pressure and fluid overload.<sup>40</sup>

Drug-induced PE is uncommon and has rarely been reported by clinicians<sup>41</sup>. The underlying drug-induced PE pathophysiology is not clear. Fluid retention, chemical inflammation, toxic effects, dose-dependent, or oxidative stress in mesothelial cells might interact with drug-induced PE<sup>15,42,43</sup>.

PE often occurs after esophageal perforation, presenting as either sympathetic effusion (with an intact pleura) or exudative PE (when the mediastinal pleura ruptures and gastric fluid is pushed into the pleura owing to negative intrathoracic pressure)<sup>44</sup>. The associated findings depend on the anatomical site of rupture. The middle esophagus borders the right pleura, whereas the lower esophagus borders the left pleura. Ruptures typically occur in the left pleural cavity. When the stomach contents enter, the intrathoracic esophagus may cause mediastinal inflammation, empyema, or necrosis. However, cervical or upper thoracic rupture is possible. Upper thoracic or mid-esophageal perforations can cause a right-sided pleural effusion or hydropneumothorax. Owing to sluggish esophageal propagation to the mediastinum, cervical ruptures are generally confined and benign<sup>45–47</sup>.

Hepatic hydrothorax is a form of PE that generally affects patients with liver cirrhosis and portal hypertension. The incidence of PEs in liver cirrhosis patients is estimated to be approximately 5–6%<sup>48</sup>. This condition is characterized by excessive fluid accumulation between the two pleura without any associated cardio-renal-pulmonary disorders<sup>49,50</sup>. Possible mechanisms of hepatic hydrothorax include hypoalbuminemia, azygos vein hypertension, and trans-diaphragmatic lymphatic ascites drainage<sup>51,52</sup>. The most frequently accepted hypothesis is that ascitic fluid passes directly through minor gaps in the tendinous tissues of the diaphragm<sup>53</sup>. Defects of < 1 cm in diameter may provide a direct connection between the pleural and peritoneal cavities, allowing ascitic fluid to flow into the pleural cavity<sup>48,54</sup>.

Rheumatological diseases associated with PEs are common. PE typically occurs in rheumatoid arthritis<sup>55</sup> and is rarely associated with systemic lupus erythematosus SLE (1–2%)<sup>56</sup>. However, other rheumatological diseases cause PEs via different mechanisms<sup>57,58</sup>. The pathogenesis

of rheumatological diseases associated with PE is typically parapneumonic PE, and the characteristic of the effusion is like parapneumonic PEs<sup>48</sup>. In SLE, it was proposed that the pathogenesis of PE might be due to autoimmune reactions due to the detection of visceral pleura immunoglobulin deposits<sup>57,59</sup>. Another possible mechanism is secondary to SLE cardiopulmonary complications, including HF, pulmonary emboli, infection, and lupus-induced nephritis<sup>57,60</sup>.

Ovary hyperstimulation syndrome (OHSS) is characterized by an increase in fluid shift into the third space and intravascular volume depletion, resulting in big hydrothorax and massive ascites in a considerable number of patients<sup>61</sup>. Furthermore, in OHSS, ascites, and PEs occur more when they conduct in vitro fertilization (5%) or intrauterine insemination procedures<sup>62,63</sup>. There are various postulations regarding the development of pleural fluid. High estrogen and human gonadotrophic hormone levels are believed the cause PEs in OHSS. They explained that because of the less lymphatic drainage on the right compared to the left pleura plus, the diaphragmatic fensters (tiny holes) are wider on the right. Pleural effusion may originate from fluid shifts from abdominal ascites that usually occur in OHSS<sup>64</sup>.

Multiple theories have tried to explain the underlying pathophysiology of fluid in the third space in OHSS. High estrogen levels are believed to be the cause of PE in severe OHSS<sup>64,65</sup>. Estrogen increases fluid and salt retention and promotes capillary permeability, leading to PEs and ascites. It was noted that PE in OHSS often manifests on the right side<sup>65,66</sup>. They explained that lymphatic outflow is less on the right than on the left, and there are larger diaphragmatic tiny fensters on the right diaphragm.

Post-radiation therapy results in complications such as PE<sup>67,68</sup>. The underlying cause of post-radiation PE is due to chronic pleuritis and lymphatic obstruction due to mediastinal fibrosis<sup>69</sup>. Over 50% of thorax radiotherapy cancer patients developed PE with a median period of 6 months at the ipsilateral side irradiation in 67% of patients<sup>70</sup>. Another study reported that PE post-irradiation occurs within 3.7 months in 24.9% of lung cancer patients treated with radiotherapy<sup>71</sup>. In contrast, one study observed that EP occurred after 25 years in patients with radiotherapy-treated lymphoma<sup>71</sup>, and another study reported post-radiation PE after 30 years.<sup>67</sup> The classification of pleural effusion according to the underlying causes is summarized in Table 1.

Legend : Pleural effusion (PE), Inappropriate secretion of antidiuretic hormone (SIADH)

#### 4. Radiological Assessment of Pleural Effusion

Radiographs often establish the existence of pleural effusion using various radiological methods. The most often used radiological tool globally is the chest X-ray, particularly

the posterior-anterior view. A chest X-ray is commonly the first diagnostic tool utilized to evaluate the existence of PE. At least 50 mL of fluid between pleura layers is present to visualize effusion in lateral upright chest radiography in the costophrenic recesses. Blunting of the costophrenic angle and hemidiaphragm obliteration are seen on a conventional posterior-anterior chest radiograph when there is an accumulation of 200–500 mL of PE<sup>71</sup>. Moreover, a supine anterior-posterior chest X-ray may fail to detect a considerable fraction of large PEs<sup>72</sup>. Lateral decubitus projections improve the sensitivity of conventional chest radiography for minimal PEs.

US and CT scans are valuable tools for confirming a PE, particularly in loculated PE, full hemithorax, opacification, or related lung parenchymal abnormalities. US and CT scans are more precise than chest X-rays in determining the root cause<sup>1,73,74</sup>. Both modalities may show tiny PEs, which are not visible on a standard chest X-ray. Furthermore, they assist with interventional methods for treating PE. Although ultrasound has high sensitivity, some radiologists consider CT a superior radiological method for investigating pulmonary embolism. MRI, on unique occasions, is used to assess uncertain CT findings. Studies showed that the MRI is more sensitive than CT scans in distinguishing between noncancerous and malignant PEs. Fluorodeoxyglucose-positron emission tomography (FDG PET/CT) may differentiate between malignant-related PEs and benign PEs. The research compared the effectiveness of CT imaging (75.0%), FDG PET imaging (91.7%), and FDG PET/CT integrated imaging (93.5%) in identifying malignant PE<sup>1,13</sup>.

##### 4.1. Chest X-rays Views Typical Findings of Pleural Effusion

PE fluid accumulations are often seen exclusively at the posterior costophrenic angle on the lateral view<sup>31</sup>. When fluid is seen at the lateral costophrenic angle on the posterior-anterior view, it is feasible to estimate a total volume of around 100 mL<sup>31</sup>. The fluid distribution in the pleural cavity is influenced by the degree of the illness, lung and chest wall compliance, capillarity of the pleural layers, and the physical properties of the fluid.

In an upright chest X-ray, minor effusion in the subpulmonary region elevates the ipsilateral hemidiaphragm. Fluid pours into the posterior (most dependent) costophrenic sulci when fluid accumulates. Small effusions are dependent opacities with meniscus-shaped posterior upward slopes. The opacity of PE fluid obscures the diaphragm silhouette (Figure 1)

A meniscus-shaped dependent opacity suggests a significant amount of free PE. The meniscus tops of both sides are about the same height anteriorly and posteriorly. The ipsilateral PE diaphragmatic contour is erased, leading to one diagram contour. Meniscus contour is determined by

Table 1: Pleural effusion classification based on the underlying causes.

| PE type According to the Cause              | Type                                                              | Pathogenesis Mechanism                                                                                                                                                                                                                    |
|---------------------------------------------|-------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Heart Failure PE                            | Usually Transudate/Exudate with excessive diuresis                | Increased fluid loss by parietal pleural capillaries, possibly decreased pleural fluid removal by parietal pleural lymphatic because of increased venous hydrostatic pressure                                                             |
| Renal Failure PE                            | Transudate                                                        | As part of fluid overload, increased capillary permeability                                                                                                                                                                               |
| Liver Cirrhosis                             | Transudate                                                        | Hypoalbuminemia, Zygote vein increased pressure, portal hypertension, trans-diaphragmatic lymphatic leakage of ascitic fluid into the pleural cavity                                                                                      |
| Hypoalbuminemia                             | Transudate                                                        | Increased parietal pleural permeability, reduction of capillary oncotic pressure                                                                                                                                                          |
| Idiopathic PE                               | Usually, it is transudate but can be Exudate.                     | unknown                                                                                                                                                                                                                                   |
| Hemorrhagic Nonmalignant                    | Exudate                                                           | Trauma damaging the pleural leading to immune complex reactions                                                                                                                                                                           |
| Tuberculosis                                | Usually, exudative                                                | Direct bacilli invasion, rupture of TB focus, medications.                                                                                                                                                                                |
| Chylous PE                                  | Exudate with high Free Fatty Acids, Triglyceride, or Cholesterol. | Increased lymphatic duct pressure, low drainage rate of pleural fluid                                                                                                                                                                     |
| Pulmonary Embolism                          | Transudate/Exudate (might be hemorrhagic)                         | Increased lung interstitial fluid due to ischemia or the production of vasoactive cytokines                                                                                                                                               |
| Parapneumonic PE                            | Exudate                                                           | Visceral pleural inflammation, infective agent virulence, and patient factors (such as age).                                                                                                                                              |
| Malignant PE                                | Exudate (can be hemorrhagic)                                      | Increased lymphatic drainage system hydrostatic pressure, inflammatory reactions, decreased vascular oncotic pressure, increased oncotic pressure in the pleural space, tumor cells in the pleural space, and damage of pleural by tumor. |
| Empyema (Pus) PE                            | Exudate                                                           | Reduced pleural pressure and enhanced capillary permeability, especially in pleural inflammation                                                                                                                                          |
| Drug-Induced PE                             | Generally, exudate                                                | fluid retention, chemical inflammation, toxic effect, or oxidative stress of mesothelial cells                                                                                                                                            |
| Post-radiotherapy                           | Exudate                                                           | Non-infective chronic pleuritis, mediastinal fibrosis, and lymphatic drainage obstruction                                                                                                                                                 |
| Esophageal rupture                          | Transudative/Exudate                                              | Sympathetic PE/ Inflammation of pleura                                                                                                                                                                                                    |
| ovarian hyperstimulation syndrome           | Exudate                                                           | Increased estrogen, increased parietal pleura permeability, diffusion of ascitic fluid through the right diaphragm.                                                                                                                       |
| Post-surgery PE                             | Mostly Transudate                                                 | Due to salt and water retention post-surgery, either due to overhydration or SIADH inappropriate secretion of ADH syndrome                                                                                                                |
| Rheumatological diseases associated with PE | Transudate/Exudate                                                | Inflammation, associated cardiopulmonary diseases, and autoimmune reactions                                                                                                                                                               |
| Sympathetic PE                              | Transudate/Exudate                                                | Unknown, but can be due to increased parietal pleural increased permeability                                                                                                                                                              |
| Idiopathic PE                               | Transudate/Exudate                                                | Unknown                                                                                                                                                                                                                                   |

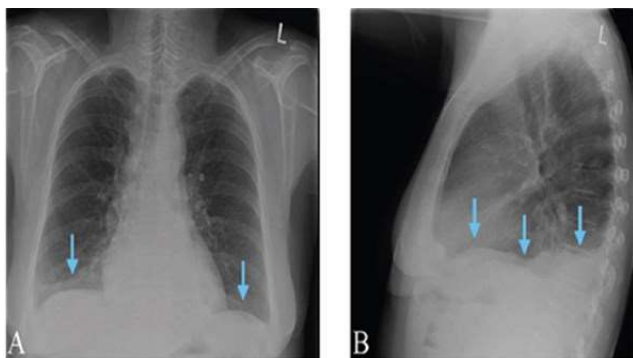


Figure 1: Chest radiograph revealed bilateral pleural effusion. A =posteroanterior view image; B = upright lateral view. Pleural effusions are indicated with a blue arrow.

X-ray beam fluid depth. When the X-ray beam is tangential to PE, it increases fluid attenuation and penetration, making the meniscal apices apparent. Laterally penetrated fluid is too shallow to cast a shadow on the X-ray, particularly in the upper effusion. A massive pleural effusion causes widespread opacity and hemidiaphragm obliteration. One diaphragm dome appears on the lateral chest X-ray view, indicating a significant pleural effusion (Figure 2).



Figure 2: Lateral Chest X-ray shows one diaphragm dome appears on the lateral chest X-ray view

A normal frontal supine view does not rule out PE. Bilateral PEs need much fluid to show noticeable radiographic changes. One investigation found that 175 ml was enough to be detected by the supine chest radiography<sup>75</sup>. In small effusions, hazy homogenous opacity with ill-defined borders usually begins in the lower

lung fields. With more fluid, the hemithorax becomes opaque, and the diaphragm disappears. This opacity may reveal lung marks like veins depending on the quantity of fluid and lung collapse. This helps appreciate the difference between opacity caused by effusion and lung parenchymal pulmonary lesions like atelectasis, emphysema, and bullae disease. The lack of an air bronchogram aids distinction. With extensive larger PEs, ipsilateral apical capping X-ray signs are common. This opacity might be because of a limited lung capacity at the apex and fluid expansion superior and lateral to the lung tissue. Over 50% of major PEs have blurred costophrenic angles due to fluid collection around the lateral costophrenic sulcus. (Figure 3) illustrates moderate and huge pleural effusions.

Figure 3 shows right and left pleural effusions with different amounts of pleural fluid.

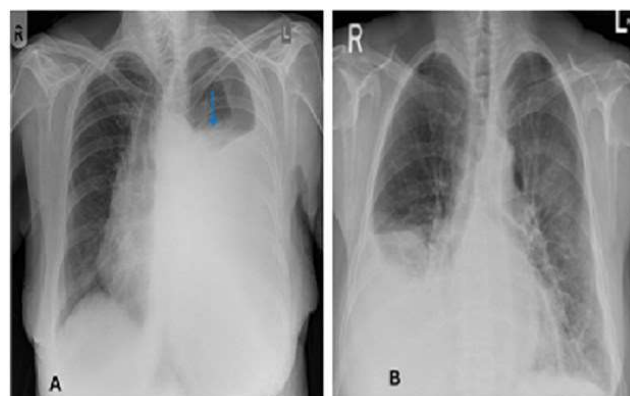


Figure 3: Chest X-ray Left (A) and Right (B) pleural effusion

The best radiographic projection for effusion detection is lateral decubitus with a horizontal X-ray beam<sup>76</sup>, detecting as minimum as 10-25 ml of effusions. The layering fluid is a dependent, finely defined linear opacity declining the lung from the chest wall and external pleural image, and the edge is a line joining the inner tips of the ribs' curvature. Subpleural fat may move the parietal pleura medially, particularly in obese people, obscuring the fluid or mimicking small PE.

Although the chest X-ray is an excellent reliable tool to identify PEs even in a small amount. Characterization of the PE cause and type is sometimes impossible. Moreover, chest X-ray is correctly interpreted, and 92% of huge PE can be read, and excluded with high confidence<sup>77</sup>. Chest wall thickness, lung parenchyma pathology, fluid septation, fluid thickness, fluid substance consistency, and fluid contents interfere with chest ray sensitivity<sup>78</sup>. Recently, it has been reported that chest X-ray alone is sometimes misleading and may miss subclinical TB<sup>79</sup>. All these obstacles affect the detection of small PEs, and the necessity of radiologist consultation and comments are required, although it increases the total cost.

In summary, upright chest X-rays identify PE well. Lateral decubitus chest X-rays may identify small free PE. Large, loculated, or unusual effusions may show significant gravitational movement to indicate their nature. Despite the higher sensitivity of the different chest X-ray projections, in many cases of PE, CT is required to detect and delineate the tiny PEs.

#### 4.2. Computed tomography

Free PE fluid appears as a crescent-shaped attenuation region in the dependent hemithorax on CT images. Most CT scans are done in the supine position. Therefore, fluid accumulates posteriorly in the costophrenic fissure. Large effusions spread fluid into the chest's apex and lung fissures. The fluid moves to the dependent part of the pleural cavity when prone or lateral is conducted, verifying also effusion fluid-free movement<sup>80,81</sup>. In contrast, the elliptical-loculated fluids are discovered in nondependent places. Although PE attenuation is normally near water but might exceed water in CT imaging, the images cannot distinguish transudative from exudative PEs. Hemothorax causes heterogeneous attenuation with enhanced dependent attenuation due to the presence of red blood cells, which can be confirmed by fluid microscopic assessment and hematocrit measurement in the PE fluid. Occasionally, chylothorax has lower attenuation than water due to the excessive protein content, mitigating the reduced attenuation fat. CT fat attenuation does not necessarily imply chylous effusion. Fat-fluid or fat-calcium levels may indicate the rare pseudo-chyle (cheliform PE)<sup>82</sup>. Chyliform PE, characterized by degenerating white and red blood cells in PE fluid, is linked to long-term EFs, including tuberculous empyema.

Pleural thickness and augmentation indicate inflammation, infection, or cancer. Lack of thickened pleural and augmentation is typical with transudative PE. Metastatic PEs or early infection may not have pleural thickening or increased attenuation. Chest X-ray or CT scan with nodular pleural thickening suggests malignant PE<sup>73</sup>. CT scanning can identify PEs; however, a modest effusion might be mistaken for pleural thickening. PE may be distinguished from airspace disorders or lung atelectasis using contrast enhancement. Contrast substance improves lung tissue, not pleural fluid. CT scanning is better than conventional radiography in detecting loculated effusions or effusions with lung illness and determining PE etiology<sup>83</sup>. PE might look like extra-pleural fat and fissure fat. Low-fat attenuation and symmetry distinguish PE from extra-pleural fat. A modest posterior costophrenic sulcus effusion, a considerable effusion with diaphragmatic convexity inversion, and lower lobe compressive atelectasis produce pseudo-diaphragms, which may mimic ascites.

Careful inspection of sequential pictures and multiplanar reconstruction may assist in determining ascites, effusion,

or both. Four indicators distinguish effusion from ascites<sup>84</sup>: A) Chest CT shows that PE has peripheral diaphragm fluid, whereas ascites have core fluid. B) PE has fluid expansion posteriorly behind the liver but not centrally. C) It is well-defined when interacting with the spleen and liver but not in PE. D) posterior, central, laterally, and peripheral diaphragm dome displacement. Each of these indications should be evaluated since they might be deceptive when used alone. Figure 4 illustrates the CT findings and characteristics of PE.



Figure 4: Bilateral pleural effusions image by computed tomography.

#### 4.3. Magnetic resonance imaging

MRI may determine pleural effusion cause. Pleural contour nodularity and/or irregularity, mediastinal pleural involvement, circumferential thickening, and chest wall and/or diaphragm infiltration imply cancer on CT and MRI scans. MRI signal intensity may help distinguish between malignant and nonmalignant PEs<sup>85</sup>. Malignant PEs are hyperintense in proton density. PEs with modest signal intensity on long-repetition imaging are dependable and indicative of benign disease. Diseases with calcification of the pleural are likely benign. Biochemical properties determine pleural fluid signal intensity. Nonhemorrhagic and nonchylous PEs typically have low T1-weighted and higher T2-weighted signal intensity. MRI morphology and signal intensity are better than CT in recognizing malignant PEs from benign PEs<sup>86</sup> (Figure 5).

#### 4.4. Ultrasonography

US confirms PEs in patients with unclear chest radiographs and guides interventional operations such as TC, biopsies, and chest drain installation. Ultrasonography helps differentiate PEs from thickening. This technique may also assess effusion causes.<sup>78</sup> Using a 3.5-MHz curvilinear



Figure 5: Right pleural effusion in Magnetic resonance image

transducer, differentiating the external pleura from the internal pleura could be impossible on certain occasions in healthy people; hence, high-frequency linear transducers are used for differentiating between the two layers of the pleura. The air-filled alveoli are echogenic, affecting visceral pleura echogenicity and limiting lung parenchyma visibility by the US.<sup>87</sup> Figure 6 shows the appearance of pleural effusion in the US.

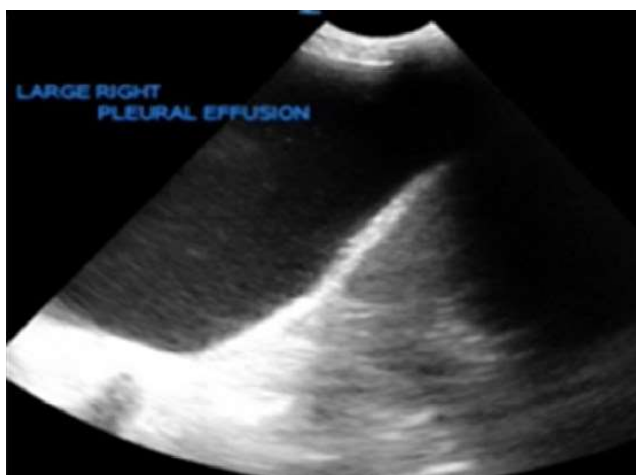


Figure 6: Right pleural effusion by Ultrasound

Respiration and posture affect effusion fluid shape in ultrasonic examination. Furthermore, PE ultrasonic appearance depends on the nature, origin, and fluid chronicity and does not correspond with the biochemical properties of effusion<sup>88</sup>.

The characteristic anechoic effusion is seen in transudates. Transudates were anechoic in 320 effusion patients; however, the echogenicity is not a differentiating finding between transudative and exudative PE fluids<sup>81</sup>. Nonetheless, pleural thickening and pulmonary parenchymal changes in presence favor exudative PEs.

Hemorrhagic or empyema pleural fluid can show echogenic pleural fluid, and the occurrence of Septa and anechoic, or echogenic exudates, complicated lung underlying diseases support exudative PE fluid. Malignant effusions are frequently anechoic, whereas exudative effusions are septated, complexed, or echogenic<sup>89</sup>. Inflammatory effusions may inhibit lung sliding due to adhesions, differentiating inflammatory PE from non-infectious PEs. Distinguishing pleural thickening from little PE is sometimes possible by Color Doppler US by showing the fluid-color sign with 89.2% sensitivity and 100% specificity. Ultrasonic examination can determine effusion volume by considerable percentages<sup>90</sup>. Pleural nodules with PE on ultrasound suggest malignant effusion; however, it is not characteristic and repeated therapeutic thoracocentesis (TC) should be conducted<sup>91</sup>.

TC and catheter effusion drainage may be guided by ultrasound<sup>82</sup>, increasing the significance of US usage in pleural effusion diagnosis and therapy. US-guided thoracocentesis is used more than CT scans. Image guiding diminishes complications and enhances procedure safety. Small catheters also have fewer complications than thoracotomy tubes. Catheter drainage of PEs is safer and has fewer complications when conducted with US or CT scanning guidance. Transcutaneous pleural biopsy is conducted chiefly using ultrasound guidance rather than CT scan guidance. Utilizing US guidance has been shown to decrease the occurrence of iatrogenic pneumothorax to 0.83%<sup>92</sup>. Percutaneous thoracic cavitation is more effective in treating PEs that appear anechoic, complicated, or complex with moving septa on ultrasound rather than echogenic or complex PEs with fixed septa. Researchers found no link between how PE looked on ultrasound and how well percutaneous pleural drainage worked. However, various studies confirmed that PE drainage under the US guide was sensitive and safe<sup>92</sup>. Radiologically guided drainage procedures have a success rate ranging from 72% to 88%. The research included 458 patients with PE and compared the success rates of drainage between normal pleural puncture and US-guided TC catheter drainage. The study found that US-guided TC had a greater success rate of drainage (84% vs 100%)<sup>1</sup>.

#### 4.5. Nuclear Imaging

Nuclear imaging investigations for pleural effusion have no documented clinical indications. FDG PET/CT distinguishes cancer from benign PE. In one investigation, FDG PET, CT, and FDG PET/CT integrated imaging detection for malignant effusion was sensitive by 91.7%, 75.0%, and 93.5% respectively<sup>13,93,94</sup>. Erasmus et al. reported that greater pleural fluorodeoxyglucose (FDG) absorption on PET scans of non-small-cell lung cancer effusions may indicate metastases<sup>94</sup>. In patients with non-small-cell lung cancer and pleural effusion, FDG-PET

scans may enhance staging with almost similar sensitivity rates. PE presence reduces ventilation and perfusion lung imaging accuracy. The affected hemithorax may show enhanced activity on 99mTc MDP bone scans due to malignant effusions.

## 5. Treatment of Pleural Effusion

Determining the underlying cause of PE and pathophysiology are crucial players in planning PE treatment. TC is the primary therapeutic method to relieve the patient's acute symptoms in most cases; however, it does not treat the underlying causes. Usually, parapneumonic PE does not need therapeutic TC, although diagnostic pleural fluid aspiration is needed to confirm the nature of PE. On the contrary, in HF, diuretics and other medications for congestive HF control are enough to control the EF, and TC is rarely required to relieve the acute symptoms of PE. Pulmonary embolism pleural effusion is usually resolved after starting anticoagulation, and TC is not indicated in almost all pulmonary embolism cases. Drug-induced PEs are managed by minimizing the use of the offending medications. Patients with significant symptomatic pleural effusions may need therapeutic thoracentesis. TB PE usually improves after TB therapy and rarely requires TC and drainage. The reappearance of symptomatic effusions is a challenge in therapy that may need several thoracenteses as in malignancy<sup>95</sup>, insertion of an indwelling intrapleural catheter, or other advanced care strategies used in chronic HF<sup>18</sup>. Postradiotherapy effusion because of lymphatic obstruction and radiation-induced fibrosis can be minimized by steroid therapy. Rheumatological disease-induced PEs are managed symptomatically and with managing the underlying disease.

Chemotherapy for the underlying malignancy in some cancer diseases is effective in treating and reducing the recurrence of PE. In most cases of malignancies associated with PEs, temporary TC or intermittent pleural drainage is required for frequent fluid drainage. In some centers, patients are offered permanent chest three ways chest tubes with locks through which they can drain fluid when they need even by their selves at home. Pleurectomy is sometimes conducted in malignant PE and some other recurrent PEs. Pleurodesis is another medical procedure for PE therapy, especially in recurrent malignant PEs.

### 5.1. Limitation

Original articles are scarce for CT, MRI, and FDG PET/CT studies and review articles because they are not commonly used to investigate PEs. This has made us ferrous to find articles that will be helpful and can be cited. Furthermore, MRI and PET/CT studies that compare their efficiency in identifying malignant and nonmalignant PEs are very few; if they were conducted, they were small studies. Moreover, we

did not include the diagnostic scheme and therapy in detail, which will make the article long and confusing. However, we briefly mention the therapeutic option.

## 6. Conclusion

Pleural effusion is usually detected unilaterally, but it is frequently bilateral and is not detected easily by the anterior-posterior X-ray, which may miss tiny ones. lateral decubitus chest X-ray has a better ability to identify tiny pleural effusions. Ultrasound is an excellent tool to identify pleural fluid and volume estimation, even in smaller pleural effusions. Furthermore, ultrasound is a cost-effective and safe way to guide pleural aspiration and thoracentesis. In some instances, computed tomography, and magnetic resonance, are used, but due to the restricted availability, affordability, and similar diagnostic output, they are not frequently utilized.

Pathophysiology mechanisms for pleural effusion include inflammation, increased permeability, tumor invasion of pleural and lymphatic drainage, and others. Understanding the pathogenesis and determining the underlying cause of pleural effusions are the best guidance for their therapy.

## 7. Authors' Contribution

All authors contributed to the completion of this work. The final manuscript was read and approved by all authors.

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## 9. Conflict of Interest

None.

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