ROLE OF D-DIMER IN DIAGNOSIS OF DIFFERENT TYPES OF PLEURAL EFFUSION

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Abstract:
Pleural Effusion (PE) is defined as collection of fluid in pleural space and classified into two categories of exudative and transudative PE. PE is the result of a wide range of medical conditions including infection, malignancy, trauma, collagen vascular disease, etc. Coagulation system plays an important role in pleural diseases. Understanding the pathophysiological mechanisms of the coagulation and pleural disorders may open possibilities for novel diagnostic and therapeutic approaches. Several studies have reported that exudative pleural effusion is associated with enhanced local fibrinolytic activity. Thus, D-dimer level; a marker of solid phase fibrin dissolution; was found to be high in patients with exudative pleural effusion. The D-dimer is a product of fibrin degradation that is formed by the sequential action of enzymes of coagulation cascade. Coagulation cascade plays an important role in pleural diseases and several studies have reported that TPE is associated with enhanced local fibrinolytic activity.

Keywords: Plueral Effusion**,** D-dimer, malignancy and pneumonia.

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Introduction:

Pleural effusion is the accumulation of fluid in between the parietal and visceral pleura, called the pleural cavity. It can occur by itself or can be the result of surrounding parenchymal disease like infection, malignancy, or inflammatory conditions. Pleural effusion is one of the major causes of pulmonary mortality and morbidity. All healthy humans have a small amount of pleural fluid that lubricates the space and facilitates normal lung movements during respiration. This delicate balance of fluid is maintained by the oncotic and hydrostatic pressure and lymphatic drainage; disturbances in any one of these systems can lead to a build-up of pleural fluid **(1).**

Pleural effusion is an excess fluid that accumulates between the two pleural layers. It is not a disease entity but is either a manifestation or a complication of pulmonary or non-pulmonary diseases and can leads to grave consequences if not managed timely. List of causes of pleural effusion is quite exhaustive. They are classified broadly into exudative and transudative effusion based on light's criteria. Congestive cardiac failure (CCF) is the most common cause of transudative pleural effusion worldwide. Among exudative pleural effusions, in the west the most common causes are malignancy and pneumonia, but in India, it is tubercular effusion followed by malignant effusion and a very few due to parapneumonic effusion (PPE) **(2).**

Pulmonary embolism (PE) is a common and fatal medical condition with high morbidity and mortality, characterized by occlusion of the pulmonary arteries **(3)**, which accounts for death in 5–10% of hospitalized patients and is the third-leading cause of death among hospitalized patients in the United States **(4)**.

Epidemiological studies have revealed that the annual incidence rates for PE range from approximately 30 to 115 per 100,000 people and longitudinal investigations have demonstrated an increasing annual incidence of PE with time. PE accounts for approximately 300,000 deaths, ranking among the top causes of death from cardiovascular disease Although PE mortality has decreased in recent years as a result of progress in PE treatment from anticoagulation or systemic thrombolysis, to interventions it remains a diagnostic and therapeutic challenge **(5)**.

Although pleural effusion is frequently observed in PE patients, it is challenging to pinpoint the precise prevalence of pleural effusion in PE patients due to conflicting research results. However, PE, the fourth most common cause of pleural effusion after congestive heart failure, cancer, and pneumonia, is also the most underdiagnosed condition among pleural effusion patients **(6)**. Although emerging evidence suggests that pleural effusion has a high incidence among PE patients and is closely associated with the prognosis of PE, the results of recent studies on the effect of pleural effusion on the prognosis of PE patients are inconsistent **(7)**. In clinical practice, the question of whether the occurrence of pleural effusion reflects high-risk PE is often raised, and the mortality rate of high-risk PE is as high as 30% if left untreated. Therefore, timely identification and adequate treatment of high-risk PE are essential. Clearly, it is important to understand the clinical correlation between pleural effusion and mortality in PE patients, and to adequately stratify and guide the treatment of PE patients **(8)**.

Clinical presentations:

The presenting manifestations of pleural effusion are largely determined by the underlying disease (Table 1). Many patients have no symptoms that can be traced solely to the effusion itself. Such symptoms, if present, reflect an inflammatory response of the pleura, a restriction of pulmonary mechanics, or a disturbance of gas exchange. The most common symptom arising from a pleural inflammatory response is pleuritic pain, which is mediated by the parietal pleura (the visceral pleura contains no nociceptors or nociceptive nerve fibers). The pain is usually felt in the region of the pathological abnormality, and it is often linked to the respiratory cycle. Such localized pleuritic pain improves or disappears as soon as a pleural effusion arises. Some patients describe a diffuse, painful sensation of pressure in the chest particularly when the pathological process directly involves the parietal pleura, e.g., in the case of a pleural empyema, a primary malignant malignant, or pleural carcinomatosis. Pleural effusions in these situations are usually of the exudative type **(6).**

Table (1): The most common causes of pleural effusion**(6)**

Congestive heart failure	Transudate	- History of heart disease - Edema, hypoxia
Cancer	Exudate	- history of cancer (lung, breast; lymphoma) - Intrathoracic mass
Bacterial pneumonia	Exudate	- Cough - Fever - Infiltrate
Pulmonary embolism	Transudate or exudate	- Dyspnea - Immobilization - Pleuritic chest pain

The most common symptom of pleural effusion is dyspnea. The severity of dyspnea is only loosely correlated with the size of the effusion. Large pleural effusions take up space in the chest that is normally filled by pulmonary parenchyma and are thus associated with a diminution of all lung volumes. Nor do the lung volumes immediately change when a pleural effusion (even a large one) is drained. The rapid clinical improvement of dyspnea after a pleural effusion is drained probably reflects the transition to a more favorable length-tension curve of the respiratory muscles, particularly the diaphragm **(9)**.

Some patients complain of a dry cough, which can be explained as a manifestation of pleural inflammation or lung compression due to a large effusion. Pleural effusions can also markedly impair the quality of sleep **(10).**

Diagnosis:

Due to the variation in clinical presentation, making a prompt diagnosis of pleural infection can require a high index of suspicion. Physical examination can be suggestive of a pleural effusion but is often unhelpful in specifically identifying pleural infection as the underlying aetiology, where a careful history is of more value. Pleuritic chest pain and dyspnoea are common. When presenting acutely and accompanied by one or more of a fever, cough and sputum production, bacterial pneumonia complicated by parapneumonic effusion is likely, and this is most commonly associated with aerobic bacteria pleural space infection**(11**).

Anaerobic bacteria are more likely to be responsible, and patients will usually have some degree of immune compromise, such as alcoholism, poor oral hygiene or frailty. This may indicate failure to recover from a preceding pneumonia, allowing time for bacteria to colonise the pleural space, or a representation of their predisposition to recurrent aspiration. Along with these characteristics, the delayed recognition caused by late presentation, results in a higher morbidity and mortality in this group**(12).**

Clinical history:

After the initial determination that either a unilateral or a bilateral pleural effusion is present, the clinical history is very important. The patient should be asked about respiratory infections in the recent past, fever, weight loss, and malaise. The temporal course is highly relevant as well: Did the symptoms arise rapidly or over a longer time, perhaps over several weeks? What other, chronic illnesses does the patient have? Information about any history of heart disease is essential, as congestive heart failure is the commonest cause of bilateral pleural effusion. Some 75% of patients with pulmonary embolism and pleural effusion complain of pleuritic chest pain. The final important components of the clinical history are the drugs currently taken and any prior exposure to asbestos **(13).**

Physical examination:

The breath sounds are uni- or bilaterally diminished or absent at the bases, and there is basal dullness to percussion. Tachypnea may be present if the effusion is large. A pleural rub can sometimes be heard in the initial stage of a parapneumonic effusion. In clinical practice, the determination whether a pleural effusion is uni- or bilateral is generally made from a chest x-ray. The history and physical examination serve as a guide to further testing and can often suggest with high accuracy whether a transudate or an exudate is present. If, for example, the patient displays the clinical signs of congestive heart failure, with peripheral edema, tachycardia, a third heart sound, distended neck veins, and bilateral dullness to percussion at the lung bases, then a pleural effusion of cardiac origin is highly likely, and we are thus probably dealing with a transudate rather than an exudate. In this situation, a diagnostic pleural tap can generally be dispensed with, and the treatment of the underlying illness is the main consideration. If the examination reveals ascites in a patient with known

hepatic cirrhosis along with evidence of a bilateral pleural effusion, hepatic hydrothorax is likely. The situation is different when unilateral dullness to percussion points to a likely unilateral pulmonary effusion. The differential diagnosis is often difficult in such cases, and the probability of an exudate is much higher **(6).**

Radiology:

If a pleural effusion is suspected, a chest x-ray should be obtained (Figure 1). A standard postero-anterior chest X-ray is frequently the first radiological test requested. It is worth noting that on many occasions, the effusion in pleural infection does not exhibit the meniscus sign due to the presence of encystment, but rather shows a steeply rising line towards the apex of the thorax (Figure 1), or even appear as an indistinct opacity that does not obscure the diaphragm shadow (Figure 2A). In such instances, thoracic computed tomography (CT) is very useful in deciphering the underlying anatomy. Significant thickening and enhancement of the parietal pleura creates the appearance commonly referred to as the 'split pleura' sign which is highly suggestive of empyema (Figure 2B). The finding of extra pleural fat hypertrophy is a valuable marker of a benign inflammatory effusion (Figure 2B), including pleural infection. In cases of multi-loculated empyema, complete mapping of the extent of the disease can only be achieved by CT. **Porcel et al. (14)** examined CT scans of patient who had pleural infection and found that the presence of air foci inside the fluid, pleural enhancement, estimated fluid volume more than 400 mLs and extraplural fat enhancement were predictors of complicated pleural infection.

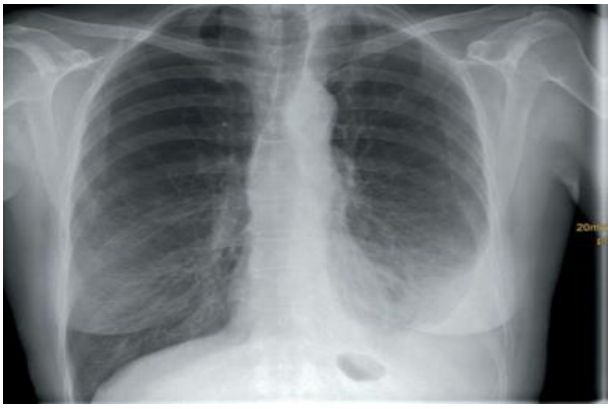

Figure (1): Chest x-ray of a 59-year-old woman with a left-sided pleural effusion. Further workup revealed a pleural mesothelioma as the cause **(**A postero-anterior view reveals effusions of volume 200 mL or larger, a lateral view effusions of volume 50 mL or larger. A lateral decubitus view can be used to confirm the free flow of the effusion around the lung**)(6).**

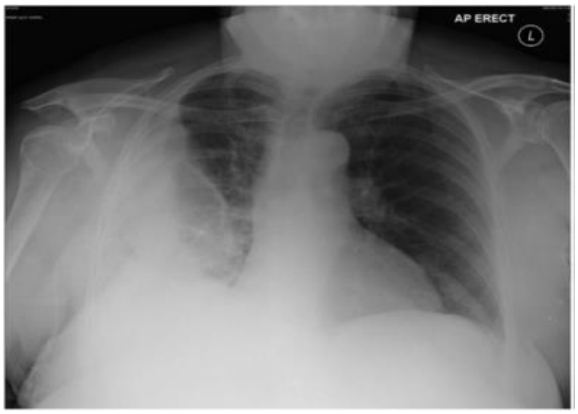

Figure (2): Chest X-ray shows the partial encystment of the pleural collection as noted by the steep upper border of the opacity **(6)**

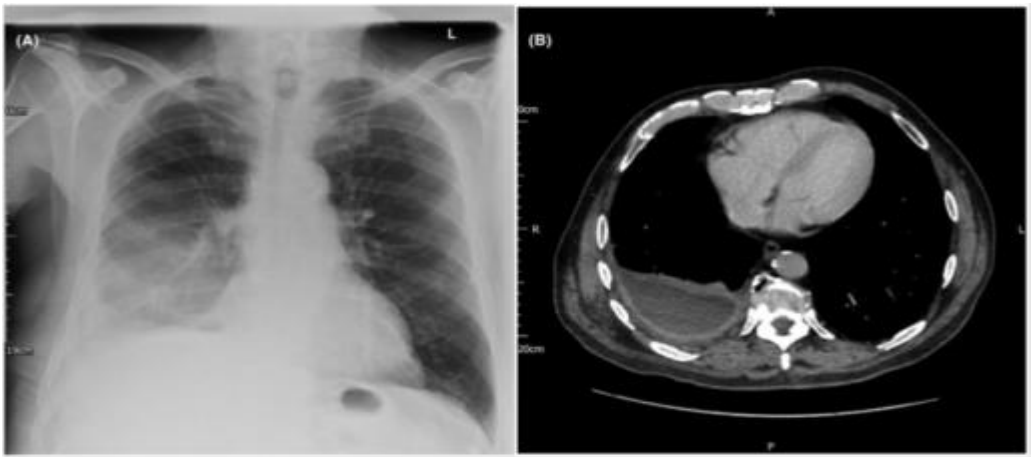

Figure (3): (A) Chest X-ray shows a rounded opacity that does not obscure the heart borders or the diaphragm. (B) Chest CT reveals posteriorly loculated pleural collection. Note the enhancing pleura (split pleura sign) and the extra peural fat hypertrophy **(6)**

Thoracic ultrasound is a vital tool in the management of pleural infection. It is superior to CT in the ability of detection of septations (Figure 4). In multiloculated collections, ultrasound helps guide the safe insertion of chest drain in to the largest loculus, which sometimes leads to complete evacuation of the infected fluid, as such loculi are often connected **(15)**.

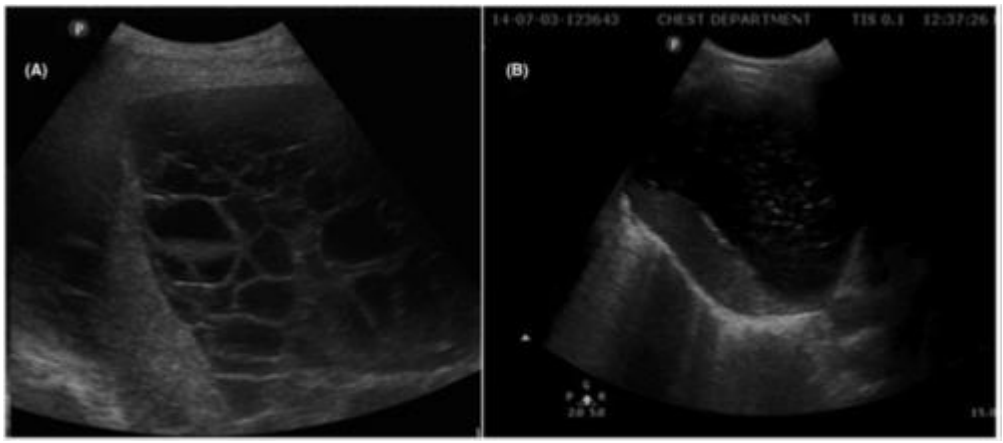

Figure (4): Ultrasound images of (A) heavily septated pleural effusion and (B) echogenic free pleural effusion **(6)**

Indications for thoracentesis:

A diagnostic puncture of a pleural effusion to obtain a small quantity of fluid (ca. 50 mL) is always indicated when the cause of the effusion is unclear. Puncture to obtain larger volumes is indicated to relieve effusion related symptoms, such as dyspnea. Timely thoracentesis or the insertion of a pleural drain is necessary if a pleural effusion is large and leads to respiratory or cardiac decompensation. An effusion in a patient with pneumonia should be tapped to rule out pleural empyema **(16)**.

Analysis of the pleural fluid:

Macroscopic appearance:

The gross appearance of the fluid may already provide clues to the diagnosis. Milky fluid is typical of chylothorax, pus is proof of empyema, and a bloody effusion is more common when a malignancy is the cause (as long as the tap itself has not caused iatrogenic bleeding). Chylothorax can be distinguished from empyema by centrifugation: chylous fluid remains milky, but empyema fluid displays a clear supernatant **(6)**.

Distinguishing transudates from exudates:

Whether a pleural effusion is a transudate or an exudate determines its further evaluation and treatment. Lactate dehydrogenase (LDH) and protein are measured in order to differentiate the two possibilities. The distinguishing criteria have proven their worth in many years of use and are 99.5% sensitive for the diagnosis of an exudate. They can correctly tell the difference between a transudate and an exudate in 93–96% of cases. Cholesterol measurement can also help: a cholesterol concentration above 55 mg/dL combined with an LDH concentration above 200 U/mL is highly specific for the presence of an exudate **(17)**.

It must be borne in mind, however, that diuretic drugs given to treat congestive heart failure can elevate the concentrations of protein, LDH, and lipids in a pleural effusion, and that obtaining effusion fluid by pleural tap after cardiac decompensation has already occurred can lead to the incorrect identification of an exudate, which will be followed by further unnecessary diagnostic testing **(6)**.

pH values:

If an infectious cause is suspected for a non-purulent pleural effusion, its pH should be tested by an appropriate method. Pleural fluid acidosis is found in complicated pleural infections, tuberculosis, rheumatoid arthritis, and malignant effusions. Among patients with malignant effusions, acidosis of the effusion fluid is correlated with shorter survival; these patients generally have more extensive disease and a lower chance of successful pleurodesis. If the pH is less than 7.2, a pleural drain should be inserted without delay, even if the effusion is clearly of parapneumonic origin **(16).**

Glucose, amylase:

The glucose concentration is normally the same in pleural fluid as in the blood. A low glucose concentration in a pleural effusion is found in empyema, tuberculosis, malignancy, and rheumatoid arthritis. One in two patients with

acute pancreatitis has a pleural effusion with an elevated amylase concentration **(6)**.

NT pro BNP:
N-terminal pro-B-type natriuretic peptide, or NTproBNP for short, is a sensitive biomarker for systolic and diastolic heart failure, and its concentrations in the blood and in pleural effusion fluid are very closely correlated. Even if an effusion is found to be of the exudative type, an elevated NTproBNP level makes it very likely that congestive heart failure is the cause. Measurement of the NTproBNP level in peripheral blood suffices in most cases. A negative NTproBNP finding in the blood rules out congestive heart failure as the cause of a pleural effusion with near-absolute certainty **(18).**

Differential blood-cell count:
A differential blood-cell count in the pleural effusion fluid can further narrow down the differential diagnosis. An elevated concentration of neutrophils is often seen in acute processes, such as parapneumonic effusion, empyema, and effusion due to pulmonary embolism. On the other hand, a predominantly lymphocytic picture is more common in tuberculosis, longstanding pleural effusions, congestive heart failure, or malignant etiology. Nonetheless, the differential blood-cell count in the pleural fluid alone does not enable precise determination of the cause of the effusion**(6)**.

Microbiological diagnostic evaluation:
Gram staining can help identify the underlying pathogen. The microbiological identification of a pathogenic organism in a non-purulent parapneumonic effusion succeeds in only 25% of cases. Microbiological investigation yields a large percentage of false-negative findings. Application of the polymerase chain reaction (PCR) with use of the 16S-rRNA gene improves sensitivity compared to conventional culture techniques **(19)**. If tuberculous pleuritis is suspected, microbiological examination and culture should be performed. If possible, 30–50 mL of fresh, untreated puncture fluid should be sent for mycobacterial diagnostic testing (caveat: not in blood-culture bottles) **(20)**.

Cytology:
In approximately 50% of lung cancers and 60% of all cancers taken together, the malignant nature of a pleural effusion can be confirmed cytologically. The yield of positive malignant diagnoses is highest for adenocarcinoma and lower for mesothelioma, squamous-cell carcinoma, lymphoma, and sarcoma. A 20–60 mL sample of the effusion fluid should be sent for cytological examination. The medium to be used should be ascertained in advance by communication with the cytopathology laboratory. For the diagnosis of mesothelioma, histological examination is always advisable **(6)**.

Malignant markers:
There is insufficient evidence to support the routine measurement of malignant markers in pleural effusion fluid, or of serum malignant markers, for the etiological categorization of pleural effusions of unclear origin. The role of mesothelin in patients with mesothelioma cannot yet be conclusively judged. In one study, the use of a multiplex protein biochip with 120 biomarkers enabled the differentiation of a malignant from a tuberculous effusion, and of an effusion due to adenocarcinoma of the lung from one due to mesothelioma **(21)** (Table 2, 3 Figure 5).

Table (2): The Light criteria for differentiating a transudate from an exudate **(6)**

A pleural effusion is an exudate if at least one of the following criteria is met:
– Protein concentration in effusion divided by serum protein concentration >0.5
– Lactate dehydrogenase (LDH) concentration in effusion >200 IU
– LDH concentration in effusion divided by serum LDH concentration >0.6

Table (3): Pleural puncture: the analysis of pleural effusion fluid **(6)**

Recommended tests for any diagnostic pleural puncture	
Lactate dehydrogenase (LDH) and protein	3–5 mL; blood drawing in parallel as per Light criteria
Microscopy and culture	5 mL; aerobic/anaerobic blood culture flasks where indicated
Cytology, differental blood-cell count	remaining volume of punctate
Recommended tests in case of particular clinical suspicion	
pH	suspected infection despite non-purulent effusion; in a heparinized blood-gas syringe
Glucose	suspected rheumatic disease

Acid-fast bacilli; culture for M. tuberculosis; PCR	30–50 mL; suspected tuberculous pleuritis; untreated fluid, not in a blood-culture flask
Triglycerides and cholesterol	chylothorax
Amylase	pancreatitis
Hematocrit	hematothorax; EDTA tube

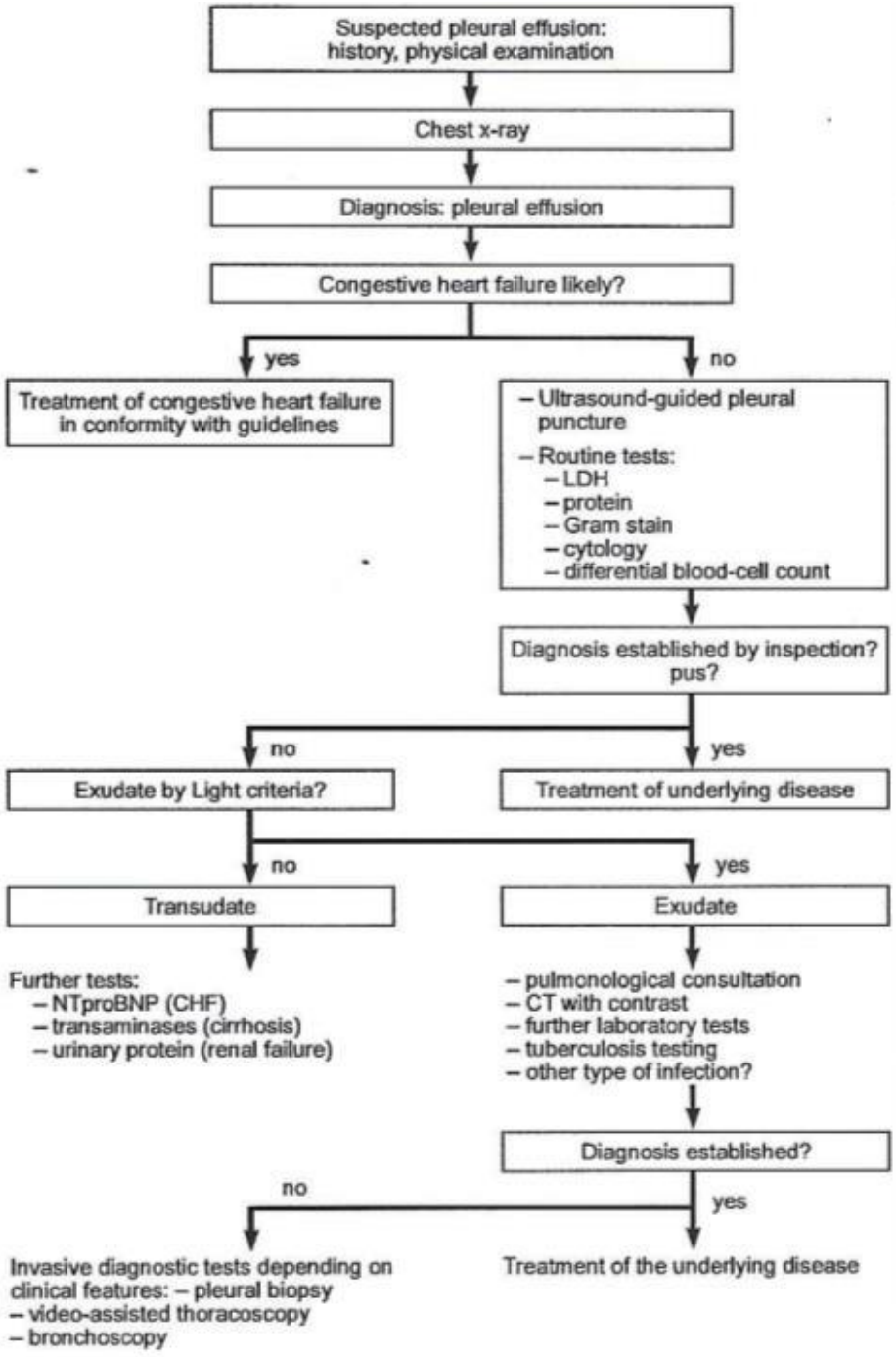

Figure (5): Practical diagnostic/therapeutic algorithm for pleural effusion **(6)** CHF, congestive heart failure; CT, computerized tomography; LDH, lactate dehydrogenase; NTproBNP, N-terminal pro-B-type natriuretic peptide.

Role of coagulation system in pleural effusions

The pleural layers covering the lungs (visceral) and the thoracic wall (parietal) define the pleural cavity, which is responsible for several important functions, including the maintenance of homeostasis. In this context, the interaction between immunologic and metabolic pleural factors should be considered. Their imbalance triggers a sequence of events that generally culminates with the development of a pleural

effusion. According to the pathologic changes, the accumulated fluid is classified as a transudate (an imbalance between the hydrostatic and oncotic pressures in a normal pleura) or an exudate (an inflammatory process with pleural injury)**(21)**.

Characteristically, an exudative effusion demonstrates increased cellularity, protein levels and inflammatory markers. The contribution of the coagulation system is fundamental to the maintenance of homeostasis and should be considered due to its close relationship to the inflammatory process. The coagulation system prevents hemorrhage and initiates tissue repair and remodeling, in addition to orchestrating cellular proliferation, cellular migration and synthesis of inflammatory mediators. The coagulation system, when chronically activated and in the presence of an inflammatory state, can generate adverse effects such as chronic release of procoagulant factors (e.g., tissue factor), cellular activation (adhesion molecules), protein modulation (transformation of fibrinogen into fibrin), and even histological changes promoted by cytokines **(22)**.

All these changes in exudative effusions contribute to tissue remodeling and lead to pleural thickening, trapped lung and functional impairment. It is worth noting that chronic transudates, which have no inflammatory response, are rarely associated with pleural thickening. To recognize the contribution of the coagulation system to the differential diagnosis of pleural effusions, the laboratory profiles of coagulation and fibrinolysis in pleural fluids of different etiologies must be evaluated**(23)**

The etiological diagnosis of the exudates was established by considering, in addition to the clinical parameters, the following criteria **(24)** .

- *Parapneumonic*: radiological study compatible with pneumonia, neutrophilic pleural fluid with a positive culture or the presence of bacteria.
- *Tuberculosis*: lymphocytic fluid (>80%) with rare mesothelial cells (<5%) and an elevated adenosine deaminase (> 40 Ul). The presence of *Mycobacterium tuberculosis* in the fluid, in the pleural fragment and/or granuloma (with or without caseation) in the histology.
- *Malignant*: positive oncotic cytology in the fluid or in the pleural fragment.

It was demonstrated that the coagulation system behaves differently in transudates and exudates, reflecting the pathophysiologic mechanisms involved in the development of pleural effusions. This may be an important addition to the methods for its diagnosis. In transudates, there is no increase in protein and cellular permeability, nor is there an inflammatory response or activation of the coagulation cascade. Homeostasis is disrupted by the imbalance between pressure and oncotic forces, resulting in fluid accumulation with minimal substrate (proteins) and reduced or absent stimuli for structural changes**(25)** .

It has been well documented that inflammatory cytokines play important roles in the coagulation and fibrinolytic systems, which, in turn, influence the inflammatory process. This inflammation-coagulation relationship is of fundamental importance to the pathophysiology of pleural effusions. The inflammatory response that follows the injury is essential in the tissue repair phase. In this context, fibrin deposition represents the substrate for anatomical reorganization and repair. However, depending on several factors, e.g., the intensity and persistence of injury, simple repair (*restitutio ad integrum*) may be replaced by fibrosis with pleural thickening and synechiae **(26)**.

Following tissue injury, vasodilatation secondary to the inflammatory process facilitates the passage of plasma and proteins into the tissue. The binding of tissue factor with factor VII (present in the plasma) forms a complex, activating and initiating the coagulation cascade culminating in the activation of factor X. When this factor acts on prothrombin, it is cleaved into two parts: thrombin and fragment 1+2; this reflects the activation of coagulation. Thrombin, acting directly on fibrinogen, produces fibrin, which is ultimately responsible for pleural thickening **(27)**.

The maintenance of physiological balance is dependent on coagulation inhibitors (antithrombin, C and S proteins). Antithrombin plays an important role by linking itself to thrombin, thus, forming the thrombin-antithrombin complex and blocking thrombin activity. However, once fibrin is formed, the physiological balance is weighted toward lysis (fibrinolysis). In the presence of fibrinolytic activity, an increase in FDP and D-dimer values is observed; the latter being specific to the lysis of polymerized and stabilized fibrin. Inflammatory processes may interfere in the coagulation cascade modifying the reparatory tissue response. In parapneumonic or hemorrhagic effusions, for example, the exaggerated deposition of fibrin frequently produces pleural thickening and septations or loculations **(28)**.

It was demonstrated that in pleural effusions, the coagulation and fibrinolysis profiles reflect the status of the pleural layers. Among inflammatory effusions (exudates), there is coagulation activation due to the production of thrombin (characterized by the increase of F1+2) and

reduction in the levels of fibrinogen (resulting from its consumption). As expected, this determines the activation of the fibrinolytic (increased levels of FDP and D-dimer) and anticoagulation (increased TAT) systems as a counterbalance to the pro-coagulation cascade. The increased formation of fibrin is part of the pathophysiologic mechanism of exudates and is confirmed in the analysis of loculated effusions, which show higher levels of inflammatory markers and lower fibrinolytic activity **(29)**.

Fibrin tissue incorporation as well as fibrinolytic activity occurring in the pleural cavity and observed predominantly in exudates may explain the low concentrations of fibrinogen and increased levels of D-dimer, fibrin degradation products and fragment 1+2 **(30)**.

Routine coagulation tests (PT, TT and APTT) are not adequate to recognize hypercoagulable states. However, they are specific for identifying coagulation deficiency factors in patients with hemorrhagic diseases. The patients in this study showed no changes in routine coagulation tests **(31)**.

The increased levels of fibrin degradation products in malignant and infectious effusions (when compared to transudates) were previously described, also those obtained with transudates, show increase levels of fibrin degradation products and D-dimer values, likely reflecting homeostatic degradation of coagulation proteins. Special characteristics have been described for malignant effusions. High levels of fibrin degradation products and fragment 1+2 (markedly higher than in serum levels) reveal greater activity of the coagulation system in the pleural space, suggesting participation of this system in invasive cancer **(32)**.

It was concluded that the coagulation system plays an important role in pleural diseases and that the understanding of pathophysiological mechanisms may open possibilities for new diagnostic and therapeutic approaches. Differences were observed between transudates and exudates, but not among subgroups of exudates. In transudates, the lower coagulation protein influx and the decreased degradation/activation reflect a lesser degree of injury and inflammatory activity. Since there is little or no injury, the coagulation system is not activated and less reparative action and remodeling occur, diminishing the probability of pleural thickening or loculations **(33)**.

Fibrinolysis and pleural effusion

Aberrant fibrin turnover and intrapleural fibrin deposition appear to play a critical role in the pathogenesis of pleural loculation and fibrosis. The use of fibrinolysins to treat intrapleural loculation and fibrosis, as may occur in hemothoraces and cases of parapneumonic effusions predisposed to organization, is predicated on the concept that disordered fibrin turnover is central to the pathogenesis of these disorders**(34)**.

The natural history of parapneumonic effusions supports this concept and involves 3 phases, including an initial exudative phase characterized by extravasation of plasma constituents into the pleural space. This phase cedes to a fibrinopurulent phase, characterized by an intense local inflammatory response. During this phase, extravascular fibrin forms a continuous film covering the visceral and parietal pleural surfaces. Subsequently, a phase of organization leads to intrapleural fibrosis and loculation **(35)**.

In hemothoraces, a similar progression of events likely contributes to intrapleural organization and fibrotic repair. Fibrin is not detectable in the normal pleural space, but extravascular fibrin deposition is a morphologic attribute of evolving pleural injury. Fibrinous adhesions rapidly form between the visceral and parietal pleural surfaces and are detectable within 1 day after pleural injury induced by intrapleural administration of tetracycline. By trichrome staining, collagen is detectable within fibrinous adhesions by 3 days after tetracycline-induced pleural injury. Morphologic observations therefore support the concept that extravascular fibrin deposition promotes intrapleural organization, loculation, and fibrosis after acute pleural injury **(36)**.

The activity of these plasminogen activators and their ability to augment local generation of plasmin-mediated fibrinolysis are subject to regulation by inhibitors, including plasminogen activator inhibitor-1 and -2 within the pleural compartment, as well as by downstream plasmin inhibitors, including 2-antiplasmin. The intricate balance between plasminogen activators, their inhibitors, and procoagulants is influenced by cytokines or other locally elaborated mediators of inflammation. On balance, the milieu in pleural injury favors coagulation based on relative overexpression of TF. It is also antifibrinolytic, based on relatively increased expression of fibrinolytic inhibitors, including plasminogen activator inhibitors and antiplasmins. Resorption and remodeling of intrapleural fibrin therefore involves diverse interactions between inflammatory mediators and expression of components of the fibrinolytic system (**37)**.

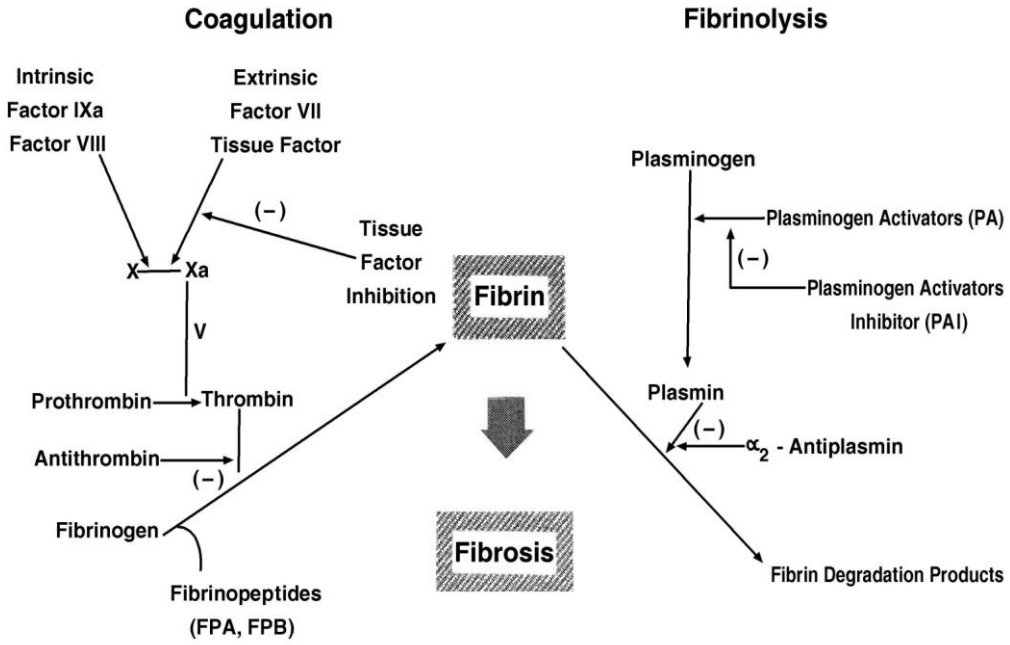

Figure 1: Simplified schematic of the relationship of coagulation and fibrinolytic pathways to fibrin deposition and fibrosis. Solid arrows indicate facilitating interactions. (-) Indicates inhibitory interactions (38)

Organization of transitional fibrin involves collagen deposition within intrapleural adhesions and along pleural surfaces, ultimately facilitating conversion of the fibrinous neomatrix to mature fibrotic tissue. Convincing evidence now supports the idea that disordered fibrin turnover is integral to fibrotic repair rather than incidental to the process. Support for the hypothesis that extravascular fibrin in pleural (or other) diseases is pathophysiologic rather than incidental has previously been reviewed. Briefly, interactions between components of coagulation and fibrinolytic pathways, including the complement and kinin systems, can amplify the local inflammatory response **(Figure 2) (39)**.

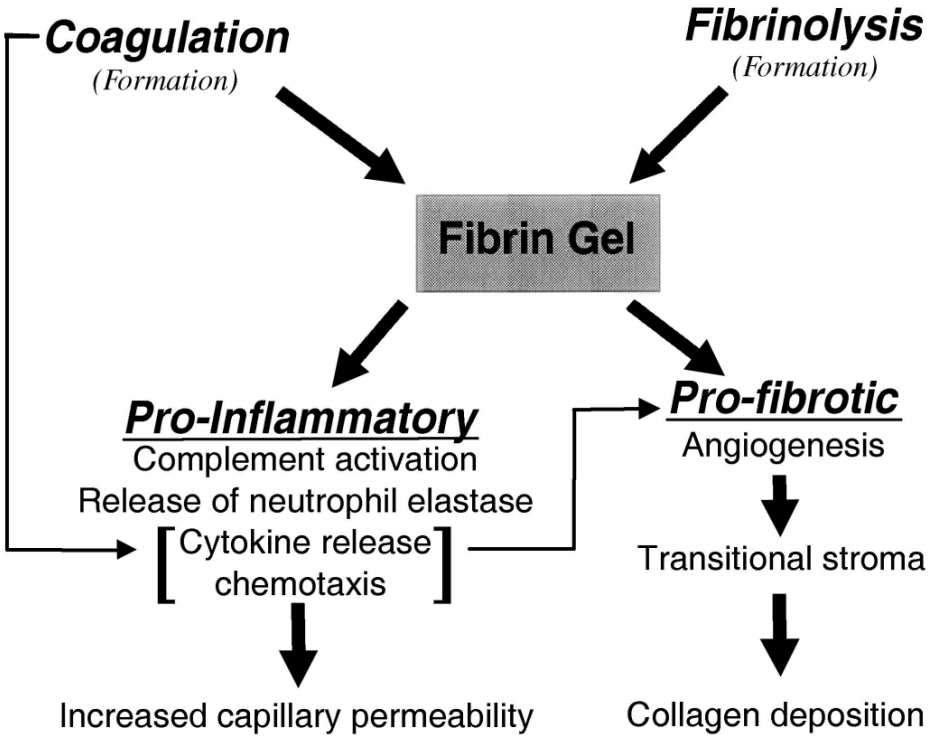

Figure 2: Proinflammatory and profibrotic effects of coagulation and fibrinolytic pathways (38)

Cytokines that have been implicated in pleural diseases, such as TNF-α or TGF-β, can induce TF, as well as endogenous fibrinolysins or their inhibitors. Thrombin can conversely promote expression of selected cytokines and induce increased vascular permeability. In addition, fibrinogen and products of its formation and catabolism can independently promote proinflammatory or reparative responses. These include immune responses, as well as those regulating vascular permeability and inflammatory cell traffic. Activation of TGF-β is also mediated by plasmin, thereby promoting fibrotic repair. TGF-β, in turn, induces PAI-1 expression, potentiating a decrement in local fibrinolysis, a pathway that occurs in both parenchymal lung injury and pleural inflammation **(40)**.

Regulation of the fibrinolytic system in pleural injury components of the fibrinolytic system, including uPA, PAI-1, and the urokinase receptor (uPAR), are all expressed within the pleural compartment and regulate the activity of endogenous fibrinolysis in the setting of pleural injury. A relatively inactive single polypeptide chain proenzyme, prouPA, or single chain uPA (scuPA) is the form of uPA released from cells. Through limited proteolysis, scuPA may be converted to the relatively more active 2-chain uPA, tcuPA, which has previously been used to effect intrapleural fibrinolysis. Intravascular thrombolysis is mainly attributable to tPA, while uPA is mainly involved in extravascular proteolysis and tissue remodeling. Both uPA and tPA are detectable within pleural fluids **(41)**.

Pleural fluid d-dimer in the diagnosis of pleural effusion

Pleural effusion has many etiologies including malignancy, infection, congestive heart failure and collagen vascular diseases. Although the pathophysiological mechanisms involved in pleural effusion are known, it is difficult to differentiate between malignant and non-malignant causes of effusion. It was shown that patients with pleural effusion due to malignancy exhibit decreased fibrinolysis. It has been hypothesized that pleural effusion causes activation of the normal mesothelial cells, which in turn is followed by activation of a coagulation cascade and the inhibition of fibrinolysis into the pleural space. The accumulations of fibrin into the pleural cavity may serve as a reliable marker for determining the cause of the pleural effusion(**42)**.

Characteristically, an exudative effusion increases the cellularity, higher protein levels and various inflammatory biomarkers. The coagulation system is fundamental for the maintenance of homeostasis and should be considered due to its close relationship to the inflammatory process. When blood enters the pleural space, the coagulation system comes into action when there is severe inflammatory response of pleura as the presence of TPE may injure pleura and induce coagulation activation, which leads to enhanced fibrinolytic activity due to the large amounts of plasminogen and plasminogen activators present in the pleural space and results in a high pleural D-dimer level. The plasminogen activators convert the plasminogen into active plasmin, which, in turn, enzymatically breaks down fibrin. The D-dimer is the primary degradation product of cross-linked fibrin which serves as a marker of coagulation with fibrinolysis **(43)**.

A previous study concluded that the levels of fluid D-dimer are higher in TPE as compared to non TPE and hence it can be used as a novel marker in the diagnosis and differentiation of TPE and non TPE **(44)**.

During fibrinolysis, fibrin and fibrinogen split to various fibrin/ fibrinogen degradation products and finally to the terminal product D-dimer in a process mediated by plasmin. It was demonstrated that malignant pleural effusion causes activation of the coagulation process in the pleural space, resulting in the formation of D-dimer as a split product of fibrin. Elevated levels of D-dimer are expected both in the blood and in the pleural fluid. High D-dimer levels were found among malignant pleural effusion.

Lately there are indications that it as a significant marker for the differentiation of malignant, parapneumonic and tuberculous effusion. Yet the differences that exist among the aforementioned coagulation factors and D-dimer indicate significant disorders which may have contributed to the demarcation of patients with pneumonia with or without pleural effusion, especially when it comes to CPPE. Coagulation disorders can lead to death in a patient as a result of developing pulmonary embolism. Different disorders can lead to dysfunction of various organs as a result of the interplay of inflammation, coagulation, and organic dysfunction **(45)**.

The role of D-dimer in pleural effusion was previously assessed. It was reported that pleural D-dimer levels measured by ELISA were significantly higher in pleural fluid from patients with tuberculosis pleuritis and empyema than the levels found in pleural effusion from patients with malignant pleural effusion. It was also found that D-dimer positively correlated with LDH in pleural effusion. In contrast, no significant difference was found in the mean pleural D-dimer

levels from different etiologies including empyema, tuberculosis, cardiac failure, and cancer. However, the number of patients was small in each disease category and therefore, their conclusions should be interpreted carefully**(42)**.

Plasminogen activators were reported to be significantly lower in malignant effusion than in other types of fluids. The concentrations of plasminogen activator inhibitor 2 in empyema and complicated parapneumonic effusions exceeded those in tuberculous effusions. In addition, the pleural fluid levels of tissue plasminogen activators were higher in patients with malignancy compared to other patients. This data support the importance of pleural injury as a cause of increased intrapleural fibrinolytic activity in malignant pleural effusion **(46)**.

Plasma D-dimer levels are found to be high in chronic malignant effusions and decreased six hours after intrapleural instillation of quinacrine. It was suggested that an activated fibrinolytic system with a chronic malignant effusion is partially deactivated after intrapleural quinacrine instillation. It was reported that impairment in fibrin formation or increased intrapleural fibrinolysis would lead to failure of pleurodesis. Fibrinolytic activity, as assessed by plasma D-dimer levels, showed a clear decline 24-hours in patients with a good pleurodesis outcome, in contrast to those with a poor outcome and to those in the control group who had no significant change in plasma D dimer levels with time **(42)**.

Two major fibrinolytic activators compared, urokinase-type plasminogen activator (u-PA) and tissue-type plasminogen activator (t-PA) in plasma and pleural effusions from malignant mesothelioma (MPM), lung cancer, and benign effusions. It was found that the fibrinolytic markers were higher in the MPM and lung cancer patients. In patients with malignant effusions from cancer, a highly activated coagulation system in the blood and their malignant effusions, as indicated by high levels of prothrombin F1.2 fragments and D-dimer (both plasma and pleural) was found. It was concluded that potential therapeutic approaches should include the application of drugs targeting the coagulation system **(47)**.

The role of plasma D-dimer was assessed in patients with lung cancer and its prognostic significance. It was concluded that plasma D-dimer might be useful for predicting the clinical outcome in patients with lung cancer. It was reported that plasma D-dimer levels decrease after response and increase with progressive disease and can act as a predictive factor for the evolution of the disease. These data suggest the significant role of fibrinolytic markers and especially the plasma D-dimer in lung cancer **(48)**.

Additionally, D-dimer is an objective biomarker for predicting PE in patients with TPE. Most patients with TPE had elevated plasma D-dimer levels. Among TPE patients, plasma D-dimer levels were higher in PE patients than in non-PE patients. To avoid unnecessary radiological tests, the rule out cut-off point of D-dimer at 1.18 mg/L rather than a fixed 0.5 mg/L or age-adjusted D-dimer level in the TPE population should be set. The imbalance of prothrombotic and antithrombotic cytokines may partly be attributed to the formation of pulmonary emboli in patients with TPE **(42)**.

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