ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ

ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ

ΠΝΕΥΜΟΝΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ

ΔΙΕΥΘΥΝΤΗΣ: ΚΑΘΗΓΗΤΗΣ Κ.Ι.ΓΟΥΡΓΟΥΛΙΑΝΗΣ

ΔΙΔΑΚΤΟΡΙΚΗ ΔΙΑΤΡΙΒΗ

<<ΘΝΗΣΙΜΟΤΗΤΑ ΟΙΑΣΔΗΠΟΤΕ ΑΙΤΙΟΛΟΓΙΑΣ

ΜΕΤΑΞΥ ΝΟΣΗΛΕΥΟΜΕΝΩΝ ΑΣΘΕΝΩΝ

ΣΤΟΥΣ ΟΠΟΙΟΥΣ ΑΝΕΥΡΕΘΗΚΕ ΥΠΕΖΩΚΟΤΙΚΗ ΣΥΛΛΟΓΗ>>

ΜΑΡΚΑΤΗΣ ΕΛΕΥΘΕΡΙΟΣ

ΙΑΤΡΟΣ ΠΝΕΥΜΟΝΟΛΟΓΟΣ

ΛΑΡΙΣΑ 2023

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«Η έγκριση της διδακτορικής διατριβής από το Τμήμα Ιατρικής της Σχολής Επιστημών Υγείας του Πανεπιστημίου Θεσσαλίας δεν υποδηλώνει αποδοχή των απόψεων του συγγραφέα (σύμφωνα με τις διατάξεις του άρθρου 202, παράγραφος 2 του Ν. 5343/1932)»

ΕΥΧΑΡΙΣΤΙΕΣ

Θα ήθελα να ευχαριστήσω τον επιβλέποντα Καθηγητή κ. Κωνσταντίνο Γουργουλιάνη για την υποστήριξή του σε όλη τη διάρκεια της εκπόνησης της διδακτορικής διατριβής.

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Αφιερωμένο στην μνήμη των ασθενών μας που έφυγαν από τη ζωή

ΠΕΡΙΕΧΟΜΕΝΑ

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INTRODUCTION

Pleural effusion (PE) results from a wide spectrum of systemic, malignant, infectious and inflammatory diseases**.** Over 50 causes have been documented, while congestive heart failure, malignancies, and pneumonia account for most of the cases **[1], [2].** Pleural effusions affect over 2 million patients per year in Europe **[3]**, 1.5 million in USA **[4]** and 200.000 in UK **[5].** The burden of PE is expanding following an increasingly older population living more with chronic diseases that associate with PEs **[6].** Quite surprisingly, even though the overall incidence of PE is estimated in 360 cases per 100.000, that is comparable to asthma and COPD **[7]**, research lags much rarer respiratory diseases (e.g., pulmonary hypertension) **[6]**.

Fortunately, recent advances in our understanding of pleural pathology **[8]**, along with the established use of thoracic ultrasound **[9]** and the emergence of minimally invasive techniques (e.g., image guided pleural biopsies, medical thoracoscopy, indwelling pleural catheters) **[10],** have generated a wave of high quality, large scale studies that changed the landscape, especially considering pleural infection and malignant pleural effusion **[11], [12], [13], [14], [15], [16].** Thus, clinical practice is now increasingly becoming evidence based and pleural medicine is recognized as an exciting subspecialty with dedicated clinicians and specialist pleural services in many hospitals **[17].**

A specific area that has attracted interest is the prognostic significance of pleural effusions. It is well established that PE significantly affect the prognosis and mortality, depending on etiology. This applies to patients with malignant pleural effusion whose mean survival is 1,5 to 7 months **[18],** to patients with

pleural sepsis **[19],** but also to patients with acute decompensated heart failure **[20].** However, their impact on morbidity and mortality of hospitalized patients comparatively has been limited studied over the past decade. In particular, Kookoolis and colleagues, in a small retrospective study of 104 patients of pathological specialties in whom pleural effusion was found on chest x-ray during admission, found in those patients mortality 15% at 30 days and 32% in 1 year. Risk factors among those patients, of which only 1 out of 10 underwent a diagnostic puncture, were age, severity of disease based on Apache score, malignancy and underlying lung disease **[21].** Debiasi and colleagues from the same center studied prospectively 308 patients that all underwent diagnostic puncture. Mortality was higher in patients with malignant effusion (37% at 30 days, 77% at 1 year) but high mortality was highlighted in patients with bilateral effusions regardless of etiology against unilateral effusions (mortality 47% at 30 days, 69% at 1 year) **[22].** Finally, Walker and colleagues prospectively studied 356 patients with nonmalignant pleural effusions in a single center. All patients underwent thoracentesis as well. Cardiac, renal, and hepatic failure were associated with 50%, 46%, and 25% 1-year mortality respectively, while bilateral and transudative effusions were associated with worse prognosis (57% and 43% 1-year mortality rate, respectively) **[23]**.

The purpose of the present study is to investigate short-term and long-term effect of pleural effusion detected in chest and/or upper abdomen CT scan, on mortality and days of hospitalization, as long as possible correlations with the size, the distribution and the etiology of PE.

GENERAL PART

CHAPTER 1

GENERAL FOR PLEURAL CAVITY AND PLEURAL EFFUSION

1.1 Embryology and anatomy of the pleural cavity

During the third week of gestation, the mesoderm differentiates into three different parts: the paraxial, the intermediate, and the lateral plates. The lateral plate has two different layers, the somatic mesoderm or somatopleure, and the splanchnic mesoderm or splanchnopleure. The somatopleure will become the parietal pleura, while the splanchnopleure is the visceral layer of the pleura. Somatopleure migrates ventrally towards the midline creating the intraembryonic cavity that will form the three central body cavities: pericardium, pleura, and peritoneum. The pleurae are serous epithelial layers (membranes) of simple squamous cells, also known as mesothelium, supported by connective tissue. The two pleurae for each thoracic cavity fold back onto themselves to form two distinct membranous structures. The inner membrane called the visceral pleura covers the lungs, while the outer membrane called the parietal pleura is attached to the chest wall **[24-26].** The visceral pleura receives blood supply from the bronchial circulation while the parietal pleura from the intercostal arteries. The parietal pleura can sense pain, nerved by the intercostals and the phrenic nerve. Conversely, the visceral pleura is nerved by the autonomic nervous system (ANS) and lacks sensory innervations **[27]**.

1.2 Physiology of pleural cavity

The physiological function of the pleural cavity is still under debate. One theory is that the slightly negative pressure (−3 to −5 cm of water) resulting from the two opposite elastic recoils of the lung and chest wall prevents atelectasis by maintaining a positive transpulmonary pressure **[28].** Another mechanical function proposed is based on pleural fluid. The pleural cavity typically contains approximately 0, 26 ml/kg bodyweight of pleural fluid produced mainly at the parietal pleura and reabsorbed by parietal pleural lymphatics. This fluid continuously lubricates the pleural surface and makes it easy for the lung to move during inflation and deflation **[29]**. Interestingly, the fact that parietal and visceral pleura define two noncontiguous spaces (hemithoraxes) seems to have a "life saving" effect in cases of thoracic trauma, in contrast to the case of North American Bison, where a single blunt can cause bilateral pneumothorax with fatal outcome **[30].**

1.3 Pleural effusion formation

According to Starling's equation, pleural fluid formation is regulated by the balance of hydrostatic and osmotic pressures. The parietal pleura receives blood supply from systemic capillaries (mainly intercostal arteries) with a high-pressure regimen and visceral pleura from both bronchial and pulmonary artery (low-pressure regimen). Considering these differences, the driving force determining the movement of the liquid has been estimated to be six cmH2O from the parietal pleura into the pleural space **[31] [figure 1].** Interstitial lymphatics mainly provides absorption through the stomata of the parietal pleura. The "stomata" are slit-shaped holes found mainly in the lower parts of

[13]

the lateral and mediastinal pleura. Above the stomata, dilated lymphatic spaces called "crypts" (lacunas) serve to collect the pleural fluid to be drained **[32].** Worthmentionly, lymphatic vessels can increase their flow rate 20 times in response to increases in pleural fluid production **[33].** Pleural effusions result from severe disruptions in the balance between production and absorption**,** and likely mechanisms are abnormalities in hydrostatic and oncotic pressures, changes in pleural membrane permeability, and blockage of lymphatic drainage **[34].** An imbalance between pressures leads to transudate PE, while local inflammation affecting membrane permeability or disruption of lymphatic drainage leads to exudative effusions **[35].**
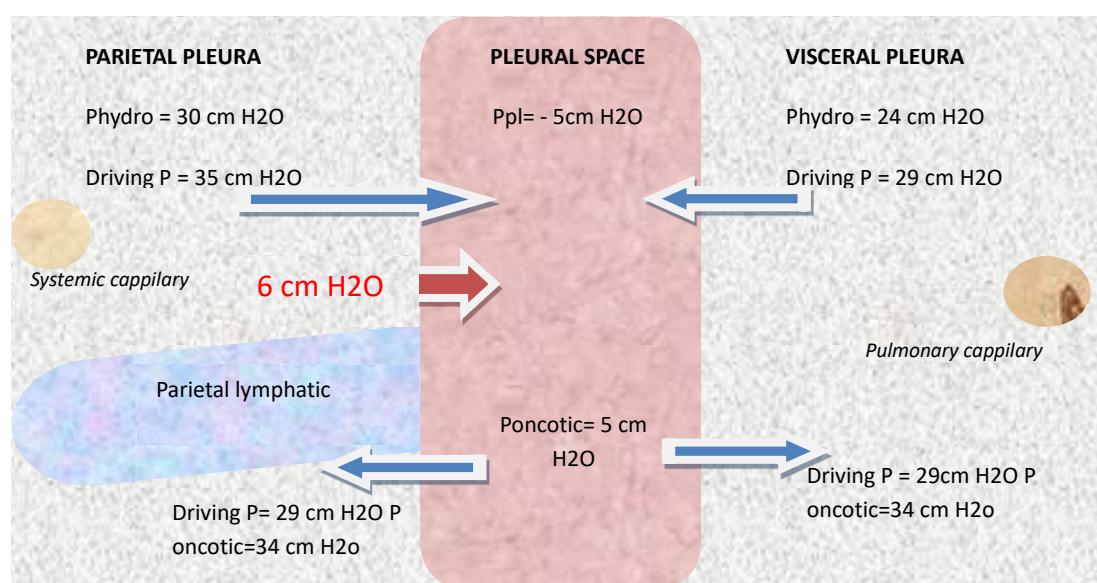

Figure 1] The physiological pleural fluid turnover

[14]

1.4 Pathophysiologic effects of pleural effusion

Pathophysiologic effects of PEs have been studied with contradictory results, partly because of the small and heterogeneous cohorts of patients studied **[36], [37].** A study investigating changes in pulmonary function, arterial blood gases, and dyspnea after thoracocentesis showed small but significant improvements in FEV1, FVC, PaO2, A-a O2 gradient, and the Borg scale in patients with the paradoxical movement of hemidiaphragm **[38].** In a prospective study of 25 patients assessing the effect of pleural effusions on exercise, thoracentesis significantly improved breathlessness and 6-min walk test **[39].** In comparison, in another study of 19 patients with large effusions, sleep quality improved after thoracentesis **[40]**. Studies on mechanically ventilated patients report improvements in oxygenation, respiratory mechanics, and diaphragmatic function after pleural fluid drainage **[41], [42].** However, in an older meta-analysis of 1124 mechanically ventilated patients with PE, fluid drainage failed to improve important clinical outcomes such as duration of ventilation or length of stay **[43].** Studies increasingly use patient-reported outcome measures to provide a better insight into the pathophysiology of PE-related symptoms **[44-46].** However, as mentioned above, designing high-quality studies on pleural physiology is quite challenging given the heterogeneity of study populations, the difficulty in optimal timing of symptom assessment, and the cofounding comorbidities that contribute to presenting symptoms **[47].**

[15]

CHAPTER TWO

DIAGNOSTIC APPROACH TO PLEURAL EFFUSIONS

2.1 Initial approach

The initial approach to the patient with PE remains a combination of clinical examination, radiological findings, and pleural fluid analysis before any other more invasive intervention is decided **[48] (Figure 2)**.

A medical history of heart failure, malignancy, liver cirrhosis, chronic hemodialysis, connective tissue disease, or recent surgeries (abdominal or cardiac) provides information for the cause of PE. Occupational asbestos exposure should raise suspicion for mesothelioma, though *medication use history* should always be obtained (amiodarone, methotrexate, nitrofurantoin are among the commonest) **[49].**

Symptoms are common but not specific. Breathlessness is the main presenting symptom, usually described as chest tightness, the effort to breathe or air "hunger" **[50].** Chest pain usually suggests pleura disease, such as pleural infection, malignancy, or pulmonary embolism. Cough is not specific, and other symptoms such as fever, hemoptysis, weight loss, and anorexia should indicate pleural infection, tuberculosis, or malignancy **[49].** An interesting cross-sectional study from India examined 278 patients admitted with respiratory symptoms in a rural hospital to evaluate the diagnostic utility of physical signs between patients with suspected PE. Asymmetric chest expansion, dull percussion, decreased or absent breath sounds, reduced vocal fremitus, and reduced vocal resonance had high diagnostic accuracy and excellent inter-observer agreement **[51].** Clinical signs suggestive of common diseases such as peripheral edema, orthopnea, elevated jugular venous pressure for HF,

[16]

ascites for hepatic hydrothorax, pericardial friction rub for pericarditis, or lower extremity swelling pulmonary embolism should guide diagnostic pathway **[52].**

2.2 Imaging

A chest radiograph is usually the first imaging modality. Signs of pleural effusion are present when the amount of pleural fluid is >50ml for lateral or >200ml for posteroanterior view **[53].** Chest radiograph may reveal concomitant pathologies including consolidations, masses, mediastinal enlargements, pleural plaques, etc. Difficulties arise in an ICU setting where supine views are less sensitive, and PE appears as a veil-like opacity in the affected side **[49]**. Massive effusions cause a 'white lung' image, and the position of mediastinum will deviate away from the PE. On the contrary, a shift toward PE raises suspicion of lung collapse **[49].** Particular attention should be paid to identifying subpulmonic effusions causing rise or inversion of hemidiaphragm and capsulated effusions mimicking masses (phantom-tumors) **[54].**

According to BTS guidelines, a contrast-enhanced CT is the next step when thoracentesis is not diagnostic, and it should ideally be performed before complete drainage **[48].** Indeed, in a series of 32 patients with pre-and post-drainage CTs, the latter failed to provide additional information in the decision-making process **[55].** CT is essential in diagnosing and managing malignant disease and empyema. Leung and colleagues showed that nodular pleural thickening, mediastinal pleural thickening, parietal pleural thickening >1 cm, and circumferential pleural thickening had specificities of 94%, 94%, 88%, and 100%, respectively, and sensitivities of 51%, 36%, 56%, and 41% respectively, in diagnosing malignancy **[56].** The accuracy of these findings was further

[17]

validated in prospective studies **[57], [58].** It is worth mentioning that retrospective studies have reported a low negative predictive value of CT in detecting malignant pleural disease, suggesting that CT alone cannot rule out malignancy **[59], [60].** Furthermore, a recent prospective study highlighted the need for CT abdomen additionally to standard imaging. In this cohort of 249 patients with unilateral effusions, clinically significant findings below the diaphragm (primary tumor, metastasis lesions, or alternative sites for biopsy) were identified in 59 patients **[61].** CT helps distinguish uncomplicated parapneumonic effusions from complicated parapneumonic effusions/empyema since pleural thickening and 'split pleura' sign, caused by the separation of parietal and visceral pleura, are both characteristic for the latter **[62-64].** Guidelines have excluded PET-CT from routine use in diagnosing pleural malignancy **[48]**. It provides only additional information in differentiating benign from malignant PEs with sensitivity and specificity between 86-95% and 61-82%, respectively **[65].** A predictive model based on PET-CT recently showed good diagnostic utility in differentiating malignant from benign PE in patients with lung adenocarcinoma. This model used surem levels of CEA, obstructive atelectasis or pneumonia, maximum standardized uptake value (SUVmax) of tumor and attachment to the pleura, SUVmax of pleura, and SUVmax of PE **[66].**

Thoracic ultrasound (TUS) has changed the landscape in diagnosing and managing pleural diseases due to its portable, non-ionizing, economic, and real-time assessment nature **[67]**. TUS is far more sensitive than chest radiograph in detecting PE (sensitivity 100% for diagnosing effusions > 100 ml) and provides additional information on the size of PE **[68]**. However,

[18]

echogenicity cannot safely discriminate between transudate and exudate **[69].** It is well established that TUS reduces complications during thoracentesis. In a large cohort of 61,261 thoracenteses, almost half performed under TUS guidance, the use of TUS reduced the risk of pneumothorax and bleeding by 19% and 68%, respectively, and the length of hospitalization and associated cost **[70].** Compared to CT, TUS allows better identification of septations **[71-73]** and even resembles CT in the characteristic diagnostic signs of malignancy (pleural nodularity, pleural thickening > 1 cm, hepatic metastasis) with pooled sensitivity and 79% and 100%, respectively **[74].** It is highly recommended that both thoracentesis and chest tube insertion be performed under TUS guidance to ensure a successful and safe procedure **[48].** Moreover, TUS should guide drain placement into the largest locule of parapneumonic effusion since different values of pleural fluid pH in different locules can misdirect management strategy **[75].** Other promising uses of TUS have emerged lately. Identification of trapped lung prior to drainage allows the optimal management choice in MPE (e.g., pleurodesis vs. indwelling pleural catheter) **[76]**. The absence of "lung sliding sign" (when normal visceral pleura moves beneath the parietal pleura) indicates the success of pleurodesis and was recently tested in a large multicenter RCT investigating routine use of TUS in pleurodesis pathways. This study showed that a TUS-guided methodology leads to shorter hospital stays without reducing the three-month success rate **[77].** Similarly, another prospective study examined whether TUS-reported adhesions pre and post-talc can predict pleurodesis success at 1-month and 3-month follow-up **[78].** Finally, a quantitative marker

[19]

of pleural inflammation based on the echogenicity of PE was currently proposed to guide future management of PPE **[79].**

2.3 Thoracentesis and pleural fluid analysis

In a typical clinical context with symptoms of heart failure and cardiomegaly with bilateral effusions in imaging, thoracentesis is not necessary. Treating the cause and follow up is warrant **[80].** However, it is worth mentioning that bilateral effusion is not an absolute marker of an underlying transudative process, and a second etiology is more common than previously believed **[81].** In a prospective study for 5 years, almost 20% of bilateral effusions were finally secondary to a malignancy **[82].** Thus, even in cases of known diseases resulting in transudates, atypical clinical features (e.g., fever, chest pain, high inflammatory markers), or suspicious TUS findings (e.g., septations) should prompt sampling of the pleural fluid **[83].** Bilateral thoracentesis is not recommended, since etiology is mostly the same in both sides **[80], [84], [85].** In any case, interpretation of pleural fluid should always be made in the context of clinical and radiological signs **[34].**

Generally, thoracentesis is considered the cornerstone of diagnosing a pleural effusion **[52].** Firstly, the appearance of pleural fluid provides information on the underlying diagnosis. Bloody fluid is noted in malignancies, infections, trauma, or coronary artery bypass surgery (CABG). A pleural fluid hematocrit > 50% of serum hematocrit is diagnostic for hemothorax. Frank pus is empyema, while milky appearance after centrifuging should raise suspicion for chylothorax **[34].** A variety of examinations is routinely asked, including ph,

[20]

biochemistry (protein, LDH, glucose), cytology for differential cell count and abnormal cells and microbiology (cultures and sensitivity) **[86].**

Dr Light's criteria, first reported half a century ago, remain of great value for differentiating transudative from exudative effusions **[87].** They were modified and further validated with great accuracy **[88].** Based on these criteria, a pleural fluid is exudate when one or more of the following criteria are met: Pleural fluid protein/ serum protein > 0.5, Pleural fluid LDH/ serum LDH >0.6 or pleural fluid LDH> 2/3 of the upper limit of normal serum LDH **[87]**. Almost 27% of heart failure-related PEs treated with diuretics will be misclassified as exudates **[89].** In such cases**,** serum to pleural fluid protein gradient > 3, 1 g/dl and high levels of serum (or pleural) NT-proBNP are diagnostic for heart failure **[90].** However, the benefit from ''overclassifying'' exudates, is that important causes of exudates such as malignancies will not be missed **[86].**

Even before biochemistry, a pleural fluid ph will be obtained. Normal pleural fluid pH is approximately 7.6, determined by the acids generated from metabolism of cells within the pleural space. It is affected in acute inflammation (e.g., infection), tumor infiltration (pleural malignancies) and chronic conditions (e.g., rheumatoid pleurisy). Low pH is most used to guide the need for chest tube drainage in pleural infection **[19], [91]** or even predict poor response of pleurodesis in malignant pleural effusions **[92].** Glucose, traditionally used alongside ph to guide diagnosis, doesn't seem to add on the information obtained from ph, as demonstrated in a recent large multi-center study **[93].** It should be mentioned that the accuracy of measured pH is dependent on sample collection method, since heparin, residual air, or even delay in analysis can change pH and impact on decision making **[94].**

[21]

Differential cell count may further direct our diagnostic thought, but it generally lacks specificity and sensitivity. Lymphocyte predominance suggests a chronic disease with heart failure, malignancy and tuberculosis being the most common diagnosis. Other etiologies include post-cardiac bypass graft, organ failure, rheumatoid arthritis and rarely parapneumonic effusions (PPE). Neutrophilic effusions indicate acute illness (pleural infection, pulmonary embolism) **[34], [95].** Eosinophilic effusions are defined as pleural fluid eosinophils >10% and occur in almost 7% of all patients with PE as shown in a large retrospective analysis of 2,205 pleural fluid samples **[96].** In a prospective study of 476 patients, survival was significantly better in patients with eosinophilic PEs than in those with non-eosinophilic. However, a malignant etiology was seen with insignificantly different prevalence between the two groups **[97]**. Moreover, eosinophilic predominance adds little to the differential diagnosis of PE as it may well arise from malignancy, infection, trauma, drugs or even unknown etiology **[98].** Given this diversity a structured approach to diagnose eosinoplhic PEs should be followed **[99].**

Cytology is widely used to establish the diagnosis of malignancy. Unfortunately, even after a second aspiration, the diagnostic accuracy doesn't exceed 80% **[100].** In a recent large UK-based prospective study of 921 patients, the overall sensitivity of fluid cytology to diagnose malignancy was 46% (95% CI 42-58%), highly dependent on the primary site of malignancy, with adenocarcinomas significantly higher sensitivity (79%) than hematological malignancies (40%) or mesothelioma (6%) **[101].** This study further suggested that patients with clinical suspicion of mesothelioma should be earlier applied

[22]

for definitive investigations (e.g., thoracoscopy) and diagnosis should not be delayed pending cytology answer **[HASSAN 2020].**

Research in biomarkers in pleural fluid has gained interest, despite being quite demanding since validating diagnostic accuracy is highly affected from the patient group studied. Nevertheless, some biomarkers have made it to everyday clinical practice. That applies especially to adenosine deaminase (ADA) that has shown strong negative predictive value in areas with low incidence for tuberculosis **[102].** Moreover, pleural fluid NT-pro-BNP is a useful biomarker with high diagnostic accuracy for PE of cardiac origin (sensitivity 94-95% and specificity 91-94%) **[103].** An ongoing study compares the diagnostic accuracy of known and novel biomarkers e.g., soluble Fas ligand, presepsin, pentraxin-3, soluble B7, IL-27 etc. **[104].**

2.4 Invasive interventions

Pleural biopsies have an increasing role in pleural effusion diagnostics. Percutaneous pleural biopsies are increasingly performed under direct CT or TUS image guidance with 70-90% **reported sensitivity.** The choice of imaging highly depends on local access and expertise but generally TUS offers a non-ionizing, safe procedure even in outpatient setting **[105-107].** Blind pleural biopsies (Abrams and Cope needle) have low sensitivity for diagnosing malignancy (<60%) and are performed nowadays only in diffuse diseases such as TB pleurisy from experienced clinicians in resource-poor settings **[108], [109].** Thoracoscopy, both medical (MT) and surgical (VATS), is the gold standard for obtaining adequate pleural tissue. It offers visual inspection of the pleural cavity and access to pleurodesis or IPC insertion (in cases of non-

[23]

expandable lung). Both procedures have high diagnostic yield (> 90%) for pleural malignancy, but MT should be preferred since it offers accepted sensitivity with lower costs and less risks for the patients **[110].** Conclusively, the trend in pleural diagnostics is towards a ''less is more'' model, given that procedures are performed in specialized pleural units, minimizing hospital admissions and shortening time to diagnosis **[83].**
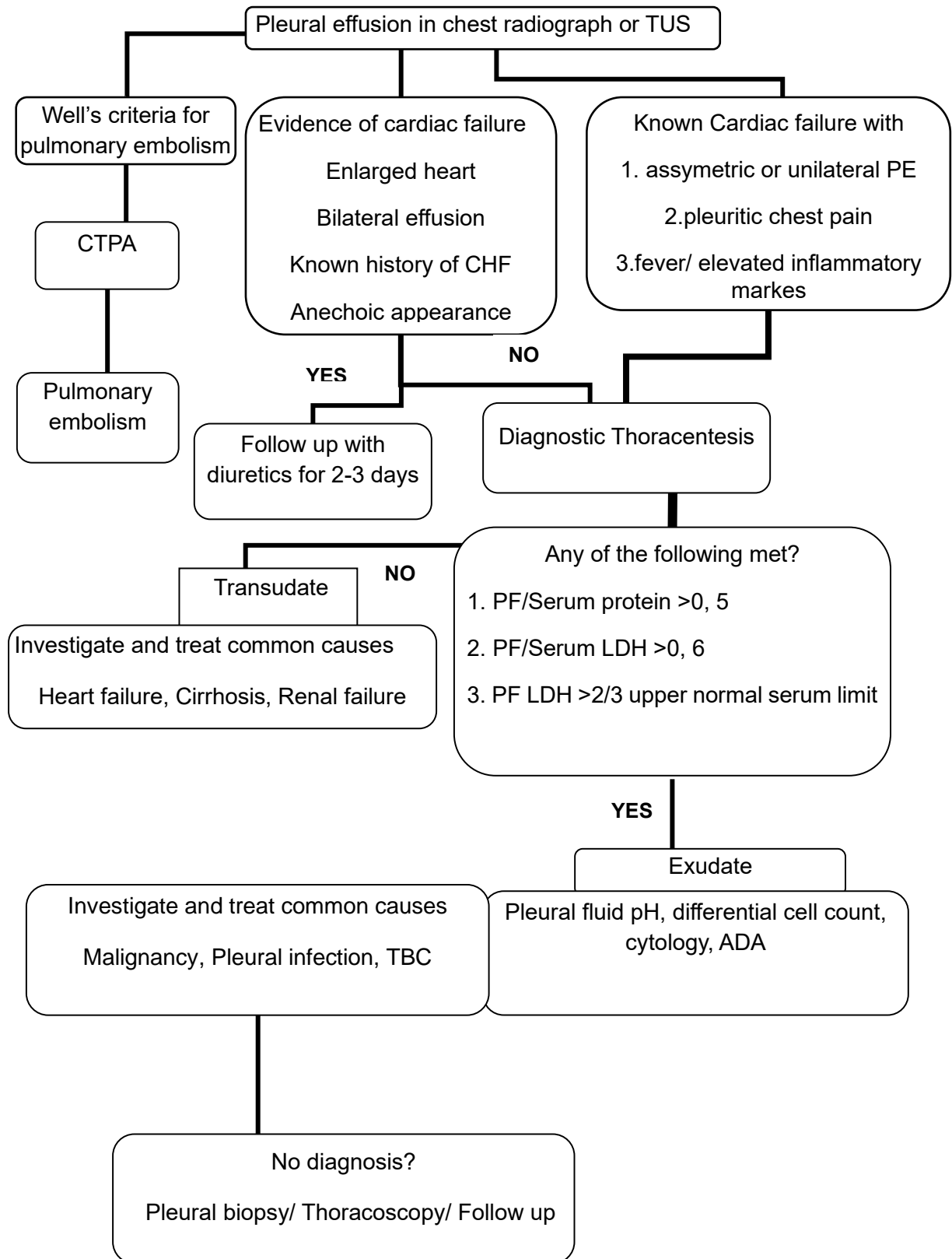
[24]

Figure 2] Initial approach to a patient with pleural effusion

[25]

CHAPTER 3

MAIN CAUSES OF PLEURAL EFFUSIONS

In an old population study from Czechoslovakia, the most common etiologies of PE were congestive heart failure (46%), malignancies (22%), parapneumonic effusions (17%), and pulmonary embolism (5.6%) **[111].** Later, Dr Light reported the annual incidence of common causes of PEs in USA, with similar results **[52].** A slightly different pattern was reported in another large study with more than 3000 patients in Spain [**2] [Tables 1-2].** Apart from these common causes, the catalogue of diseases known to cause PE is long, with more than 50 documented diseases **[Table 3].**

MAREL	CHF 46%	MPE 22%	PPE 17%	Emb 5.6%
LIGHT	CHF 33%	PPE 20%	MPE 13%	Emb 10%
PORCEL	MPE 27%	CHF 21%	PPE 19%	TB 9%

Tables 1] Leading causes of PE in different regions

Heart failure	500,000	Viral disease	100,000
Pneumonia	300,000	Post coronary-artery bypass	50,000
Cancer	200,000	Cirrhosis	50,000
Pulmonary Embolism	150,000	Gastrointestinal disease	25,000
		Tuberculosis 2,500	

Table 2] Annual incidence of leading causes of PE in USA [52]

[26]

Transudative effusions	Exudative pleural effusions
1. *Congestive heart failure* 2. *Cirrhosis* 3. *Nephrotic syndrome* 4. *Peritoneal dialysis* 5. *Hypoalbuminemia(albumin,<1.5mg/dl)* 6. *Superior vena cava obstruction* 7. *Myxedema* 8. *Urinothorax* 9. *Glomerulonephritis* 10. *Cerebrospinal fluid leak to pleura*	1. *Infectious*: bacterial, viral, tuberculosis-related, fungal, parasitic 2. *Neoplasmatic*: metastatic disease (e.g., lung cancer, breast cancer, lymphoma) 3. Paramalignant effusions: reactive pleuritis due to underlying lung cancer 4. *Pulmonary embolism* 5. *Gastrointestinal disease:* pancreatitis, cholecystitis, abscess, post abdominal surgery 6. *Heart diseases:* post coronary artery bypass graft (post-CABG) surgery, post cardiac injury (Dressler syndrome), pericardial disease 7. *Gynecologic*: ovarian hyperstimulation, Meigs' syndrome, endometriosis 8. *Collagen vascular disease*: rheumatoid arthritis, systemic lupus erythematosus, drug-induced lupus, Sjogren syndrome, Churg-Strauss syndrome, Wegener granulomatosis 9. *Medications*: nitrofurantoin, dantrolene, methysergide, dasatinib, amiodarone 10. Methotrexate, interleukin-2, clozapine 11. *Hemothorax* 12. *Other:* a. Chylothorax (trauma or lymphoma) b. Sarcoidosis c. Trapped lung d. benign asbestos pleural effusion e. uremia, yellow nail syndrome f. drowning, amyloidosis, electrical burns g. iatrogenic effusion, h. capillary leak syndromes i. extramedullary hematopoiesis

Table 3] Differential diagnosis of pleural effusion [52]

[27]

3.1 Heart failure

Congestive heart failure (CHF) is a common disease affecting over 23 million people worldwide **[112]**. During the last twenty years, mortality rates have ranged from 10–20% during the first month after hospital admission to 30–45% after one year and over 50% within five years of diagnosis **[113-117].**

In a meta-analysis of 31 studies including more than 40,000 patients, HF with reduced ejection fraction (EF) demonstrated a higher risk of death than patients with preserved EF **[118].** Other predictors of increased mortality are male sex, old age, low blood pressure, renal dysfunction, low blood sodium level, high brain natriuretic peptide level, advanced New York Heart Association functional class, diabetes, high weight or body mass index, and low exercise capacity **[119]**, **[120]**. Recently, a prediction tool under the acronym "proSCANNED" has been proposed using Nt-proBNP, smoking, COPD, age, use of beta-blockers, and NYHA score **[121].**

CHF is the commonest cause of PE, resulting in 500,000 cases per year in the USA **[52].** PE is detected in almost 90% of patients with acute decompensated HF on CXR or CT **[122], [123].** Mechanisms of pleural fluid accumulation are unclear, and there is a debate on whether the elevation of systemic or pulmonary pressure leads to pleural effusion development. Increased systemic pressure leading to filtration across the systemic circulation of the parietal pleura and decreasing lymphatic flow through an increase in the downstream venous pressure could possibly lead to effusion formation. Conversely, elevated pulmonary pressure could also induce pleural effusion by increasing filtration across the pulmonary circulation of the visceral pleura **[124].** Recent data suggest that left atrial dysfunction may be a key factor in the pathogenesis

[28]

of pleural effusion **[125]**, while others suggest that the formation of pleural effusion is strongly related to diastolic dysfunction, loss of left atrial compliance, and a higher *E/A* ratio in echocardiogram **[126]**.

According to BTS guidelines, in a typical clinical context with symptoms of heart failure combined with cardiomegaly and bilateral pleural effusions in imaging, thoracentesis is not necessary **[48].** However, a second etiology is more common than previously believed **[127].** When aspirated, HF-related PEs are transudates based on Light's criteria in 75% of cases. As mentioned above, when treated with diuretics, heart failure-related pleural fluids have increased protein resulting in their misclassification as exudates. A serum NT-proBNP > 1500pg/ ml or serum to pleural fluid protein gradient > 3, 1 g/dl are helpful in such cases. Specifically, BNP has shown 97% sensitivity and 91% specificity in diagnosing HF **[90].**

Most cardiac-induced pleural effusions will improve with medical management **[123].** However, patients with recurrent symptomatic PEs, despite medical therapy, must undergo thoracentesis and drainage primarily for palliative purposes. Repeated thoracentesis may be required; however, the potentially significant risk of frequent hospitalizations and aspirations warrants more permanent management. Although chemical pleurodesis is commonly used in the treatment of MPE, reports of pleurodesis in NMPE are scarce. A small retrospective study showed successful pleurodesis in 80% of cases when performed during thoracoscopy **[128]**. Another study compared pleurodesis to IPC, reporting no significant differences in symptom relief but significantly shorter hospitalizations, lower rates of operative morbidity and readmissions in the IPC group **[129]**. In a recent single-center retrospective study, 54 patients

[29]

with CHF and hepatic hydrothorax receiving IPC experienced adequate symptom relief with acceptable procedure safety especially regarding HF patients **[130]**. Of course, these results are based on small studies with short follow-up periods, and further validation is required **[131].**

The prognostic role of HF-related pleural effusions is not well established. In a Spanish cohort of 2,703 patients, the presence of pleural effusion in CXR was associated with a higher rate of adverse events after discharge **[132].** Similarly, Kataoka et al. showed that pleural effusion detected in ultrasound has a high diagnostic accuracy for detecting worsening HF during follow-up **[133].** However, in a prospective study of 100 patients, pleural effusion failed to predict mortality during a 6-month follow-up **[134].** As mentioned before, large refractory symptomatic PEs requiring aspiration have a poor prognosis. Two retrospective single-centered studies with patients undergoing thoracentesis reported one-year mortality rates of 53% and 50%, respectively **[22], [23].**

3.2 Hepatic hydrothorax

A small number of patients with liver cirrhosis and ascites (5-10%) will develop hepatic hydrothorax (HH), defined as a large transudative PE usually over 500 ml, with no other obvious cause (heart, lung, or kidney diseases) **[135].** The diagnosis is evident in the presence of known liver disease but might prove more challenging in the absence of a history of liver disease **[136].** HH is usually right-sided since the main mechanism suspected of pathogenesis is the direct passage of ascetic fluid through diaphragmatic defects (small holes sided in the right diaphragm, through which fluid moves to pleural cavity driven from negative intrathoracic pressure) **[137].** Azygous vein hypertension, lymphatic duct leakage, hypoalbuminemia, and heart failure might also contribute to pleural fluid accumulation **[138].**

Loop diuretics, salt restriction, and avoidance of medication that decrease arterial blood pressure are usually first-line management. Unfortunately, 21-26% of patients will suffer from refractory HH requiring thoracentesis and further interventions **[139]**. Liver transplantation is the ideal option, but most patients are not eligible or die waiting for a transplant. Other treatment options that serve as a bridge to liver transplantation and relief from dyspnea or even improve survival should always be evaluated **[140]**. Transjugular intrahepatic portosystemic shunts (TIPS) decrease the portal pressure by creating a vascular intrahepatic bypass and can be a life-saving treatment with success rates between 58-73% **[141]**. However, hepatic encephalopathy, severe heart failure, pulmonary hypertension, and severe liver disease (MELD score>18) are contradictions for TIPS **[142].** Indwelling pleural catheters (IPCs) are also used in HH as a bridge to transplantation or for palliative treatment, often achieving

[31]

spontaneous pleurodesis **[143].** However, they should be used with caution since patients with cirrhosis are at high risk for infection and bleeding due to immunosuppression, thrombocytopenia, and coagulopathy **[144]**. Spontaneous bacterial empyema is an uncommon complication with high mortality. It refers to the infection of HH with no signs of pneumonia. Pathogenesis involves the entry of the organism from bacteremia or infected ascitic fluid. Pleural fluid is a transudative despite positive cultures. Escherichia coli is the most common pathogen, and early initiation of empiric antibiotics is recommended **[145], [146].** Finally, open thoracotomy or VATS with simultaneous pleurodesis have been described **[146].**

Limited data exist on mortality in patients with HH. A study of 77 patients reported 30-day, 90-day, and one-year mortality rates of 10%, 26%, and 57%, respectively **[147].** Similarly, in a population-based study of 3,487 cirrhotic patients with pleural effusion requiring drainage, 30-day, 90-day, 1-year, and 3-year mortalities were 20.1%, 40.2%, 59.1%, and 75.9%, respectively **[148].** Finally, a recent large retrospective study of 763 consecutive patients with cirrhosis and ascites showed that patients with HH have a significantly higher long-term mortality rate when compared to patients with no HH. Overall survival was 49.5%, 36.1%, and 15.4%, at 1, 2, and 5 years respectively, in the HH group and 51.5%, 46.4%, and 30.9%, respectively, in the control non-HH group (Log Rank—0.05) **[149].**

3.3 Kidney failure

Chronic kidney disease (CKD) is an increasing health problem with an estimated prevalence of about 13.4% **[150].** In 1990, it was the 27th leading cause of death, while in 2010, it came up to be 18th **[151].** CKD is defined as abnormalities of kidney structure or function that exist for more than three months and have implications for a patient's health **[152].**

Pleural effusion is a common clinical presentation of CKD and can be unilateral or bilateral, mild or massive, transudative or exudative. The most common causes of transudative PEs are fluid overload, heart failure, and nephrotic syndrome, while pneumonia, pulmonary embolism, tuberculosis (TB), or connective-tissue diseases can cause exudative PEs **[140].** Worthmentiongly, an important cause of exudative PE is uremic pleurisy which is a diagnosis of exclusion that persists or recurs despite aggressive hemodialysis (HD). It causes necrotizing inflammation and results in a typical blood-stained lymphocytic exudate **[153].** It is reported in 4–24% of cases in long-term hemodialysis patients and **[154], [155].** Uremic effusion is not related to the severity of uremia **[153]** and may develop during any stage of the uremia. Uremic effusions cannot always be cured by hemodialysis, but they can recur despite hemodialysis **[156].** It should also be mentioned that patients with renal failure are at increased risk of pneumonia due to impaired immunity. Therefore, parapneumonic effusions are responsible for 10–24% of PEs in long-term hemodialysis patients **[154]**.

Most data on the incidence of PE in patients with CKD come from retrospective studies on long-term dialysis patients. In a series of 257 patients receiving long-term hemodialysis, the incidence of PE was 20%, and PEs were mostly bilateral

[33]

transudates **[154].** Another large multicenter study of patients undergoing ambulatory peritoneal dialysis reported an incidence of PE of 1.6% **[157].** Interestingly, a recent prospective study examined all CKD patients with PE at all stages of the disease, including the dialysis population. Transudative pleural effusion was present in 75.7% of patients, with fluid overload and heart failure being the commonest causes, while 24.3% of patients had exudative pleural effusion with tuberculosis being the commonest etiology **[158].**

In refractory cases of PE, repeated thoracentesis is the followed step, but the patient faces risks. More invasive interventions are not well studied. There is little evidence for pleurodesis **[159].** IPC was used successfully in a small series of patients with renal failure, but larger prospective studies are needed **[160]**. Treatment with VATS pleurodesis and diaphragmatic defect repair has also been reported in the literature, with a successful outcome in a follow-up period of 4 to 30 months **[161]**, **[162].**

Data on mortality are scarce. A small cohort of patients undergoing peritoneal dialysis with exudative PE had 60% 3-year mortality **[163],** while another cohort of 14 patients with renal failure reported 57% 1-year mortality **[22]**. A large retrospective study examined patients over a four-year period and showed that PE is significantly associated with poor prognosis after adjusting for age, heart disease, or serum albumin level **[164].**

[34]

3.4 Pleural infection

3.4.1 Epidemiology

Pleural infection (PI) is a disease known since ancient times. Around 500 BC, Hippocrates gave a description of the disorder, including treatment with open thoracic drainage **[165].** It is a common clinical condition, complicating almost 20% of patients with pneumonia when detected with chest radiography and even more with TUS **[166].** PI affects more than 65,000 patients each year in the United States and the United Kingdom **[167],** while there is a well-described trend to rise during the last decades **[168], [169].** The main reason for this increase is the aging population living more with health problems associated with pleural infection **[170]**. Interestingly, a systematic review with over 200,000 patients with pleural infection showed that almost 72% had comorbidities (respiratory and cardiac diseases were the most reported) **[171].** Moreover, the increased awareness of clinicians, the better diagnostic techniques **[172]**, the increasing role of thoracic ultrasound, and the changing microbiology of PI affecting the yield of existing vaccines **[173-176]** also contribute to this trend**.**

3.4.2 Pathogenesis/ microbiology

Pleural infection is an ''umbrella'' term including all stages of a continuous process ranging from the 'simple' self-resolving parapneumonic PE to the 'complicated' fibrinopurulent collection and empyema (frank pus in the pleural cavity). Research efforts have been impeded by the lack of a survivable murine model that will reliably allow the investigation of the pathogenesis of pleural organization and remodeling **[177].** Existing data are based on in vitro studies. There is a complex interplay between different cells of immunity, mediators of

[35]

inflammation, coagulation cascade, and the offending organism, only a small part of which we understand thus far **[178].** In the first stage, known as the ''exudative'' phase, fluid moves into the pleural space due to increased capillary vascular permeability, accompanied by the production of proinflammatory cytokines such as interleukin 8 (IL-8) and tumor necrosis factor-a (TNFa). In this initial phase, pleural fluid has a normal glucose level and pH >7.2, no bacteria, and most of the time will resolve spontaneously with antibiotic therapy **[179].** If treatment fails, the disease will progress to the ''fibrinopurulent'' stage with increasing fluid accumulation and bacterial invasion across the damaged endothelium. The exposure of mesothelial cells of pleura to bacteria leads to inflammatory response, coagulation, and fibrinolysis disorders **[180].** Reduced fibrinolytic activity leads to fibrin deposition producing loculations and adhesions. This procedure is related to elevated plasminogen activator inhibitor (PAI) 1 and 2 levels and reduced tissue plasminogen activator (tPA) levels and may also relate to treatment failure and poor outcomes **[181],** **[182**]. This phase is characterized by a fall in pleural fluid pH and glucose and high levels of lactate dehydrogenase due to bacterial metabolism and neutrophil activity **[183], [184].** The final stage, known as the 'organizing' stage, is characterized by the proliferation of fibroblasts, pleural scarring, and fibrosis leading to lung entrapment and impaired lung function. This process is driven by mediators such as platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β) **[185], [186].** It is well documented that the microbiology of PI differs from that of community-acquired pneumonia, reflecting the differences in oxygen concentration and ph between pleural cavity and lung parenchyma **[172], [187].** Accordingly, a metagenomic study showed

[36]

that a large subgroup of community-acquired empyema is caused by oral bacteria, sharing the same route of infection and risk factors with oral/ sinus-derived brain abscesses. Authors suggested the term 'primary empyema' for this type of pleural infection **[188] (figure 3).**
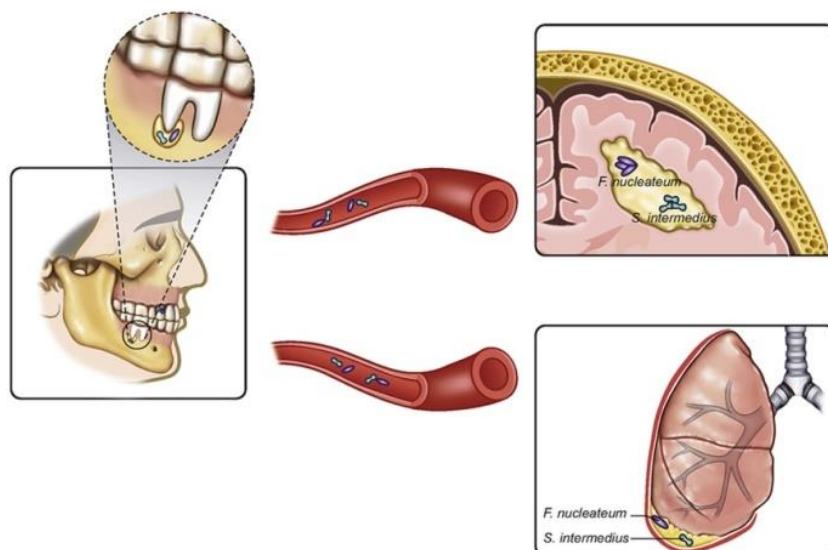
Figure 3] '' Primary empyema'' [188].

In the last 20 years, studies have reported viridans Streptococci as the most common pathogen in community PI **[173], [189-194],** while in hospital-acquired infections, Staphylococcus aureus and Gram-negative bacteria outweigh, especially in patients with chronic diseases requiring frequent hospitalization and intensive care **[190], [194], [195].** However, a recent systematic review reported that Staphylococcus aureus appears to be the leading cultured pathogen globally **[196] (Table 4).** Anaerobic bacteria are difficult to be cultured and often underestimated in the data. Characteristically, a study designed to address this question reported that 74% of all pleural fluid samples showed anaerobic bacteria, while 60% of all positive samples showed co-infection with aerobic and anaerobic bacteria **[197].** Finally, TB is an important cause of

[37]

empyema and should not be overlooked **[193].** Differences in microbiology between regions or countries suggest that more local epidemiology studies are needed to guide better antibiotic and therapeutic strategies **[173], [194], [192], [198].** Accordingly, a recent study from Greece examined 158 patients with culture-positive community-acquired PI both retrospectively and prospectively. Streptococci (especially non-pneumococcal) were the most common pathogens isolated and were sensitive to the combination of respiratory fluoroquinolone with ceftriaxone or an aminopenicillin/lactamase inhibitor **[199].**

Community – acquired pleural infection	Hospital acquired pleural infection
Gram positive aerobes 65% • *Viridans group streptococci 26.6.%* • *Streptococcus pneumoniae 18.2%* • *Staphylococcus aureus 15.3% (67% methicillin-sensitive)*	**Gram positive aerobes 51.5%** • *Staphylococcus aureus 33.6% (42% methicillin-sensitive)* • *Enterococcus spp. 10.7%* • *Viridans group streptococci 9.8*
Gram negative aerobes 17.1% • *Enterobacteriaceae 10.8%* • *Klebsiella sp 4.2%* • *Pseudomonas spp. 3%*	**Gram negative aerobes 37.5%** • *Enterobacteriaceae 17.8%* • *Pseudomonas spp. 8.9%* • *Klebsiella sp 7.6%*
Anaerobes 17.1%	**Anaerobes 11%**

Table 4] Microbiology of pleural infection [196]

[38]

3.4.3 Diagnosis

Diagnosis of PI is based on clinical, radiological, and microbiological findings. It remains challenging and requires a high level of clinical suspicion. Aerobic bacteria usually cause acute disease with fever, thoracic pain, cough, sputum, and rise in inflammatory markers. On the contrary, the atypical clinical presentation with anorexia and loss of body weight is attributed to anaerobic pathogens, commonly seen in old patients with dementia or patients with bad oral hygiene and alcohol abuse. Hospitalized patients with impaired consciousness are at increased risk of aspiration, thus commonly affected by gram-negative gut bacteria **[200-202].**

All patients with suspected PI require diagnostic aspiration since pleural fluid characteristics remain the most reliable diagnostic test, except for small effusions (i.e., <10 mm thickness) that will usually resolve with antibiotics. Traditionally, an exudate with pH <7.2, glucose <2.2mmol/l, and LDH>1000IU/l is highly suggestive of a complicated parapneumonic effusion or empyema (diagnosed macroscopically as frank pus) and requires chest tube drainage **[200] (Figure 4).**

Much research during the last years is focused on biomarkers that would rapidly and safely diagnose PI. However, to this end, no single biomarker is pathognomonic or can outweigh the classical criteria **[203-207].** When used in combination with the classical biomarkers, CRP level was a valuable adjunct for treating patients with non-purulent PI **[208-210].** Moreover, the combination of CRP and ADA levels can successfully discriminate between malignant, tuberculous, and parapneumonic effusions **[211], [212].** Likewise, a combination of traditionally used parameters (leukocyte count and neutrophil

[39]

percentage) with inflammatory biomarkers (CRP and IL-6) improved diagnosis as compared to the biomarkers alone **[213].** Presepsin was found to resemble the pattern of CRP **[214],** while procalcitonin failed to show superiority and is not routinely suggested **[215], [216].** Finally, the pleural LDH/pleural ADA ratio was also proposed for distinguishing PIs from other diseases **[217]**. In conclusion, experts suggest that a single biomarker cannot accurately predict PI and**,** like any other laboratory exam, should be interpreted within a clinical context **[218]**, **[219].**

The diagnostic yield of pleural fluid culture is low, ranging between 20-40%, while administration of pleural fluid to blood culture bottles raises the sensitivity to 60% **[172].** New molecular techniques such as multiplex PCR and next-generation sequencing outperform conventional microbiology in sensitivity and specificity, though specific assays to cover common pathogens are needed **[220], [221].** Interestingly, the AUDIO study showed that pleural biopsies could increase the microbiological yield compared to fluid or blood culture. Interestingly in the same study, the biopsy positivity was not affected by antibiotic administration, possibly explained by the limited penetration of antibiotics into the pleural space **[222].**

Chest radiography is usually the first examination in a patient with a pleural infection. PE should be recognized from the classic meniscus sign (Ellis-Damoiseau line), a low-density opacity obscuring the hemidiaphragm, or even suggested from the blunting of the posterior costophrenic angle in a lateral x-ray **[223].** Thoracic ultrasound (TUS) has emerged as an essential tool in diagnosing and managing PI. Both aspiration and chest tube insertion should be performed under TUS guidance to ensure a successful and safe

[40]

procedure **[200]**. Septations and loculations can be better recognized with TUS than CT and may predict failed medical treatment and the need for management escalation **[190].** Chest CT holds a limited role in lung parenchyma cases that must be carefully examined or suspected of lung cancer **[200].** Pleural thickening is almost always seen in empyema, while the 'split pleura' sign caused by the separation of parietal and visceral pleura is characteristic in both CPPE and empyema **[62-64].**

3.4.4 Management

Despite being such an old disease, management of PI is still controversial, largely empiric, and varies between different centers **[225], [226].** The first approach in a patient with parapneumonic pleural effusion is adapting the antibiotic scheme according to possible pathogens and local resistance patterns while waiting for culture results. As mentioned above, in community-acquired pneumonia, Gram-positive and anaerobic pathogens should always be covered. Even with a positive, aerobic culture, it is reasonable to continue anaerobic coverage given the frequency anaerobes infect empyema and the unsuccessful culturing of this organism **[200].** Penicillin, combined with b-lactamase inhibitors, metronidazole, and cephalosporins, penetrate the pleural space well. Antibiotics should aim at Gram-negative, MRSA, and anaerobic bacteria in hospital-acquired infections. Intravenous administration of antibiotics can be switched to oral when clinical and biochemical improvement is seen, though the duration of therapy varies between centers from 2 to 6 weeks **[200], [227].** Further research on antibiotic concentrations in human pleural fluid is needed to improve rates of antibiotic failure **[173], [218],**

[228]. There is currently no solid evidence base for the routine use of intrapleural antibiotics **[227].**

Early and adequate nutrition of the patient, though often underestimated, is an old-documented, crucial step in PI management that also affects prognosis **[200], [229], [230].** Moreover, prophylaxis against thrombosis with low-molecular-weight heparin treatment is strongly recommended **[200].**

Regarding drainage, pleural fluid pH< 7, 2 is still considered the most reliable marker to insert a chest tube aside from recognition of frank pus, positive microbiology, or the presence of septations **[203].** Caution should be paid since some patients with an initial pleural pH >7.2 will finally need chest tube drainage or even surgery due to the heterogeneity of pleural fluids in different loculated collections. Thus, unsatisfactory clinical progress indicates the need for repeated pleural fluid sampling **[75].** Generally, the time of drainage varies among clinicians and institutions. However, no significant difference in terms of short-term mortality was applied by early (<24 hours) versus later chest tube insertion in a recent retrospective study **[231].** Large size effusions should be drained in a definite way rather than multiply aspirated **[200], [232], [233]**. The size of the chest drain is also a subject of debate. BTS guidelines suggest that small-bore catheters should be adequate for most cases **[200].** The only randomized controlled trial assessing this question showed that small-size tubes demonstrate no difference in mortality or the need for surgery and better results in pain scores compared to large-bore drains **[234].**

There is conflicting evidence regarding intrapleural fibrinolytic therapy, which is generally indicated for non-operable patients **[235], [236].** In a large randomized controlled trial (MIST2 trial) in 11 centers in the United Kingdom

from December 2005 to November 2008, the early combination therapy with DNase and tPA improved fluid drainage, reduced the days of hospitalization, and the need for surgical referral **[12].** The findings were further validated with high success (90%) and low complication rates, mostly bleeding (5%) **[237-239].** Many issues are yet to be addressed, such as the proper timing and the dosage of therapy to achieve personalized therapy **[240], [225].** A recent prospective multicenter RCT involving 32 patients who underwent MT or IPFT for pleural infection showed that when used early in a complicated parapneumonic effusion or empyema, MT is safe and might shorten hospital stays for selected patients as compared with IPFT therapy **[241].** Surgery has consistently been recognized as an essential step in the management of pleural infection, though ongoing debate exists around patient selection **[201], [233], [242], [243].** A Cochrane review showed no difference in mortality between the surgical and non-surgical approaches **[244].**

Regarding surgery options, there is a clear trend towards the less invasive technique of video-assisted thoracoscopic surgery (VATS), as it has reported fewer complications and fewer days of admission, maintaining similar efficacy with open surgery **[242], [245-247].** An ongoing RCT under the name MIST-3 compares early administration of intrapleural enzyme treatment versus early surgery **[248].** Finally, a multicenter pilot RCT in six Australian centers evaluated the effects of corticosteroids in PI. Eighty patients were randomized and received dexamethasone or a placebo. No primary benefits were reported in the cortisone group regarding vital signs, inflammatory markers, need for drainage, radiographic improvement, duration of antibiotic therapy, and median hospitalization **[249].**

Pleural effusion in the clinical context of infection

Sample fluid with image guidance if possible

Purulent = empyema

Non purulent

Gram stain or culture positive

Intercostal drainage

Sample ph

Intercostal drainage

Ph>7.2

Ph<7.2

Drainage not required
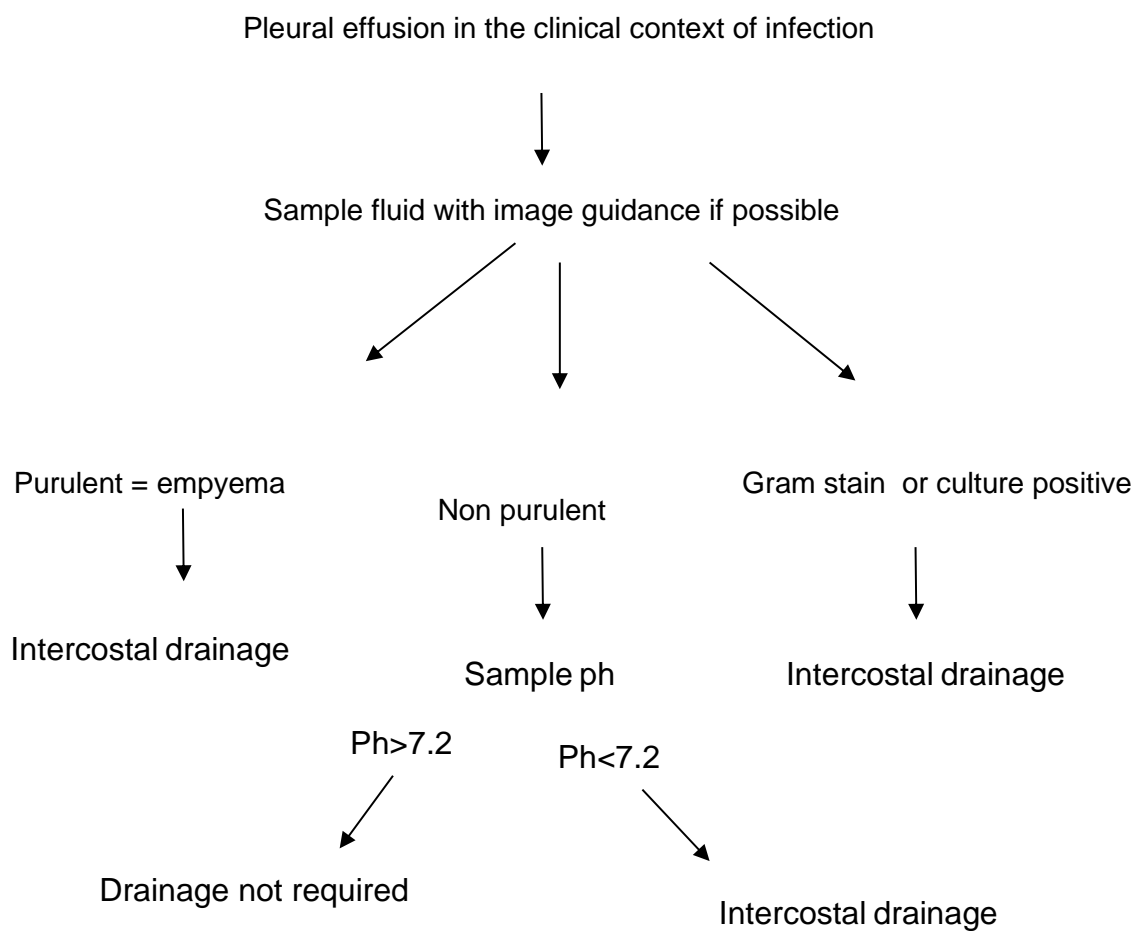
Intercostal drainage

Figure 4] Algorithm for the initial approach to a pleural infection

3.4.5 Prognosis

Unfortunately, almost 20% of the patients with PI will fail treatment and be referred to surgery **[11], [19].** Mortality ranges from 4 to 22% with high variation between age groups (very low in young patients, > 20% in aged population) and stage of disease **[11], [19], [166], [189], [194], [250], [251].** Most patients will be hospitalized for more than 15 days or even a month, adding to the significant economic burden of the disease **[11].** The scoring system RAPID (an acronym for Renal, Age, Purulence, Infection source, and Dietary factors) was proposed to help clinicians identify patients likely to have a poor outcome at presentation and ideally guide therapy. The score was created using data from two large multicenter studies, MIST1 and MIST2, and was independently associated with mortality at three months **[252].** The score was later validated, confirming it is a useful tool for identifying patients at high risk of mortality, prolonged hospitalization, and increased healthcare costs both short and long-term **[253-255].** The PILOT study prospectively validated the RAPID score in 542 patients from everyday clinical practice and showed that an increase in the score increased 30-day mortality **[256].** However, the risk of death does not mean they need surgery which is the asked information most of the time. Patients with high RAPID risk scores are often bad candidates for surgery regarding their performance status. On the other hand, conservative management with prompt antibiotics and intrapleural therapies can cure nearly 90% of patients without further surgical interventions **[257].** Randomized controlled trials are needed to identify the most effective initial treatment modality for medium- and high-risk patients **[254].**

[45]

3.5 Malignant pleural effusions

3.5.1 General

Malignant pleural effusion (MPE) affects almost 15% of patients with underlying malignancy and more than 750,000 patients across Europe and the USA each year. Since cancer rates are increasing and new therapies allow patients with malignancies to live longer, the burden of MPE is also increasing **[258].** Carcinomas of the lung, breast, and lymphomas frequently cause malignant pleural effusions (MPEs), with lung cancer accounting for almost 1/3 of clinical cases **[259].** MPE is a devastating disease associated with a life expectancy between 1, 5 to 9 months. Management is mostly palliative and should ideally be assessed on a case-by-case basis **[260].**

Estimated life expectancy, individual patient's preferences, comorbidities, presence of loculations or trapped lung, and type of cancer should all be considered **[261].** Recent advances in our understanding of MPE pathogenesis **[8]**, the expanding use of TUS **[262]**, and interventional techniques (IPC) **[13]** have resulted in an update of the guidelines **[258], [263].**

Prognostic scores using type of cancer, clinical and sonographic factors, and novel biomarkers have emerged to personalize treatment and further understand the underlying mechanisms of disease progression **[264-267].** Thus, the research direction has changed from trying to control fluid accumulation to patient-centered outcomes (e.g., symptoms, quality of life, hospitalizations) **[268]** and ambulatory management of patients **[16].**

[46]

3.5.2 Pathogenesis

Direct invasion of tumor cells and blockage of drainage system was traditionally believed to be the primary mechanism of MPE formation **[269].** However, recent research has emphasized the role of tumor-host interactions in the pleural microenvironment **[8].** Vascular endothelial growth factor (VEGF), a mediator of endothelial permeability, was initially proposed as a critical cytokine in MPE pathogenesis alongside other cytokines fostering MPE formation, e.g., interleukins IL-21 and IL-17, chemokine ligands CCL-2 and CXCL-12**,** tumor necrosis factor (TNF), osteopontin (OPN) and angiopoietin **[270-274].** Considering these findings, the new concept of MPE pathogenesis is based on the model of interaction between tumor and host cells (mesothelial, endothelial, myeloid, and lymphoid cells). Oncogene signals (e.g., EGFR) and transcriptional programs (NF-kB, Stat3) causing gene expression, imbalance between mediators promoting or inhibiting vascular permeability (e.g., VEGF, TNF, CCL2, OPN, endostatin) and host cells, all react in a complex loop to induce inflammation, angiogenesis, vascular leakage and pleural metastasis **[8].** Recent research has identified novel proteins (TIMP1, GSN, VCAN, and MIF) with different molecular pathways in patients with malignant pleural effusions, findings that need to be further investigated **[265].**
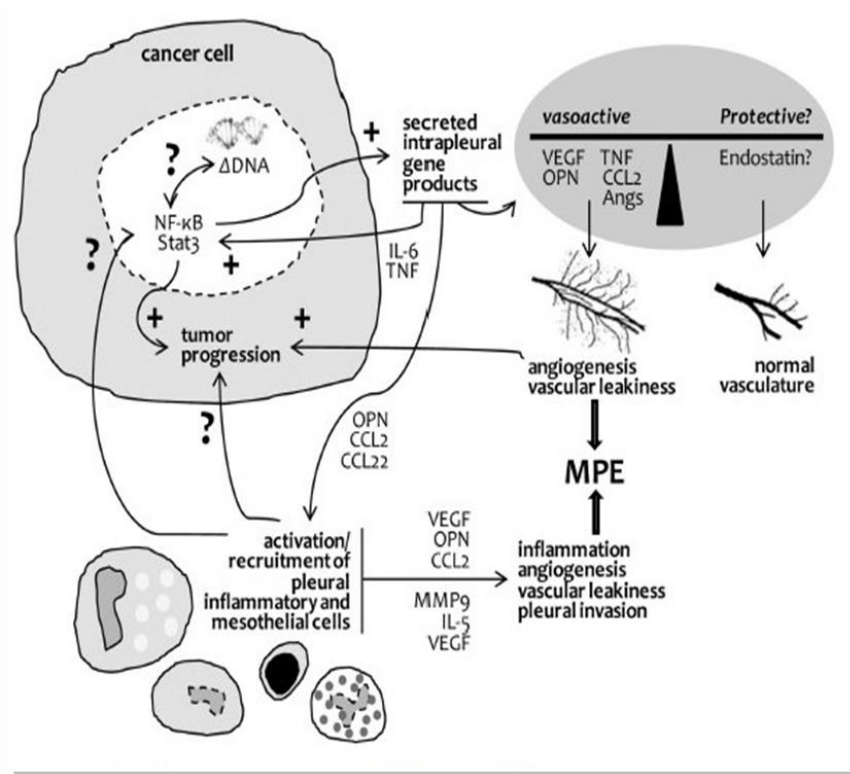
Figure 5] Tumor–host interactions in pathogenesis of MPE [8].

3.5.3 Diagnostic approach

Three out of four patients with MPE will present with a symptom, most likely dyspnea, while the rest are asymptomatic with incidental findings on imaging. Breathlessness can be multifactorial, so other pathologies such as carcinomatous lymphangitis, bronchial obstruction, pulmonary embolism, heart failure, and chronic pulmonary diseases may contribute to presenting symptoms and should always be evaluated **[127].** Chest pain, when present, is intense, requiring strong analgesics, and derives from malignant involvement of the parietal pleura or metastatic disease in the thoracic cage. Constitutional

[48]

symptoms such as weight loss, anorexia, or other respiratory symptoms may exist **[260], [275].**

As mentioned above, CT thorax has shown high specificity but low sensitivity in separating benign PE from MPE **[56],** with one out of three patients having MPE despite a negative scan **[59].** Nevertheless, computerized tomography (CT) is a long-established and widely used diagnostic step after the initial detection of a suspected MPE in CXR **[207].** The extent of the initial scan is debated, but a retrospective study showed that including abdomen/pelvis increases the diagnostic yield by 12% **[61].** Ultrasound is highly recommended before any pleural intervention, having excellent accuracy and reducing the risk of pneumothorax by 19% **[70].** Signs of MPE in TUS resemble CT findings, including pleural/ diaphragmatic thickening and pleural/ diaphragmatic nodules with excellent specificity but lower sensitivity **[74].** Positron emission tomography (PET) has moderate sensitivity and specificity for the diagnosis of malignancy (82% and 74%, respectively), as it will not detect early-stage tumors and will misclassify inflammatory pleuritis as malignancy **[65].** Magnetic resonance (MR) offers higher sensitivity when chest-wall and diaphragm are involved in malignancy. However, the low diagnostic yield in detecting lung lesions and limited access have excluded MR's routine use from standard diagnostic tests in MPE **[48].**

Thoracentesis is a crucial but usually not definite step in the diagnostic approach. Pleural fluid is mostly lymphocyte exudate, although it can also be transudative **[276].** The appearance in half of the cases is hemorrhagic and in 11% bloody **[277].** A definite diagnosis requires the identification of malignant cells in pleural fluid or tissue **[278].** The diagnostic performance of cytology is

[49]

low, near 60%, with higher sensitivity in ovarian carcinomas and adenocarcinomas (80%) and very low in mesothelioma (6%) **[101].**
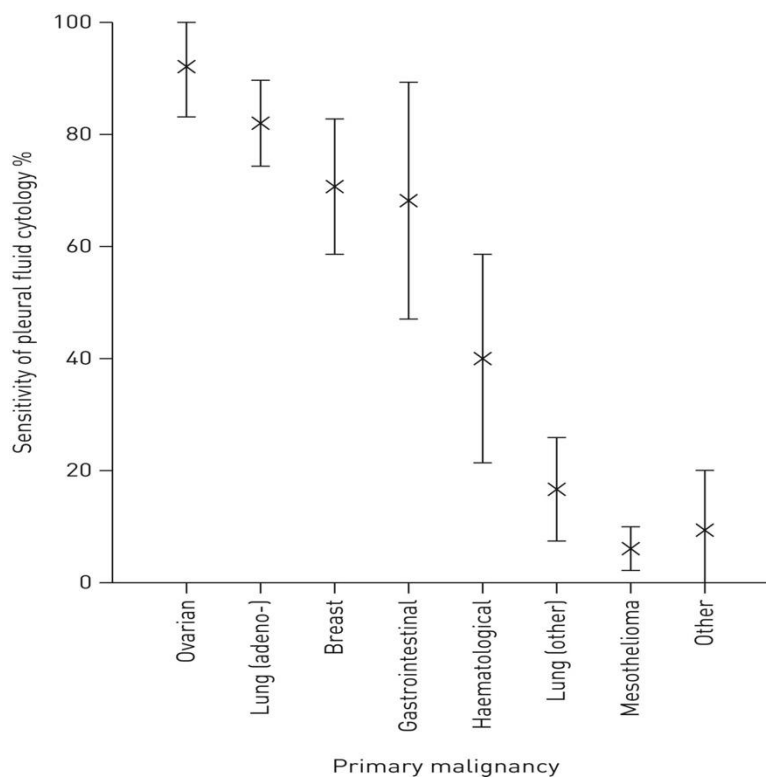

Figure 6] Sensitivity of pleural fluid cytology by malignancy [101]

Data on whether a high volume of pleural fluid adds to the diagnostic yield of cytology is controversial **[279].** An amount of 20–40 cc of pleural fluid and two aspirations should be adequate for the diagnosis **[48].** The cytological examination involves identifying benign or malignant cells and further characterizing the malignancy as primary pleural or metastatic **[258].** Immunohistochemistry helps differentiate reactive mesothelial cells from malignant pleural mesothelioma cells and adenocarcinoma metastases **[280]**. Recently, liquid biopsy methods identifying circulating tumor DNA, microRNA, and tumor cells from patients' blood have

[50]

proven helpful in detecting *EGFR* mutations **[281], [282].** Biomarkers have not proven helpful in diagnosing MPE and can only be used as a rule in tests to identify patients who will most likely benefit from further invasive procedures in suspected MPE **[283].** A scoring system based on six easily accessible clinical variables (fever, erythrocyte sedimentation rate, ADA on pleural fluid, CEA on pleural fluid and serum, effusion/serum CEA) exhibited good diagnostic performance for identifying MPE but requires prospective validation **[284].**

Since cytology does not always offer a definite diagnosis, the pleural biopsy is the next step in the diagnostic pathway of MPE **[258].** The sensitivity of ultrasound or CT-guided biopsy ranges from 87–94% **[100], [285]** like thoracoscopy **[286].** The biopsy is performed via thoracoscopy (medical or surgical) when pleural thickening is absent or difficult to access. Mortality and complication rates are low Endoscopy has the advantages of simultaneously visualizing the affected pleura, performing biopsy and drainage, or even pleurodesis (given that the possibility of the trapped lung is excluded). Medical thoracoscopy is helpful in patients, not candidates for surgery or at increased risk of complications **[110], [287].**

Pleural manometry has been used to identify a nonexpendable lung and hence pleurodesis failure by evaluating pleural elastance (lungs' ability to return to its natural position). However, routine use of manometry does not reduce chest discomfort or prevent re-expansion side effects **[288].**

3.5.4 Management

As mentioned above, MPE treatment is palliative, directed to relief form symptoms. Repeated thoracentesis and more definite interventions to offer long-term relief such as pleurodesis, insertion of an indwelling pleural catheter (IPC), or surgery are examined on a case by case basis, considering multiple prognostic scores and patient's preferences.

Symptoms generally improve after drainage, but pleural effusion always relapses within the first month; thus, a definitive intervention must be planned (IPC, pleurodesis, or both) **[277]**. Repeated thoracentesis is the preferred strategy when life expectancy is limited, fluid re-accumulates slowly, or the patient does not wish invasive interventions **[260], [263].**

Pleurodesis prevents reaccumulating of pleural fluid by forcing the adhesion of the two layers of the pleura. It improves dyspnea, increases survival, and reduces the length of hospital stay and the need for future interventions **[13], [15], [289-291]. However,** it is not recommended in the presence of trapped lung (30% of all cases) or multiple septations **[258].** Talc is the most widely used particle and can be administered either through the thoracoscope tube as an aerosol (talc poudrage) or via an intercostal tube as a suspension (talc slurry).
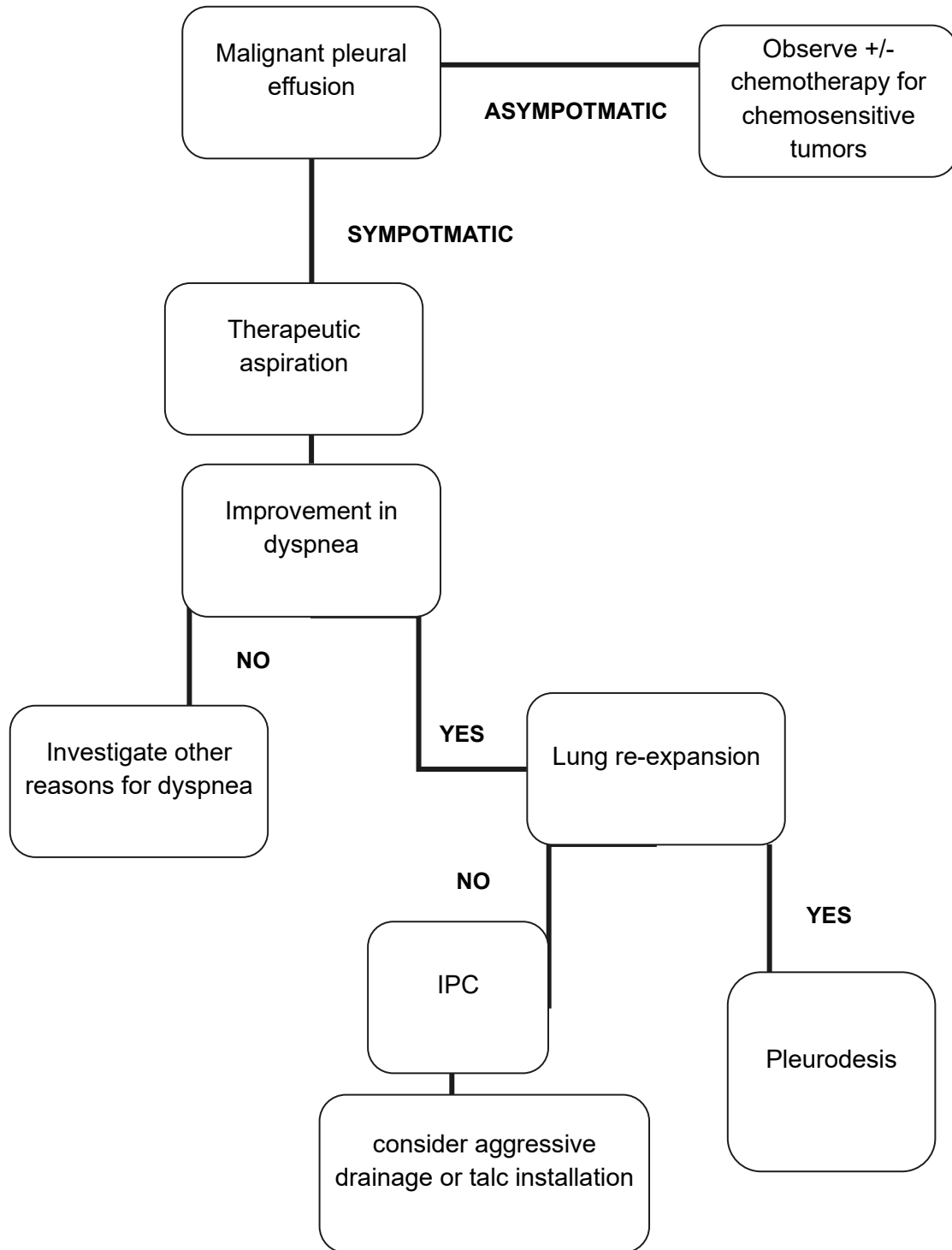
[52]

Figure 7] Algorithm for the management of malignant pleural effusion

[53]

A meta-analysis of 80 randomized trials including 5507 patients showed that both talc poudrage and talc slurry are effective methods for achieving a pleurodesis **[292].** Large-particle talc (>15 *µm*) is preferred to prevent the development of acute respiratory distress syndrome **[293], [294].** TIME-1 trial suggested that wide-bore chest tubes may be superior to smaller tubes regarding pleurodesis efficacy, without clinically significant pain differences. However, smaller tubes are more comfortable for patients. an inflammatory response in the pleura. The same study revealed that the administration of nonsteroidal anti-inflammatories to control pain does not affect pleurodesis outcomes **[14].** Interestingly, a TUS scanning protocol uses sonographic evidence of pleural adherence to predict pleurodesis success in a multicenter randomized controlled trial **[7].**

Indwelling Pleural Catheters (IPCs) are silicone tubes with one-way valves inserted percutaneously and maintain lung expansion by intermittently draining pleural fluid. IPCs are as effective as pleurodesis with talc slurry at relieving dyspnea and can be used in the presence of a trapped lung **[13], [295]**. A systematic review of 19 studies involving 1,370 patients showed an improvement in symptoms in 95% of cases. Spontaneous pleurodesis caused by local inflammation is seen in 46–70% of cases. When pleurodesis is succeeded, the catheter can be removed **[297]**. The superiority of one technique over another (IPC vs. talc pleurodesis) is a matter of debate. IPC requires shorter hospital stay procedures **[297]** and is more effective in the presence of a trapped lung or in patients with a poor functional status that cannot tolerate pleurodesis.

[54]

Moreover, IPC is suitable for ambulatory patients, although drainage is more time-consuming and requires intensive care in patients who have undergone unsuccessful pleurodesis. However, IPCs are associated with higher complication rates; drain blockade or malposition (<5%), catheter rupture, subcutaneous and pleural infections (0–12%), though without significant morbidity **[295], [298], [299].** IPCs can be cost-effective in patients with limited life expectancy (<3 months), whereas talc pleurodesis in patients with a higher life expectancy **[300].** AMPLE study compared the length of hospital stay in patients treated with IPC versus talc pleurodesis. The median hospital stay was ten days in the first group versus 12 in the second group **[15].** AMPLE-2 trial compared daily drainage versus drainage only in the presence of symptoms and found no differences in dyspnea relief but a higher rate of pleurodesis success with the more invasive method **[301]**. Similar results were reported in the ASAP trial, where daily drainage led to a higher rate of autopleurodesis and a faster time to remove of catheter **[302].** The ongoing AMPLE-3 trial compares talc pleurodesis through IPC with VATS in MPE management **[303].** Outpatient administration of talc pleurodesis through IPC compared to IPC alone resulted in a significantly higher chance of pleurodesis at 35 days with no adverse effects **[16].** The impact of ambulatory management with combined IPC plus pleurodesis on quality of life is studied in the ongoing OPTIMUM trial **[304].**

Current guidelines do not recommend the use of specific antitumor treatment (chemotherapy, targeted therapy, or immunotherapy) before the standard interventions **[258], [263].** Small studies have suggested that chemotherapy may be effective as first-line treatment in certain chemo-sensitive tumor types (e.g., limited-disease small cell lung cancer) **[305]**. However, no RCTs have

[55]

compared palliative procedures with antitumor treatment. The use of intra-pleural bevacizumab in MPE associated with NSCLC and EGFR-TKIs in patients with mutated EGFR should be further studied **[306], [307].**

TIME2	2012	IPC versus talc pleurodesis	No significant difference in dyspnea
TIME1	2015	Size of chest drainage Use of nonsteroidal anti-inflammatory drugs (NSIAD)	Wide-bore chest tubes noninferior regarding pleurodesis success, no significant difference in pain NSAID do not affect pleurodesis success
AMPLE	2017	IPC versus talc pleurodesis	Lower hospitalization days in IPC group
ASAP	2017	IPC daily drainage versus symptom-guided drainage	Daily drainage offers higher pleurodesis success, no difference in dyspnea
AMPLE2	2018	IPC daily drainage versus symptom-guided drainage	Daily drainage offers higher pleurodesis success, no difference in dyspnea
IPC plus	2018	Outpatient talc pleurodesis through IPC versus IPC alone	Pleurodesis in 43% and 23% respectively
TIME3	2018	Intrapleural urokinase versus placebo	Urokinase does not improve pleurodesis success rate or dyspnea
TAPPS	2019	Talc poudrage (thoracoscopic) versus talc slurry (via chest drain)	Similar pleurodesis failure rates (22% , 24% respectively)
OPTIMUM	Ongoing	Outpatient talc pleurodesis through IPC versus chest drainage pleurodesis	Primary outcome measure : Quality of life
AMPLE3	Ongoing	IPC versus VATS pleurodesis	Requirement for ipsilateral pleural procedure

Table 6] *Randomized controlled trials on the management of MPE*

[56]

The role of palliative care in a disease with such a poor prognosis should not be underestimated. It has been demonstrated that patients with advanced lung cancer receiving early palliative care had significantly improved quality of life and survival with less aggressive care at the end of life, compared with those receiving standard care **[308].** Further research is required to define optimal treatment according to patient-centered outcomes. Careful consideration is essential for future trials to minimize the risk of bias and standardize outcome measures **[292].**

3.5.5 Prognosis

A survival analysis of three large cohorts showed a wide range from less than 50 days in urological cancer, sarcoma, and melanoma to 339 days for patients with mesothelioma, while lung cancer had a median survival of 74 days **[264].** Given this poor prognosis, practical prognostic tools are crucial to personalize treatment. During the last twenty years, many prognostic factors have been reported to affect mortality, such as age, tumor type, performance status, comorbidities, blood and pleural fluid features **[264], [309-315],**

LENT score (LDH level, ECOG performance status, neutrophil-to-lymphocyte ratio, and tumor type) was the first validated score for MPE prognosis **(Table 7).** It was developed using data from 789 patients from three international centers. Baseline factors with the most robust predictive ability were included in the model. Final scores separated patients into low-, moderate- or high-risk groups, with a median survival of 319, 130, and 44 days. The high-risk group's 1-month and 6- month survival was 65% and 3%, respectively **[264].** Recently, the PROMISE study combined biological and clinical parameters to assess

[57]

three-month mortality**.** The proposed score consists of seven parameters, all independently associated with survival: Previous therapy (chemotherapy and radiotherapy), increased levels of WBC and CRP, decreased hemoglobin, performance status, type of cancer, and pleural fluid TIMP1 (a glycoprotein that promotes proliferation anti-apoptotic activity). **[265].**

VARIABLE	VALUE	SCORE			
L PF LDH (IU/l)	<1500 >1500	0 1	**Risk categories**		**Score**
E ECOG PS	0 1 2 3-4	0 1 2 3	**Low risk**		**0-1**
			Moderate risk		**2-4**
N neutrophil-to-lymphocyte ratio	<9 >9	0 1	**High risk**		**5-7**
T Tumor type	Mesothelioma Hematological malignancy Breast cancer Gynecological cancer Renal cancer Lung cancer Another tumor	0 1 2			

Table 7] LENT prognostic score for MPE [264]

3.6 Pulmonary embolism

Acute pulmonary embolism (APE) is characterized by occlusion of pulmonary arteries by a thrombus and remains a common major health problem. A Danish national cohort reported an increased prevalence from 45 to 83 cases per 100,000 **[317].** Similarly, a recent Greek study increased from 5 to 24 cases per 100,000 population from 2013 to 2017 **[318]**. Mortality is decreasing as a result of advances in therapy **[319]** but remains significant, ranging from 5 to 30% within the first month of admission to hospital **[320]**. The incidence of pleural effusion in patients diagnosed with pulmonary embolism varies significantly between 16 to 61% **[321-324].** APE is the cause of almost 6% of all unilateral effusions **[325], [326]** and should be suspected in every undiagnosed pleural effusion since it is commonly overlooked **[327].** Effusions can be bilateral or unilateral and mostly small-sized, occupying less than 1/3 of hemithorax not requiring aspiration **[321], [323], [326-328].** A small PE in a clinical context typical of embolism that resolves with treatment does not warrant further interventions. However, an effusion that increases in size despite optimal therapy should be aspirated to rule out other causes of PE, e.g., pleural infection or hemothorax **[327], [328].**

The clinical significance of pleural effusion in APE remains unclear, with scarce and conflicting data. PE was not a predictor of mortality or adverse outcome in a cohort from Korea, though it correlated with disease severity **[323].** Conversely, studies from China and Turkey showed that pleural effusion was associated with higher mortality and could probably predict poor outcomes **[329], [330].** In a recent retrospective study from China, the presence of PE was associated with increased admission days, rates of

[59]

respiratory failure, and in-hospital mortality; however, it could not independently predict in-hospital mortality **[324].** Finally, a retrospective analysis of 343 patients showed that bilateral effusions in patients with APE are related to higher in-hospital mortality than unilateral PE or no PE **[331].**

3.7 Tuberculous pleuritis

Tuberculosis (TB) is a disease that can be prevented and treated - yet it is a major public health problem and a leading cause of morbidity worldwide. An estimated 10 million were diagnosed with TB in 2019, and there were an estimated 1.2 million deaths among HIV-negative people and another 208.000 deaths among HIV-positive people **[332].** Almost 3% - 25% of patients with TB present with tuberculous pleural effusion (TPE), depending on region **[333-335].** TPE mostly develops from primary infection in regions with high TB incidence (Southeast Asia, Africa). However, in low-incidence regions, it results from the reactivation of latent infection **[336].**

Pathogenesis of TB pleuritis was traditionally believed to be based on a Th1 - driven immune reaction after the entrance of bacilli into the pleural space **[336] [337].** This theory is questioned from recent data suggesting that TPE represents a stage in a continuous spectrum rather than a different condition from pleural infection **[338].**

Most TB pleural effusions are benign conditions that undergo complete spontaneous resolution within 2–4 months of onset. Patients tend to be younger in regions with high TB prevalence and older in developed regions with low TB prevalence. They present with subacute illnesses, fever, cough, and pleuritic chest pain. Pleural effusion is mostly lymphocytic exudate through lymphocyte

[60]

predominance is questioned in recent data, possibly due to the increased use of ultrasound detecting TPE in earlier neutrophilic stages **[336]**. Interestingly, 10% of patients have evidence of a mild-to-moderate restrictive impairment on pulmonary function testing **[338], [339].**

The radiological features of TB pleuritis are nonspecific, and the most common finding is a unilateral moderate-sized effusion, occupying less than two-thirds of the hemithorax. Bilateral effusions and massive effusions are rarely seen **[340].** Chest CT shows micronodules and interlobular septal thickening distinguishing TB from other pleural infections **[341]**, **[342]**. In chronic TB pleurisy, residual pleural thickening and fibrothorax are reported **[343]**.

The diagnostic yield of mycobacterial culture from the pleural fluid is low in most studies. However, recent data suggest that new culture methods have increased the yield and the combination of pleural fluid and sputum cultures is a reasonable approach in endemic areas **[338].** Biopsies under guidance and thoracoscopy remain the gold standard for a definite diagnosis since microbiological studies have shown low diagnostic yield and long division time **[344].** Medical thoracoscopy will identify almost 100% of cases of TB effusion. The diagnosis is confirmed from the presence of caseating granulomas, acid-fast bacilli, or a positive culture with overall sensitivity between 70–100% **[345], [346].**

Biomarkers in pleural fluid have been thoroughly studied due to the insensitivity or invasiveness of the diagnostic approaches **[347].** ADA is a purine-degrading enzyme predominantly found in T-lymphocytes and has shown high sensitivity to establish a TBP diagnosis. In low incidence areas, ADA<30 IU/L has a substantial negative predictive value, helping to avoid unnecessary

empirical *anti-tuberculosis* treatment **[102], [348].** However, a patient with ADA>35 IU/L should undergo a biopsy to obtain microbiological confirmation and sensitivity data. Some studies suggest that IL-27 alone or combined with ADA may reach a sensitivity of 100% **[349], [350]**. Recent data proposed that PF T-SPOT assay could add to ADA's diagnostic yield, especially in cases with ADA<40 IU/L **[351].**

Regarding prognosis, older age, HIV co-infection, lower concentrations of proteins in PF, positive PF cultures, presence of malignancy, acute renal failure, steroid use, history of stroke, and pulmonary involvement have all been associated with higher mortality rate **[352], [353], [354].**

The recommended treatment for TPE is the same as for pulmonary TB with a 6-month regimen divided into two months of isoniazid, rifampicin, ethambutol, pyrazinamide, and four months of isoniazid, rifampicin **[355].** Other choices have been tested with excellent results **[356], [357].** In cases of thickening of the pleura, definite intervention should not be delayed **[358].** The current recommendation is against routine use of corticosteroids **[359]** since data to support its use are insufficient and more data on the long-term impact of PTE on respiratory function are needed **[360].** TB effusions that cause dyspnea should be drained. The use of intrapleural fibrinolytic results in reduced residual pleural thickening, faster functional recovery time, and resolution of the effusion **[361], [362].** Finally, medical thoracoscopy may be an effective option **[363]**. Open thoracotomy and decortications have reasonable outcomes in selected patients **[364],** while VATS techniques have shown comparable results **[365].**

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3.8 Post cardiac injury

The post-cardiac injury syndrome (PCIS) is a general term referring to a heterogeneous group of conditions with autoimmune-mediated pathogenesis, including post myocardial infarction syndrome or Dressler's syndrome, post pericardiotomy syndrome (PPS), and post-traumatic pericarditis **[366].** PCOS is a diagnosis of exclusion, and at least two of the following five diagnostic criteria should be fulfilled (i) fever without alternative causes, (ii) pericarditic or pleuritic chest pain, (iii) pericardial or pleural rubs, (iv) evidence of pericardial effusion and (v) pleural effusion with elevated CRP **[366], [367].** However, these recommendations of ESC in 2015 have received criticism due to the irrelevance of most diagnoses in recent prospective studies **[368], [369].**

Experts suggest aspirin and colchicine for initial treatment, glucocorticoids for recurrence or contraindications to aspirin, and one-month colchicine prophylactic after surgery **[367].** Recurrence has been reported between 10% and 15% of cases. Thus, patients need long-term follow-up **[370].**

Thoracic X-ray reveals unilateral (usually left) or bilateral pleural effusion, while most patients (>80%) have combined pleuropericardial involvement **[371], [372].** Recurrent large, symptomatic pleural effusions should be further managed with thoracoscopic pleurodesis or insertion of an indwelling pleural catheter **[373].**

The prognosis of PCIS is generally good with low complication rates for recurrences, cardiac tamponade, or constrictive pericarditis **[366], [367].** However, recent studies found an association with mortality during the first two years after cardiac surgery, supporting prophylactic methods to prevent PPS **[369].**

[63]

Late post-myocardial infarction pericarditis, also known as Dressler's syndrome, has become quite rare in developed countries, while prior to reperfusion therapy, it was reported with an incidence of 5%. Diagnosis and treatment are similar to that generally recommended for PCIS **[374].** Pleural effusions occur in more than 85% of patients after CABG. They are primarily small unilateral and left-sided effusions, while approximately 10% of the patients will have more significant effusions **[375].** In the early stages (within 30 days after surgery), these large effusions, when aspirated, are hemorrhagic and eosinophilic, while later, they turn into yellow lymphocytic exudates **[376].** Most patients with large effusions are treated successfully with one to three therapeutic thoracentesis**,** though persistent cases resulting in trapped lung and surgical intervention have been reported **[377].**

3.9 Connective tissue diseases

Research on benign non-infective PEs is limited**.** A retrospective study highlighted the challenge in diagnosing and managing connective tissue disease (CTD) related PEs and the need for a multidisciplinary approach **[378].** Although various CTDs can affect the pleura, the most reported in clinical practice are rheumatoid arthritis and systemic lupus erythematosus. Systemic sclerosis, ankylosing spondylitis, eosinophilia-myalgia syndrome, mixed connective tissue disease, polymyositis, and dermatomyositis syndromes appear with pleural effusions much rarer **[378].**

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease that most often affects the small joints of the hands and wrists **[379]**. RA-associated pleural disease is the commonest form of RA-associated lung disease, more

frequently seen in middle-aged males **[380]**. Effusions are exudative, mostly unilateral on the left side; however bilateral pleural effusions have been reported. Regarding pleural fluid, common pleural fluid characteristics are : ph<7.2, glucose 10-30 mg/d, high total protein, LDH >1000 U/l and rheumatoid factor (RF) >1:320 **[381].** The main symptoms reported are chest pain, fever, and dyspnea. Most RA-associated PEs will resolve spontaneously or with the initiation of specific RA treatment and thus do not necessitate additional management. In breathlessness and chest pain, thoracocentesis is recommended or even pleural biopsy if the diagnosis is in doubt **[382].**

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that primarily affects females of childbearing age. Symptoms include fever, fatigue, lymphadenopathy, chest pain, arthralgia, oral and neuropsychiatric disturbance **[383].** Pleural effusions occur in 17–60% of SLE patients and, like rheumatoid arthritis, are the most common pulmonary manifestation of the disease **[384].** Effusions can also be related to medication associated with SLE treatment **[385].** Pleural effusions are exudative, bilateral, and small to moderate-sized, though large unilateral effusions have been reported. Pleural fluid is characterized by total protein >3.5 g/dl, glucose levels around 60 mg/dL, pH >7.30 and low LDH <500 IU/l **[386].** In most cases, small effusions are asymptomatic and self-resolve. Nonsteroidal anti-inflammatory drugs (NSAIDs) or a short course of oral corticosteroids are highly effective **[387].** In cases of large volume pleural effusion, thoracocentesis is performed to manage chest pain and breathlessness. In a large multicenter study of 1,000 patients, pleural involvement was found to predict survival **[388].**

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3.10 Less common cause

Patients with acute pancreatitis (AP) often present with respiratory symptoms ranging from mild hypoxemia to severe ARDS and radiological complications such as atelectasis, pleural effusions, pulmonary infiltrates, and edema **[389].** The incidence of pleural effusion is 50% in recent reports based on pleural fluid detected on CTs **[390].** PE is usually small-sized and resolves during recovery. When related to the presence of pancreaticopleural fistula, pleural effusion is large, refractory to drainage, with a high level of amylase > 1000 U/L and protein > three g/dl **[391].** Diagnosis can be challenging when respiratory disorders overweigh abdominal symptoms. In a study from Japan, 71 out of 113 patients presented with thoracic symptoms, whereas only 23 patients complained of upper abdominal pain **[392].** Thus, pleural fluid amylase should always be measured in an undiagnosed exudative pleural effusion **[393]**. In its complicated form, AP has a high mortality rate ranging from 14% to 30%, and respiratory complications proceed other organ failures (heart, liver, kidney) **[394]**. In identifying patients at risk early in the disease, pleural effusion and severe hypoxemia at presentation have been found to predict complications and poor outcomes **[395], [396].** Moreover, pleural effusions evaluated by ultrasonography seem to predict disease severity more accurately than other widely used severity scores (Ranson, Apache II) **[397].**

Chylothorax is an exudate with a milky appearance and high triglyceride content (>110 mg/dl), mainly resulting from chyle accumulating into the pleural cavity due to thoracic duct leak. Pleural fluid is a lymphocytic exudate. However, a transudate or a neutrophil-predominance may signify additional underlying pathologies. Therefore, chylothorax should be suspected in milky effusions and

patients with co-morbidities or a history of chest/neck trauma. When triglyceride exhibits nondiagnostic values 50-110 mg/dl, analysis for the presence of chylomicrons should be asked **[398].**

Urinothorax is the presence of urine in the pleural space. Depending on the underlying pathology, urinothorax is divided into obstructive or traumatic. Although urinary tract obstruction is common in clinical practice, obstructive urinothorax is only referred to in small series or case reports. Urinothorax is usually unilateral with fluid collecting ipsilateral to the side of injury, although there have been reported cases of pleural effusion on the contralateral side **[399].** Traumatic urinothorax has been related to blunt abdominal trauma and iatrogenic injury in nephrostomy tube placement, kidney biopsy, or other intraabdominal surgical procedures **[399].** Urinothorax is usually unilateral with fluid collecting ipsilateral to the side of injury, although there have been reported cases of collection on the contralateral side **[400].** Urinothorax is generally transudate with low glucose and low pH. The diagnosis is made by the measurement of the pleural fluid creatinine level. A ratio of pleural fluid to serum creatinine greater is traditionally considered diagnostic **[401],** but recent reports question the sensitivity of this marker **[399]**

Meigs' syndrome is a rare condition defined as the combination of ascites, pleural effusion, and benign ovarian fibroma. It is diagnosed with the remission of symptoms after tumor resection, and ovarian carcinoma is ruled out **[402]**. Cancer antigen-125 (CA-125) is often elevated **[403]**. Pseudo-Meigs presents with ascites, pleural effusion, and benign tumors of the ovary (other than fibromas) or malignant tumors. Pleural effusions typically are exudative and occur on the right side **[404].**

[67]

CHAPTER 4

MORTALITY AMONG PATIENTS WTH PLEURAL EFFUSION

Despite the increasing burden of pleural disease, epidemiological data are scarce and mainly based on single-center studies and few population-based studies. A widely cited epidemiological study from Czechoslovakia in 1993 reports an incidence of 70 and 250 cases per 100,000 population for malignant and nonmalignant effusions, respectively **[106].** We reported above how pleural effusions affect prognosis and mortality depending on common underlying diseases, especially MPE, pleural infection, and organ failure (even though less well established). However, the impact of pleural effusions of any etiology on morbidity and mortality of hospitalized patients comparatively has been limited studied. Lately, three single-center studies have improved our understanding of mortality associated with pleural effusions.

A retrospective study of 104 patients was the first to associate mortality with all-cause pleural effusions. The mean age of patients was 72.7 years, and only 10% underwent diagnostic thoracentesis. The authors reported 15% and 32% 1-month and 1-year mortality, respectively. The severity of illness and malignancy was associated with short-term mortality, while age, the severity of illness, cancer, and pulmonary disease with one-year mortality. Interestingly, a short-term survival benefit from thoracentesis was reported, but the number was not statistically significant. It was the first study to underline that physicians may not be aware of the high mortality associated with pleural effusions **[21]**.

Another prospective study of 308 patients, all undergoing diagnostic thoracentesis, reported an overall mortality of 21% and 51% for 1- month and 1-year, respectively. It was the first study to associate bilateral effusions with

[68]

the outcome and highlighted the increased mortality in this group of patients (47% in 1 month and 69% in 1 year). Besides that, malignant effusions had the highest mortality (37% and 77% for one month and 1year respectively), and multiple benign diseases such as cardiorenal, hepatorenal, malnutrition, and hypoalbuminemia were also associated with increased mortality (29% and 55% for one month and one year) respectively **[22]**.

Finally, Walker et al. examined 356 patients with nonmalignant pleural effusions **[23]**. All patients underwent thoracentesis, and the median age was 68 years. Organ failure was associated with a poor prognosis. The documented one-year mortality was 50% for patients with heart failure, like patients admitted with decompensated HF **[405]** and more than patients living with NYHA class IV CHF **[406].** For renal failure, one-year mortality was 46%, far more than a regular patient receiving dialysis **[407],** but it was statistically insignificant because of the small number of cases. Finally, regarding hepatic-related effusions, 1-year mortality was 25%, like a high MELD score, which indicates liver transplantation **[408]**. Following the previous findings of Debiasi et al., bilateral effusions and transudates were associated with a worse prognosis. The authors concluded that nonmalignant effusions are not a benign process, primarily related to organ failure and resistance to medical therapy requiring thoracentesis. However, these patients were selectively referred to a specialty center and probably did not represent the typical distribution of pleural effusions seen in general practice. Characteristically, in the heart failure group, bilateral effusions were underrepresented and exudates overrepresented, suggesting that small heart failure–related bilateral transudates were not referred for this study.

SPECIFIC PART

CHAPTER 5

METHODS

We conducted a prospective multicenter observational study in Corfu General Hospital Pulmonary Department and University of Larissa Pulmonary Department. Successive patients hospitalized between January 2018 and January 2020 that underwent computed tomography of the thorax and/or abdomen and in which PE was detected, were admitted to the study, regardless of etiology. The study protocol was approved by the respective ethics committees and study participants gave written informed consent.

Upon recruitment in the study, for each subject, we recorded demographics, smoking habit, Charlson comorbidity index (CCI), department in which subjects were admitted, main diagnosis of admission (ICD-10), and severity of disease (calculated by APACHE II and SOFA scores).

Further, PEs were quantified by size based on the division of the hemithorax on computed tomography (CT) into 4 quadrants as small (0–25%), moderate (25–50%), and large (50–100%) by the mid-clavicular line. In cases of doubt, the small effusion was up to 3 cm in size and the medium >3 cm up to 10 cm. In cases where the atelectatic lung was surrounded by fluid, this was counted in the total size of the effusion. This method has been described by other researchers to increase agreement on the classification of collections by size among clinicians **[409].** We also recorded whether effusions were unilateral or bilateral. In the latter case, the size of the largest collection was calculated. Type of CT (thorax, contrast-enhanced, computed tomography pulmonary angiography, and abdominal) was recorded in all cases. The effusions were not

[71]

necessarily tapped for inclusion in the study. A diagnostic puncture was performed if deemed necessary. In these cases, diagnosis and treatment depended on the best medical practices and the judgment of the treating physician. If a diagnostic puncture was performed, Light's criteria were applied. The definite etiology of the effusion was determined by two pulmonary physicians. Electronic medical records of the respective hospitals were used to retrieve data on the survival of the patients in 1 month and 1 year, as well as the total days of hospitalization and other adverse outcomes.

CHAPTER 6

STATISTICAL ANALYSIS

For continuous variables, the mean, standard deviation, and range or median, 25th and 75th percentiles, and range were used after testing for normal distribution. The continuous variables were tested for normality using the Shapiro-Wilk test. For categorical variables, the frequencies and percentages are presented. SOFA score and APACHE II score were analyzed as categorical variables (SOFA: 0–1, 1–2, 2–3, 3–4, 4–5, >5 and APACHE: 0–4, 5–9, 10–14, 15–19, 20–24, 25–29). Univariate logistic regression was performed to identify statistically significant variables associated with 1-month and 1-year mortality. Then, all the statistically significant variables except the "transudate vs. exudate" variable were used for the construction of a model using multivariate logistic regression. For the construction of the model backward, stepwise selection approaches were used. The variable "transudate vs. exudate" was excluded due to the small number of observations compared to the other variables (201/508). Kaplan-Meier curves are presented regarding 1-month and

1-year survival. A $p < 0.05$ was considered statistically significant. All statistical analyses were performed using Stata/ IC version 15.1.

CHAPTER 7

RESULTS

A total of 508 subjects were included in the analysis. Table 8 presents the demographics and the characteristics of pleural effusions. The mean age of the patients in our study was 78 years and most patients were admitted to Pulmonary Departments with median hospitalization ranging from 8 to 12.5 days, while most patients underwent thoracic CT. Pleural effusions were mostly small-sized, equally unilateral, or bilateral. When thoracentesis was performed exudates were more common ($n = 160$, 79.65%). Heart failure, malignant pleural effusion, and pleural infection were the leading diagnosis. Organ failure (liver, renal) and other exudates followed. Descriptive statistics of study subjects separated by outcome and short/ long term prognosis are shown in Table 9.

Age (years)	78, range 67-85	**Type of CT**	
Male	292 (57.48%)	Thorax	278 (54, 7%)
Smoking	298 (58.66%)	Abdominal	92 (18, 1%)
Charlson Index	5, range 3-5.5	CTPA^	78 (15, 35%)
Apache Score	10, range 7-15	Thorax & abdominal	60 (11, 81%)
Sofa Score	2, range 1-3	**Distribution**	
Department of admission		Unilateral	255 (50.2%)
Pulmonary Department (PD)	312 (61.42%)	Bilateral	253 (49.8%)
Internal Medicine (IM)	108 (21.26%)	**Size of effusion**	
Surgical Department	40 (7.87%)	Small	277 (54.53%)
Cardiology Department	36 (7.09%)	Medium	138 (27.17%)
Intensive Care Unit	12 (2.36%)	Large	93 (18.31%)
Days of admission		**Thoracentesis**	201 (39.57%)
Heart failure	10	Transudate	41 (20.4%)
Malignant pleural effusion	8	Exudate	160 (79.6%)
Pleural infection	10	**Diagnosis**	
Organ failure	10.5	Heart failure	158 (31.1%)
Pulmonary embolism	12	Malignant pleural effusion	112 (22.05%)
Connective tissue disorders	8.5	Pleural infection	90 (17.72%)
Tuberculosis	12.5	Organ failure	44 (8.66%)
Other exudates	10	Other exudates *	37 (7.28%)
Multiple benign	13	Pulmonary embolism	24 (4.72%)
etiologies		Multiple benign etiologies	23 (4.53%)
		Connective-tissue disease	16 (3.15%)
		Tuberculosis	4 (0.79%)

Table 8] Demographics and characteristics of pleural effusions (n = 508).

	1 month outcome		1 year outcome	
	Survivors	**Non-survivors**	**Survivors**	**Non-survivors**
Age years	75 (65–84)	83 (72–88)	73 (60–82)	79 (71–85)
In hospital days	10 (6–15)	10.5 (7–17.25)	10 (6–15)	10 (6–15)
CCI	4.0 (3–5)	5.0 (5–6)	4 (2–5)	5 (4–6)
APACHE II score	10.0 (5–13)	15.0 (13.75–19)	8 (4–12)	10 (7–15)
SOFA score	1.0 (1–3)	3.0 (3–4.25)	1 (1–2)	2 (1–3)
Male sex	223 (57)	68 (60)	143 (56)	80 (59)
Smoking	224 (57)	73 (64)	146 (57)	78 (57)
Size				
Small	218 (55)	57 (50)	158 (62)	62 (46)
Moderate	109 (28)	29 (25.5)	68 (26)	40 (29)
Large	66 (17)	28 (24.5)	31 (12)	34 (25)
CT				
Thorax wo contrast	142 (36)	53 (46)	91 (36)	51 (38)
Thorax with contrast	115 (29)	27 (24)	77 (30)	38 (28)
CTPA	71 (18)	7 (6)	50 (19)	21 (15)
Abdomen	65 (17)	27 (24)	39 (15)	26 (19)
Unilateral /bilateral	215 (55)	33 (29)	140 (54)	82 (60)
	178 (45)	81 (71)	117 (46)	54 (40)
Loculation	131 (33)	32 (28)	82 (32)	49 (36)
Thoracentesis	168 (43)	33 (29)	101 (39)	67 (49)
Exudate/transudate	138 (82)	21 (64)	85 (84)	54 (80)
	30 (18)	12 (36)	16 (16)	13 (20)

Continuous variables are depicted as median with interquartile range (25–75) in parenthesis and categorical outcomes as absolute n with% frequency in parenthesis. Charlson comorbidity index, APACHE II and SOFA scores are presented in this table as continuous variables. CCI, Charlson comorbidity index; CT, computed tomography; CTPA, computed tomography pulmonary angiography; PPE, parapneumoic effusion; CTD, connective tissue disease; APACHE II, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment.

Table 9] Comparative characteristics for short and long-term outcome.

Mortality rates are illustrated in Figures 8, 9. Overall mortality across all groups was 22.6% ($n = 115$) at 1 month and 49.4% ($n = 251$) at 1 year. Patients with large effusions exhibited higher mortality than patients with small effusions at 30 days (30 vs. 20.9%, $p = 0.095$) and significantly higher at 1 year (66.6 vs. 43.3%, $p < 0.01$). Regarding distribution, patients with bilateral effusion exhibited significantly higher mortality than patients with unilateral effusions at 1 month (32 vs. 13.3%, $p = 0.005$) and higher at 1 year (53.3 vs. 45.5%, $p = 0.78$). Regarding diagnosis, short-term mortality was higher (30–35%) for pleural effusions secondary to organ failure (heart, liver, renal) and multiple benign etiologies, while MPE and other exudates (pleural infection, pulmonary embolism) followed with 22 and 13%, respectively. Patients with MPEs and organ failure experienced the worst prognosis at 1 year (mortality 74 and 51–59%, respectively) while pleural infection followed with 33.3%.
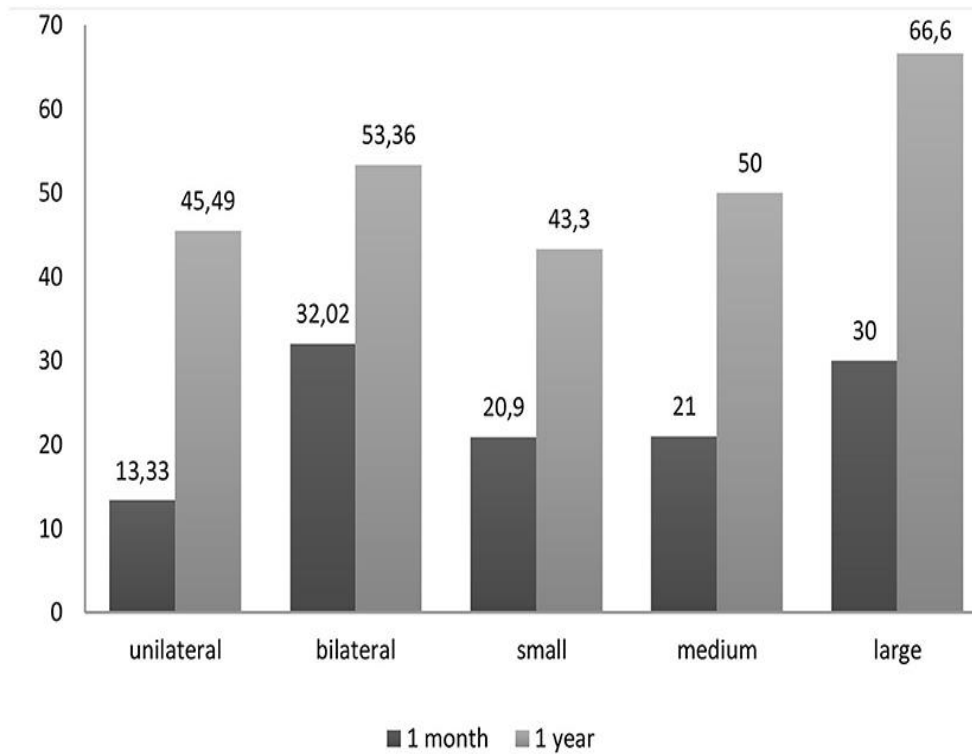
[76]

Figure 8] Percent mortality based on the distribution and size of the PE
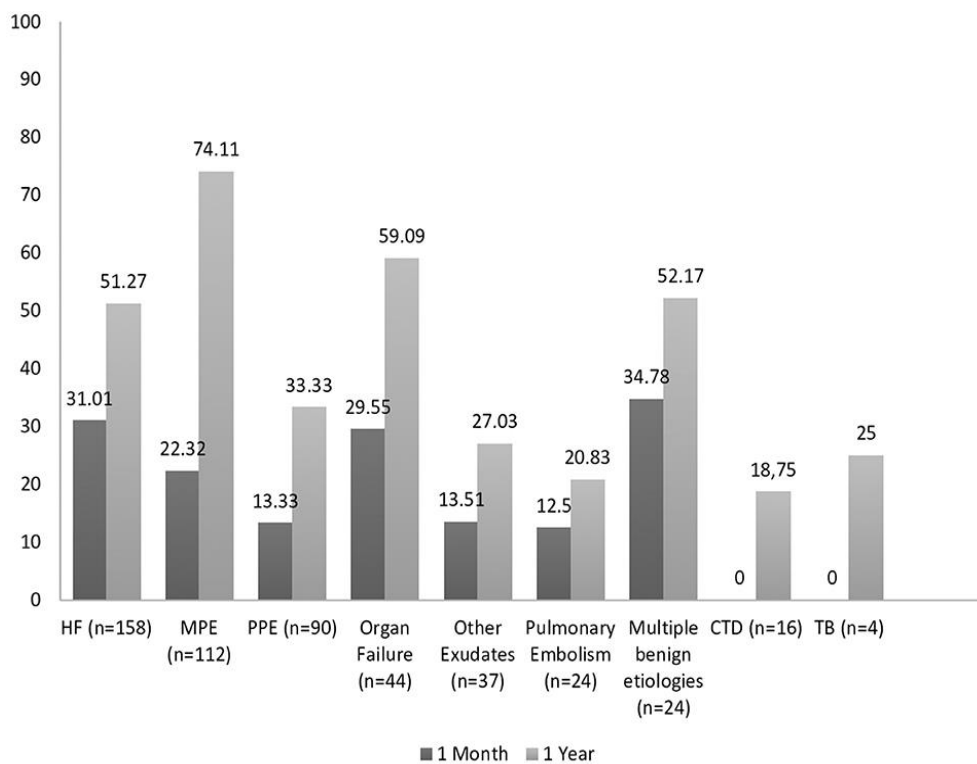
Figure 9] Percent mortality based on the diagnosis of the PE

[77]

In Tables 10-12, univariate and multivariate predictors of mortality are displayed. On univariate analysis, significant variables associated with mortality in 30 days were age, CCI, APACHE score, SOFA score, and bilateral distribution. Of note, thoracentesis and CTPA showed a strong negative association with mortality (Table 10). On multivariate analysis, only age, CCI, APACHE score, SOFA score, and bilateral distribution were associated with mortality (Table 12). Regarding long-term mortality, on univariate analysis age, CCI, APACHE score, SOFA score, large size, and malignant etiology predicted mortality, while CTPA showed a protective effect (Table 11). On multivariate analysis that followed, the only significant predictors were CCI, APACHE score, SOFA score, and malignant etiology (Table 12).

Sofa score	OR	95% CI	P-value
1–2 vs. 0–1	7.636	2.962–19.681	<0.001
2–3 vs. 0–1	22.782	9.056–57.314	<0.001
3–4 vs. 0–1	28.597	10.925–74.855	<0.001
4–5 vs. 0–1	27.908	9.882–78.814	<0.001
>5 vs. 0–1	36.117	11.095–117.573	<0.001
APACHE II			
10–14 vs. 0–4	19.563	2.615–146.352	0.004
15–19 vs. 0–4	76.5	10.297–568.342	<0.001
20–24 vs. 0–4	130.768	16.151–1058.793	<0.001
25–29 vs. 0–4	425	23.04–7839.536	<0.001
Charlson comorbidity index	1.53	1.319–1.776	<0.001
Bilateral vs. Unilateral	3.061	1.957–4.788	<0.001
Age	1.048	1.028–1.068	<0.001
Large vs. Small	1.627	0.958–2.761	0.072
CTPA vs. Thorax & abdominal	0.271	0.103–0.711	0.008
Thoracentesis	0.539	0.343–0.846	0.01

Significant variables associated with mortality were age, CCI, APACHE score, SOFA score, and bilateral distribution. OR, Odds Ratio; CIs, confidence intervals.

Table 10] Univariate predictors of mortality at 1 year.

Sofa score	OR	95% Cls	*p*-value
1–2 vs. 0–1	2.464	1.506–4.031	<0.001
2–3 vs. 0–1	6.783	3.846–11.965	<0.001
3–4 vs. 0–1	10.577	5.123–21.46	<0.001
4–5 vs. 0–1	8.584	3.807–19.355	<0.001
>5 vs. 0–1	5.519	2.115–14.401	<0.001
APACHE II			
5–9 vs. 0–4	1.981	1.047–3.745	0.036
10–14 vs. 0–4	2.829	1.553–5.155	0.001
15–19 vs. 0–4	11.363	5.827–22.156	<0.001
20–24 vs. 0–4	25.566	7.991–81.79	<0.001
Charlson index	1.59	1.41–1.794	<0.001
Large vs. Small	2.617	1.599–4.281	<0.001
Age	1.05	1.035–1.066	<0.001
HF vs. MPE	0.368	0.217–0.622	<0.001
PPE vs. MPE	0.175	0.095–0.321	<0.001
Embolism vs. MPE	0.092	0.031–0.269	<0.001
CTD vs. MPE	0.081	0.021–0.303	<0.001
Exudates vs. MPE	0.129	0.056–0.3	<0.001
CTPA vs. other CTs	0.373	0.187–0.747	0.005

Significant variables associated with mortality were age, CCI, APACHE score, SOFA score, large size, and malignant etiology. OR, Odds Ratio; Cis, confidence intervals; HF, heart failure; MPE, malignant pleural effusion; PPE, parapneumonic pleural effusion; CTD, connective tissue disease; CTPA, CT pulmonary angiogram.

Table 11] Univariate predictors of mortality at 1 year.

[80]

1 month	OR	95% Cls	*p*-value
Age	1.05	1.035–1.066	<0.001
Charlson index	1.53	1.319–1.776	<0.001
Apache 15–19 vs. 0–4	2.912	1.604–5.286	<0.001
Apache 20–24 vs. 0–4	4.277	1.686–10.847	0.002
Apache 25–29 vs. 0–4	17.074	1.741–167.42	0.015
Sofa 1–2 vs. 0–1	5.129	1.942–13.545	0.001
Sofa 2–3 vs. 0–1	9.824	3.589–26.89	<0.001
Sofa 3–4 vs. 0–1	9.726	3.3–28.666	<0.001
Sofa 4–5 vs. 0–1	8.419	2.604–27.217	<0.001
Sofa>5 vs. 0–1	9.883	2.582–37.832	0.001
Bilateral	2.07	1.235–3.471	0.006

1 year	OR	95% Cls	*p*-value
Charlson index	1.303	1.059–1.604	0.012
Apache 15–19 vs. 0–4	2.96	1.617–5.419	<0.001
Apache 20–24 vs. 0–4	7.675	2.426–24.279	0.001
Sofa 2–3 vs. 0–1	2.37	1.264–4.444	0.007
Sofa 3–4 vs. 0–1	3.157	1.406–7.09	0.005
Other exudate vs. MPE	0.077	0.027–0.219	<0.001
HF vs. MPE	0.091	0.039–0.212	<0.001
Organ failure vs. MPE	0.093	0.032–0.268	<0.001
Pulmonary embolism vs. MPE	0.094	0.025–0.35	<0.001
Multiple benign vs. MPE	0.119	0.035–0.407	0.001
PPE vs. MPE	0.182	0.088–0.378	<0.001
Bilateral	1.868	0.989–3.529	0.054
Age	1.026	0.999–1.054	0.063
Large vs. small	1.771	0.955–3.287	0.07

Table 12] Multivariate predictors of mortality.

We also analyzed subjects who underwent thoracentesis (Table 13). Exudates excluding MPEs exhibited a survival benefit at both 1 month and 1-year observations. Due to the smaller *n* sample, fluid characteristics were not included in the multivariate analysis.

1 Month	OR	95% Cis	*p*-value
Exudate vs. Transudate	0.209	0.075–0.585	0.003
1 Year			
Exudate vs. Transudate	0.219	0.098–0.488	<0.001

Exudates excluding MPEs exhibited a survival benefit at both 1-month and 1-year observations. OR, Odds Ratio; Cls, confidence intervals.

Table 13] Transudates versus exudates (excluding MPEs) on mortality.

A separate analysis of solely MPEs is depicted in Table 14. Cox proportional hazards regression analysis identified high APACHE score and bilateral distribution as the factors associated with worse survival among MPEs.

Variables		Hazard ratio	95% confidence intervals	p
Age	72 (67–81)	1.015	0.9885–1.043	ns
Female sex	36 (32)	1.092	0.5813–1.964	ns
Smoking	84 (76)	0.97	0.4792–1.941	ns
Unilateral/Bilateral PE	92 (83)/19 (17)	3.49	1.700–6.969	0.0005
Small/moderate/large PE	25 (22)/44 (40)/42 (38)	0.76	0.4613–1.253	ns
APACHE II score	10 (5–15)	1.06	1.005–1.125	0.035
SOFA score	2 (1–3)	0.86	0.6845–1.056	ns
CCI	4 (4–5)	1.12	0.9076–1.385	ns
In-hospital days	8 (5–15)			
Survival days from diagnosis	100 (39–339)			

Continuous variables are presented as median (interquartile range) and categorical outcomes as absolute n (% frequency). Survival analysis is performed using Cox proportional hazards regression (significant p < 0.05). PE, pleural effusion; APACHE II, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; CCI, Charlson comorbidity index.

Table 14] Prognostic characteristics of survival in subjects with Malignant pleural effusions.

[83]

Finally, figure 10 contrasts the Kaplan-Meier survival curves by

(a,b) Distribution of PE. In both time periods, the presence of bilateral pleural effusion was associated with lower survival probability.

(c,d) Size of PE. In both time periods, the presence of large pleural effusion was associated with lower survival probability.

(e,f) Diagnosis of PE. Short-term survival is lower for patients with pleural effusions secondary to organ failure and multiple benign etiologies, while long-term survival is worse for patients with MPE.
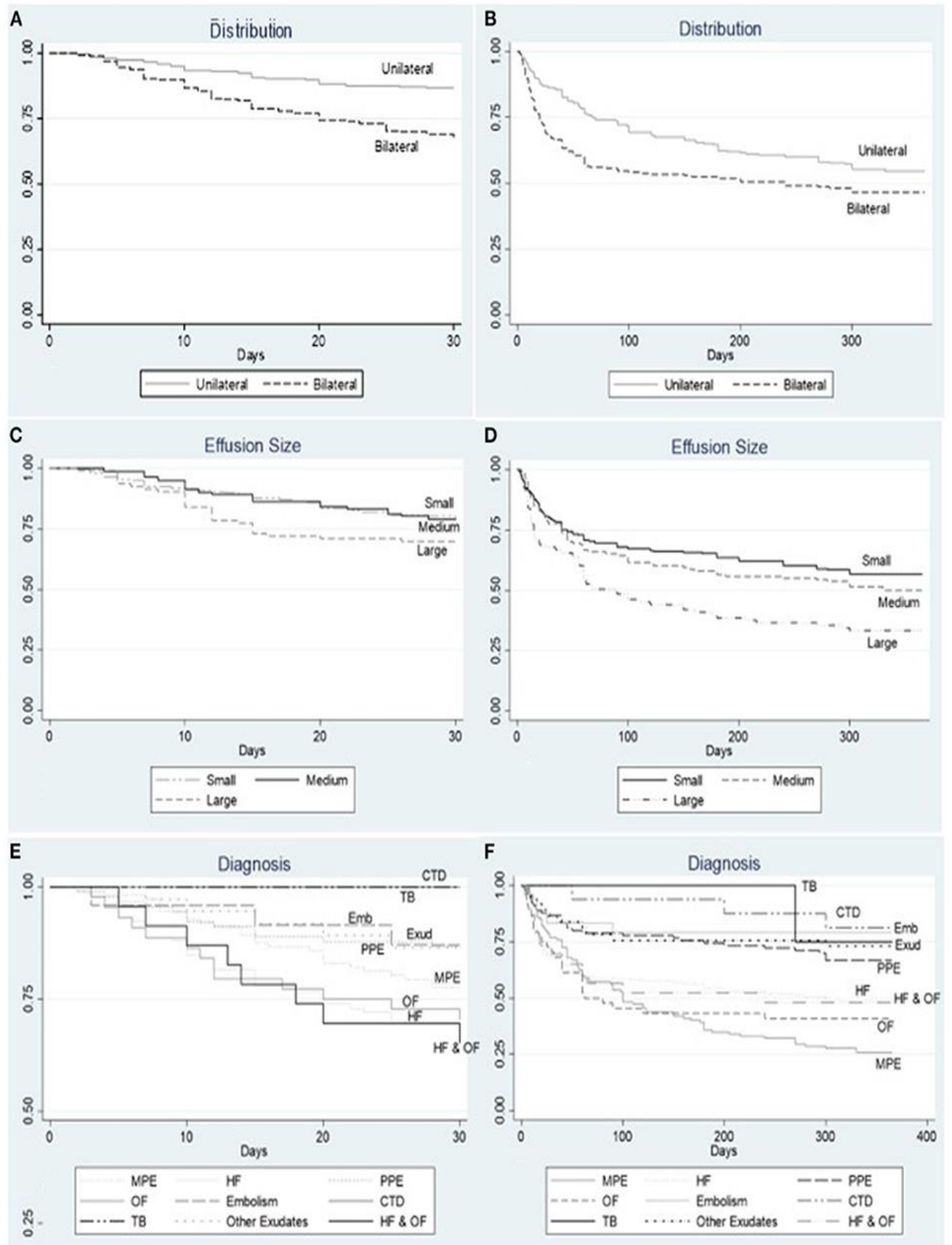
Figure 10] Kaplan Meier survival curves

[85]

CHAPTER 8

DISCUSSION

We performed a multicenter prospective observational study and demonstrated that PEs carry significant morbidity and mortality. Among all clinical parameters studied, short-term mortality was associated in our study with increased age, bilateral effusions, APACHE II and SOFA scores, and a high Charlson comorbidity index. Long-term mortality was found associated with a high Charlson comorbidity index, APACHE II and SOFA scores, and the presence of malignant pleural effusion. Overall mortality in our study was 22, 6% at 1 month and 49, 4% at 1 year, similar to previous findings of Debiasi and colleagues (21% at 30 days and 51% at 1 year). Kookolis and colleagues in a retrospective study reported overall mortality of 15% at 30 days and 32% in 1 year **[21], [22].** These findings taken together illustrate a significant burden of pleural effusions in patients needing hospitalization in pulmonary or in other departments.

APACHE II score ranging from 10 to 14 is found to be associated with 7–15% in-hospital mortality **[410],** Sofa score above 2 is related to an increased risk of in-hospital mortality **[411],** and Charlson comorbidity index above 5 is associated with 80% 10 year-mortality **[412].** In our study worse APACHE II and SOFA scores were significant predictors of both short-term and long-term mortality. This was also demonstrated by Kookoolis et al. **[21].** On the other hand, a novel finding of our study is the association of the Charlson comorbidity index with mortality. Thus, our findings suggest that the occurrence of pleural effusion in an aged individual with already multiple comorbidities may lead to

acute decompensation as demonstrated by clinical severity scores. Therefore, these patients upon admission should be monitored closely.

Congestive heart failure (HF) is the most common cause of PE **[52]** however the prognostic role of HF-related effusions is not well-established. In a prospective study of 100 patients, PE didn't predict outcome or mortality during a 6-month follow-up **[134].** Ercan and colleagues reported favorable survival (81% at 1 year, *n*= 151) when effusions were incidentally observed in transthoracic echocardiogram **[119]**. However, recent prospective studies report high mortality at 1 year (near 50%), suggesting that HF-related PEs, especially large refractory cases requiring aspiration, have a poor prognosis **[22], [23].**

Regarding other benign etiologies, mortality rates are also high. Walker and colleagues reported that 25% of patients with liver failure die within 1 year **[23].** In a population-based study of 3.487 cirrhotic patients with PE requiring drainage, 30-day and 1-year mortality were 20.1 and 59.1%, respectively **[148]**. Mortality in PE associated with renal etiology is not well-studied, yet a study of a small cohort of 14 patients with renal failure showed 14 and 57% 30-days and 1-year mortality, respectively **[22].** We report here significant high mortality rates for all patients with organ failure (20–30% in 1 month and 50–60% in a year).

Malignant pleural effusion (MPE) affects almost 15% of patients with underlying malignancy and is associated with a poor life expectancy **[258].** Like other studies, we demonstrated that MPE is associated with high mortality rates; 22% at 30 days and 74% at 1 year. Regarding long-term outcomes, patients with MPE had the worse prognosis of all underlying etiologies. Among MPEs we

found bilateral distribution and high APACHE score, indicating acute but also chronic health decompensation, associated with worse outcomes. Given this poor outcome, prognostic tools are crucial to personalize treatment and avoid unnecessary interventions **[264], [265].**

It has been documented that PEs are poor prognostic signs in patients with pulmonary infection, especially when they are large, bilateral, or associated with empyema **[19], [413], [230].** Mortality rates range from 1% in simple uncomplicated parapneumonic pleural effusions to 30% in empyema or even 50% in ICU patients **[414-416], [252].** Our study shows a significant risk of death in hospitalized patients with pleural infection (13.3% at 30 days), however exudative effusions had a favorable prognosis as opposed to transudative effusions (Table 13).

It has been established that the presence of bilateral PEs in patients with community-acquired pneumonia is an independent predictor of 30-day mortality with a relative risk of 2.8 **[413].** However, Debiasi and colleagues first reported the association between bilateral PEs of any etiology and mortality. They reported 1-month mortality rates of 17% for unilateral vs. 36% for bilateral PEs, and 1-year mortality rates 47 and 69%, respectively **[22].** Similarly, Walker and colleagues reported 1 year mortality rates of 20 and 57% for unilateral vs. bilateral effusions **[23].** In accordance with these findings, we reported 1-month mortality rates of 13.3% for unilateral vs. 32% for bilateral effusions. At 1 year our rates increase to 45.5 and 53.4%, respectively. Bilateral PEs in our study reflect the increased mortality rates observed in heart, liver, kidney, or multi-organ failure patients. Therefore, the presence of bilateral PE regardless of etiology predicts significant mortality.

[88]

We also report a possible negative association between thoracentesis and mortality at 30 days. Kookoolis and colleagues first documented a protective role of thoracentesis in a retrospective cohort. Existing guidelines don't recommend thoracentesis in patients within a clinical context highly suspicious of transudative PE **[48].** Our finding might be due to underlying exudative etiologies, necessitating thoracentesis more commonly than transudates, since in our study exudates as we already mentioned had a better prognosis than transudates. We may not make a conclusive comment regarding the significance of thoracentesis in the present study, since not all effusions were aspirated. Further, undergoing thoracentesis may be a confounding signal reflecting the patient's clinical status allowing a procedure or not.

The same applies to CTPA that also showed a protective role since CTPA is usually performed in unilateral PEs in patients with lower clinical severity scores and underlying exudative etiologies (e.g., pulmonary embolism). Inhomogeneous CT requirement for inclusion in this study might introduce recruitment and confirmation bias, with mode of CT selected dependent on clinical and laboratory subjects' condition. Therefore, the clinical utility of each CT mode cannot be commented in our study. We believe however that this method allowed us to include more compromised patients and to better quantify the pleural effusion.

To our knowledge, this study is the largest prospective study on mortality in hospitalized patients with PE regardless of etiology and thoracentesis or not. Charlson comorbidity index, clinical severity scores, bilateral distribution, and malignancy reflect on mortality of PEs. As to the limitations of our study, our cohort represents hospitalized patients thus our results cannot be generalized

to an outpatient setting. The limited number of subjects that underwent thoracentesis did not allow effusion discrimination by Light's criteria to be included in the multivariate analysis.

CHAPTER 9

CONCLUSIONS

Pleural effusion is a marker of advanced disease. In our study, 20% of hospitalized patients died within 30 days and almost 50% within a year. Mortality tops within the first month in patients with pleural effusions related to organ failure, while patients with malignant pleural effusions have the worst long-term outcome. Independent predictors of mortality, apart from the Charlson comorbidity index, APACHE score, and SOFA score, are age and bilateral distribution in the short term and malignancy in the long term. Transudative effusions are possibly associated with worse outcomes.

ABSTRACT

Background Pleural effusions (PE) occur frequently in hospitalized patients. Data regarding their prognostic significance are scarce.

Objective Explore the impact of PEs on mortality among hospitalized patients.

Methods This is a prospective observational study in two hospitals. Successive patients that underwent computed tomography of thorax and/or abdomen and in which PE was detected, were admitted to the study, regardless of etiology. PE was classified by size on CT, anatomical distribution, diagnosis and Light`s criteria. Charlson comorbidity index (CCI), APACHE II and SOFA scores were calculated. Mortality at 1 month and 1 year were recorded.

Results 508 subjects with mean age 78 years. Overall mortality was 22.6% at 1 month and 49.4% at 1 year. Short-term mortality was higher (30%-35%) for patients with organ failure and long-term for patients with MPE (74%). Bilateral effusions were associated with higher mortality than unilateral effusions at 1 month (32% versus 13.3% p=0,005) and large effusions with higher mortality than small effusions at 1 year (66.6%, versus 43.3%, p<0, 01). On multivariate analysis age, CCI, APACHE score, SOFA score and bilateral distribution were associated with mortality in 1 month. Regarding long-term mortality the only significant predictors were CCI, APACHE II, SOFA and malignant etiology. Exudates (excluding MPE) exhibited a survival benefit at both 1 month and 1 year but due to smaller sample, fluid characteristics were not included in the multivariate analysis.

[91]

Conclusions Pleural effusion is a marker of advanced disease. Mortality tops within the first month in patients with pleural effusions related to organ failure, while patients with malignant pleural effusions have the worst long term outcome. Independent predictors of mortality, apart from CCI, APACHE II and SOFA scores, are age and bilateral distribution in the short-term, and malignancy in the long-term.

[92]

ΠΕΡΙΛΙΨΗ

Εισαγωγή Η επίπτωση των υπεζωκοτικών συλλογών (ΥΣ) στη νοσηρότητα και τη θνησιμότητα νοσηλευόμενων ασθενών έχει μελετηθεί περιορισμένα.

Σκοπός Να διερευνήσουμε την επίπτωση της ΥΣ στη θνησιμότητα νοσηλευόμενων ασθενών καθώς και τις πιθανές συσχετίσεις με το μέγεθος, την εντόπιση και την τελική διάγνωση της ΥΣ.

Υλικό-Μέθοδος Προοπτική μελέτη παρατήρησης σε δύο Νοσοκομεία. Ασθενείς που νοσηλεύτηκαν και υποβλήθηκαν σε αξονική τομογραφία θώρακος ή άνω κοιλίας και στις οποίες ανευρέθη ΥΣ ανεξαρτήτως αιτιολογίας εισήχθησαν στη μελέτη. Με την εισαγωγή τους κατεγράφησαν τα επιδημιολογικά χαρακτηριστικά, ο δείκτες Charlson comorbidity index (CCI), τα σκορ βαρύτητας APACHE II και SOFA και η κύρια διάγνωση. Κάθε ΥΣ ποσοτικοποιήθηκε με βάση τη διαίρεση του ημιθωρακίου σε 4 τεταρτημόρια ως μικρή (0-25%), μέτρια (25-50%), μεγάλη (50-100%) και καταγράφηκε εάν είναι εγκυστωμένη και αμφοτερόπλευρη. Οι ΥΣ δεν παρακεντήθηκαν απαραιτήτως. Όποτε πραγματοποιήθηκε παρακέντηση τα αποτελέσματά της καταγράφηκαν. Τέλος καταγράφηκε η θνησιμότητα στον ένα μήνα και ένα χρόνο.

Αποτελέσματα 508 ασθενείς, μέση ηλικία 78 έτη. Οι ΥΣ ήταν κυρίως μικρού μεγέθους, εξίσου αμφοτερόπλευρες και ετερόπλευρες. Η καρδιακή ανεπάρκεια, η κακοήθης υπεζωκοτική συλλογή (ΚΥΣ) και η υπεζωκοτική λοίμωξη ήταν οι συχνότερες διαγνώσεις. Η συνολική θνησιμότητα ήταν 22,6% στον 1 μήνα και 49,4% στο 1 έτος. Η βραχυπρόθεσμη θνησιμότητα ήταν υψηλότερη (30-35%) σε ασθενείς με ΥΣ από ανεπάρκεια οργάνων (καρδιά, ήπαρ, νεφρά) ενώ η μακροπρόθεσμη θνησιμότητα σε ασθενείς με ΚΥΣ (74%). Οι αμφοτερόπλευρες

[93]

ΥΣ σχετίζονται με σημαντικά υψηλότερη θνησιμότητα σε σχέση με τις ετερόπλευρες στον 1 μήνα (32% έναντι 13,3% p = 0,005) ενώ οι μεγάλες ΥΣ σχετίζονται με υψηλότερη θνησιμότητα σε σχέση με τις μικρές ΥΣ στο 1 έτος (66,6%, έναντι 43,3%, p <0, 01). Στη μονοπαραγοντική ανάλυση οι μεταβλητές που σχετίζονται με τη θνησιμότητα στις 30 ημέρες ήταν η ηλικία, ο δείκτης Charlson, τα σκορ APACHE II και SOFA και η αμφοτερόπλευρη εντόπιση. Η παρακέντηση και η διενέργεια CTPA έναντι άλλων αξονικών (θώρακος, κοιλίας) έδειξαν μια ισχυρή αρνητική συσχέτιση με τη θνησιμότητα. Ωστόσο στην πολυπαραγοντική ανάλυση μόνο οι παράγοντες ηλικία, CCI, APACHE , SOFA και αμφοτερόπλευρη κατανομή σχετίζονται με τη θνησιμότητα. Όσον αφορά τη μακροπρόθεσμη θνησιμότητα, στην μονοπαραγοντική ανάλυση ο δείκτης Charlson, τα σκορ APACHE II και SOFA, το μεγάλο μέγεθος και η κακοήθεια προέβλεπαν θνησιμότητα. Στην πολυπαραγοντική ανάλυση, οι μόνοι σημαντικοί προγνωστικοί παράγοντες ήταν οι CCI, APACHE II, SOFA και η κακοήθης αιτιολογία. Τα εξιδρώματα (εξαιρουμένων των ΚΥΣ) παρουσίασαν καλύτερη επιβίωση τόσο για τον 1 μήνα όσο και για 1 έτος αλλά λόγω μικρότερου δείγματος δεν συμπεριλήφθηκαν στην πολυπαραγοντική ανάλυση.

Συμπεράσματα Η υπεζωκοτική συλλογή είναι δείκτης προχωρημένης νόσου. Στη μελέτη μας το 20% των νοσηλευόμενων ασθενών απεβίωσε τον πρώτο μήνα και σχεδόν το 50% μέσα σε ένα χρόνο. Η θνησιμότητα κορυφώνεται εντός του πρώτου μήνα σε ασθενείς με υπεζωκοτικές συλλογές που σχετίζονται με ανεπάρκεια οργάνων, ενώ οι ασθενείς με κακοήθεις υπεζωκοτικές συλλογές έχουν τη χειρότερη μακροπρόθεσμη έκβαση. Ανεξάρτητοι προγνωστικοί δείκτες θνησιμότητας, εκτός από τον δείκτη Charlson και τα σκορ APACHE II και SOFA, είναι η ηλικία και η αμφοτερόπλευρη κατανομή βραχυπρόθεσμα και

η κακοήθεια μακροπρόθεσμα. Οι διιδρωματικές συλλογές πιθανώς σχετίζονται

με χειρότερα αποτελέσματα.

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REFERENCES

1.   Sahn SA. The value of pleural fluid analysis. Am J Med Sci. 2008 Jan; 335(1):7-15.

2.   Porcel JM, Esquerda A, Vives M, Bielsa S. Etiology of pleural effusions: analysis of more than 3,000 consecutive thoracenteses. Arch Bronconeumol. 2014 May; 50(5):161-5.

3.   Sahn SA. Pleural effusions of extravascular origin. Clin Chest Med. 2006 Jun;27(2):285-308.

4.   Porcel JM, Statophoulos G, Lee YC. Advances and controversies in pleural diseases. J Thorac Dis. 2015 Jun;7(6):961-3.

5.   Psallidas I, Rahman NM. Advances in pleural disease. Eur Respir Rev. 2016 Jun;25(140):108-9.

6.   Maldonado F, Lentz RJ, Light RW. Diagnostic approach to pleural diseases: new tricks for an old trade. F1000Res. 2017;6:1135

7.   Bødtger U, Halifax RJ. Epidemiology: why is pleural disease becoming more common? In Maskell NA, Laursen CB, Lee YCG, Rahman NM, editors, Pleural Disease. Sheffield, UK: European Respiratory Society. 2020. p. 1-12.

8.   Stathopoulos GT, Kalomenidis I. Malignant pleural effusion: tumor-host interactions unleashed. Am J Respir Crit Care Med. 2012; 186(6):487-492.

9.   Heffner JE, Klein JS, Hampson C. Diagnostic utility and clinical application of imaging for pleural space infections. Chest. 2010 Feb;137(2):467-79.

10.   Akulian J, Feller-Kopman D. The past, current and future of diagnosis and management of pleural disease. J Thorac Dis. 2015 Dec; 7(Suppl 4):S329-38.

11.   Maskell NA, Davies CW, Nunn AJ et al. First Multicenter Intrapleural Sepsis Trial (MIST1) Group. U.K. Controlled trial of intrapleural streptokinase for pleural infection. N Engl J Med. 2005 Mar 3;352(9):865-74.

12.   Rahman NM, Maskell NA, West A, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection. N Engl J Med. 2011;365(6):518-526.

13.   Davies HE, Mishra EK, Kahan BC, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. JAMA. 2012 Jun 13;307(22):2383-9.

14.   Rahman NM, Pepperell J, Rehal S, et al. Effect of Opioids vs NSAIDs and Larger vs Smaller Chest Tube Size on Pain Control and Pleurodesis Efficacy Among Patients With Malignant Pleural Effusion: The TIME1 Randomized Clinical Trial. JAMA. 2015 Dec 22-29;314(24):2641-53.

15.   Thomas R, Fysh ETH, Smith NA et al. Effect of an Indwelling Pleural Catheter vs Talc Pleurodesis on Hospitalization Days in Patients With Malignant Pleural Effusion: The AMPLE Randomized Clinical Trial. JAMA. 2017 Nov 21; 318(19):1903-1912.

16.   Bhatnagar R, Keenan EK, Morley AJ, et al. Outpatient Talc Administration by Indwelling Pleural Catheter for Malignant Effusion. N Engl J Med. 2018 Apr 5; 378(14):1313-1322.

17.   Evison M, Blyth KG, Bhatnagar R, et al. Providing safe and effective pleural medicine services in the UK: an aspirational statement from UK pleural physicians. BMJ Open Respiratory Research 2018;5: e 000307.

18.   Zamboni MM, da Silva CT, Baretta R, et al. Important prognostic factors for survival in patients with malignant pleural effusion. BMC Pulm Med 2015;15:29.

19.   Davies CW, Kearney SE, Gleeson FV. Predictors of outcome and long-term survival in patients with pleural infection. Am J Respir Crit Care Med 1999; 160 (5 Pt 1):1682–1687

20.   Kataoka H. Pericardial and pleural effusions in decompensated chronic heart failure. Am Heart J. 2000 May;139(5):918-23.

21.   Kookoolis AS, Puchalski JT, Murphy TE. Mortality of Hospitalized Patients with Pleural Effusions. J Pulm Respir Med. 2014 Jun;4(3):184

22.   DeBiasi E, Pisani MA, Murphy TE, et al. Mortality among patients with pleural effusion undergoing thoracentesis. Eur Respir J 2015; 46:495–502.

23.   Walker SP, Morley AJ, Stadon L et al. Nonmalignant Pleural Effusions: A Prospective Study of 356 Consecutive Unselected Patients. Chest. 2017 May;151(5):1099-1105.

24.   Lee KF, Olak J. Anatomy and physiology of the pleural space. Chest Surg Clin N Am. 1994 Aug;4(3):391-403.

25.   Wang NS. Anatomy of the pleura. Clin Chest Med. 1998 Jun;19(2):229-40.

26.   Charalampidis C, Youroukou A, Lazaridis G. Pleura space anatomy. J Thorac Dis. 2015 Feb; 7(Suppl 1):S27-32.

27.   Mahabadi N, Goizueta AA, Bordoni B. Anatomy, Thorax, Lung Pleura and Mediastinum. 2021 Feb 7. In: StatPearls [Internet].

28.	Lai-Fook SJ. Pleural mechanics and fluid exchange. Physiol Rev 2004; 84: 385-410

29.	Noppen M, De Waele M, Li R et al. Volume and cellular content of normal pleural fluid in humans examined by pleural lavage. Am J Respir Crit Care Med. 2000 Sep;162(3 Pt 1):1023-6.

30.	Grathwohl KW, Derdak S. Buffalo chest. N Engl J Med 2003; 349: 1829.

31.	Basille D, Chevalier K, Andrejak C, et al. Pleural transudate: pathophysiology during superior vena cava syndrome. ERJ Open Res 2019; 5: 00251-2018

32.	Wang NS. The preformed stomas connecting the pleural cavity and the lymphatics in the parietal pleura. Am Rev Respir Dis 1975; 111(1):12-20

33.	Miserocchi G. Physiology and pathophysiology of pleural fluid turnover. Eur Respir J. 1997 Jan;10(1):219-25.

34.	Mercer RM, Corcoran JP, Porcel JM, Rahman NM, Psallidas I. Interpreting pleural fluid results Clin Med (Lond). 2019;19(3):213-217.

35.	Feller-Kopman D, Light R. Pleural Disease. N Engl J Med. 2018 Feb 22;378(8):740-751.

36.	Garske LA, Kunarajah K, Zimmerman PV. In patients with unilateral pleural effusion, restricted lung inflation is the principal predictor of increased dyspnoea. PLoS One. 2018 Oct 3;13(10):e0202621.

37.	Muruganandan S, Azzopardi M, Thomas R et al. The Pleural Effusion And Symptom Evaluation (PLEASE) study of breathlessness in patients with a symptomatic pleural effusion. Eur Respir J. 2020 May 14;55(5):1900980.

38.	Wang LM, Cherng JM, Wang JS. Improved lung function after thoracocentesis in patients with paradoxical movement of a hemidiaphragm secondary to a large pleural effusion. Respirology. 2007 Sep;12(5):719-23.

39.	Cartaxo AM, Vargas FS, Salge JM, et al. Improvements in the 6-min walk testand spirometry following thoracentesis for symptomatic pleural effusions.Chest 2011; 139:1424–1429

40.	Marcondes BF, Vargas F, Paschoal FH, et al. Sleep in patients with largepleural effusion: impact of thoracentesis. Sleep Breath 2012; 16:483–489.

41.	Razazi K, Thille AW, Carteaux G, et al. Effects of pleural effusion drainage onoxygenation, respiratory mechanics, and hemodynamics in mechanically ventilated patients. Ann Am Thorac Soc 2014; 11:1018–1024

42.	Umbrello M, Mistraletti G, Galimberti A, et al. Drainage of pleural effusion improves diaphragmatic function in mechanically ventilated patients. Crit Care Resusc. 2017 Mar;19(1):64-70.

43. Goligher EC, Leis JA, Fowler RA, et al. Utility and safety of draining pleural effusions in mechanically ventilated patients: a systematic review and meta analysis.Crit Care 2011; 15:R46.

44. Mishra EK, Corcoran JP, Hallifax RJ et al. Defining the minimal important difference for the visual analogue scale assessing dyspnea in patients with malignant pleural effusions. PLoS One. 2015 Apr 15;10(4):e0123798.

45. Argento AC, Murphy TE, Pisani MA. Patient-Centered Outcomes Following Thoracentesis. Pleura (Thousand Oaks). 2015 Jan-Dec;2:2373997515600404

46. Psallidas I, Yousuf A, Talwar A et al. Assessment of patient-reported outcome measures in pleural interventions. BMJ Open Respir Res. 2017 Jul 3;4(1):e000171.

47. Thomas R, Lee YCG, Mishra EK. The pathophysiology of breathlessness and other symptoms associated with pleural effusions. ERS Monograph. 2020;2020(9781849841160):13-28.

48. Hooper C, Lee YC, Maskell N; BTS Pleural Guideline Group. Investigation of a unilateral pleural effusion in adults: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010 Aug;65 Suppl 2:ii4-17.

49. Rahman NM, Chapman SJ, Davies RJ. Pleural effusions: a structured approach to care. Br Med Bull. 2005; 72(1): 31-47.

50. Porcel JM. PLEASE, take a deep breath. Eur Respir J. 2020 May 14;55(5):2000501.

51. Kalantri S, Joshi R, Lokhande T et al. Accuracy and reliability of physical signs in the diagnosis of pleural effusion. Respir Med. 2007 Mar;101(3):431-8

52. Light RW. Pleural effusions. Med Clin North Am. 2011 Nov; 95(6):1055-70.

53. Blackmore CC, Black WC, Dallas RV, Crow HC. Pleural fluid volume estimation: a chest radiograph prediction rule. Acad Radiol. 1996 Feb;3(2):103-9.

54. Duerden L, Benamore R, Edey A. Radiology in pleural disease: what is the role of chest radiographs, CT and PET in modern management? Eur Respir Monogr 2020; 87: 48-72

55. Corcoran JP, Acton L, Ahmed A. Diagnostic value of radiological imaging pre- and post-drainage of pleural effusions. Respirology. 2016 Feb; 21(2):392-5.

56. Leung AN, Muller NL, Miller RR. CT in differential diagnosis of diffuse pleural disease. AJR Am J Roentgenol 1989; 154:487e92.

57. Scott EM, Marshall TJ, Flower CDR, et al. Diffuse pleural thickening: percutaneous CT-guided cutting needle biopsy. Radiology 1995;194:867e70.

58. Traill ZC, Davies RJO, Gleeson FV. Thoracic computed tomography in patients with suspected malignant pleural effusions. Clin Radiol 2001;56:193e6.

59. Hallifax RJ, Haris M, Corcoran JP, et al. Role of CT in assessing pleural malignancy prior to thoracoscopy. Thorax 2015; 70: 192–193.

60. Tsim S, Stobo DB, Alexander L, et al. The diagnostic performance of routinely acquired and reported computed tomography imaging in patients presenting with suspected pleural malignancy. Lung Cancer 2017; 103: 38–43

61. Syer T, Arnold DT, Patole S. Investigation of a unilateral pleural effusion: What CT scan coverage is optimal? Thorax. 2020 Jun; 75(6):503-505.

62. Waite RJ, Carbonneau RJ, Balikian JP et al. Parietal pleural changes in empyema: appearances at CT. Radiology. 1990 Apr;175(1):145-50.

63. Takasugi JE, Godwin JD, Teefey SA. The extrapleural fat in empyema: CT appearance. Br J Radiol. 1991 Jul;64(763):580-3.

64. Tsujimoto N, Saraya T, Light RW et al. A Simple Method for Differentiating Complicated Parapneumonic Effusion/Empyema from Parapneumonic Effusion Using the Split Pleura Sign and the Amount of Pleural Effusion on Thoracic CT. PLoS One. 2015 Jun 15;10(6):e0130141.

65. Porcel JM, Hernández P, Martínez-Alonso M et al. Accuracy of fluorodeoxyglucose-PET imaging for differentiating benign from malignant pleural effusions: a meta-analysis. Chest. 2015 Feb; 147(2):502-512.

66. Li Y, Mu W, Li Y et al. Predicting the nature of pleural effusion in patients with lung adenocarcinoma based on 18F-FDG PET/CT. EJNMMI Res. 2021;11(1):108.

67. Banka R, Skaarup S, Mercer R, Laursen C. Thoracic ultrasound: a key tool beyond procedure guidance. Eur Respir Monogr 2020; 87: 73-89

68. Kalokairinou-Motogna M, Maratou K, Paianid I et al. Application of color Doppler ultrasound in the study of small pleural effusion. Medical ultrasonography. 2010; 12(1):12–16.

69. Asciak R, Hassan M, Mercer RM et al. Prospective Analysis of the Predictive Value of Sonographic Pleural Fluid Echogenicity for the Diagnosis of Exudative Effusion. Respiration. 2019; 97(5):451-456.

70. Mercaldi CJ, Lanes SF. Ultrasound guidance decreases complications and improves the cost of care among patients undergoing thoracentesis and paracentesis. Chest. 2013 Feb 1;143(2):532-538.

71. Mcloud T, Flower C. Imaging of the pleura: sonography, CT, and MR imaging. AJR Am J Roentgenol 1991;156:1145e53.

72. Wu RG, Yuan A, Liaw YS et al. Image comparison of real-time gray-scale ultrasound and color Doppler ultrasound for use in diagnosis of minimal pleural effusion. Am J Respir Crit Care Med. 1994 Aug;150(2):510-4.

73. Chen CH, Chen W, Chen HJ et al. Transthoracic ultrasonography in predicting the outcome of small-bore catheter drainage in empyemas or complicated parapneumonic effusions. Ultrasound Med Biol. 2009 Sep; 35(9):1468-74.

74. Qureshi NR, Rahman NM, Gleeson FV. Thoracic ultrasound in the diagnosis of malignant pleural effusion. Thorax. 2009 Feb; 64(2):139-43.

75. Maskell NA, Gleeson FV, Darby M. Diagnostically significant variations in pleural fluid pH in loculated parapneumonic effusions. Chest. 2004 Dec; 126(6):2022-4.

76. Salamonsen MR, Lo AKC, Ng ACT. Novel use of pleural ultrasound can identify malignant entrapped lung prior to effusion drainage. Chest. 2014 Nov;146(5):1286-1293

77. Psallidas I, Hassan M, Yousuf A, et al. Role of thoracic ultrasonography in pleurodesis pathways for malignant pleural effusions (SIMPLE): an open-label, randomised controlled trial. Lancet Respir Med. 2022 Feb; 10(2):139-148.

78. Corcoran JP, Hallifax RJ, Mercer RM et al. Thoracic Ultrasound as an Early Predictor of Pleurodesis Success in Malignant Pleural Effusion. Chest. 2018 Nov; 154(5):1115-1120.

79. Varsamas C, Kalkanis A, Gourgoulianis KI. The Use of a Novel Quantitative Marker of Echogenicity of Pleural Fluid in Parapneumonic Pleural Effusions. Can Respir J. 2020 Oct 5; 2020:1283590.

80. Ferreiro L, San José ME, Gude F. Unilateral or Bilateral Thoracocentesis for Bilateral Pleural Effusion. A Prospective Study. Arch Bronconeumol. 2016 Apr; 52(4):189-95.

81. Johnson JL. Pleural effusions in cardiovascular disease. Pearls for correlating the evidence with the cause. Postgrad Med 2000; 107: 95 – 101

[101]

82.   Valdés, D. Álvarez, J.M. Valle, A. Pose, E. San José. The etiology of pleural effusions in an area with high incidence of tuberculosis. Chest, 109 (1996), pp. 158-162

83.   Hassan M, Munavvar M, Corcoran JP. Pleural interventions: less is more? In: Maskell NA, Laursen CB, Lee YCG, et al., eds. Pleural Disease (ERS Monograph). Sheffield, European Respiratory Society, 2020; pp. 90–104

84.   Kalomenidis I, Rodriguez M, Barnette R et al. Patient with bilateral pleural effusion: are the findings the same in each fluid? Chest. 2003 Jul;124(1):167-76.

85.   Puchalski JT, Argento AC, Murphy TE et al. Etiologies of bilateral pleural effusions. Respir Med. 2013 Feb;107(2):284-91

86.   Sundaralingam A, Bedawi EO, Rahman NM. Diagnostics in Pleural Disease. Diagnostics (Basel). 2020 Dec 4; 10(12):1046.

87.   Light RW, Macgregor MI, Luchsinger PC. Pleural effusions: the diagnostic separation of transudates and exudates. Ann Intern Med. 1972 Oct;77(4):507-13.

88.   Heffner JE, Brown LK, Barbieri CA. Diagnostic value of tests that discriminate between exudative and transudative pleural effusions. Primary Study Investigators. Chest. 1997 Apr; 111(4):970-80.

89.   Vives M, Porcel JM, Vicente de Vera M et al. A study of Light's criteria and possible modifications for distinguishing exudative from transudative pleural effusions. Chest. 1996 Jun; 109(6):1503-7.

90.   Porcel JM. Identifying transudates misclassified by Light's criteria. Curr Opin Pulm Med 2013; 19: 362–367

91.   Light RW, Girard WM, Jenkinson SG, et al. Parapneumonic effusions.Am J Med 1980; 69:507-12.

92.   Rodriguez-Panadero F, Lopez-Mejias J. Survival time of patients with pleural metastatic carcinoma predicted by glucose and pH studies.Chest1989; 95:320-4.

93.   Fitzgerald DB, Leong SL, Budgeon CA, et al. Relationship of pleural fluid pH and glucose: a multi-centre study of 2,971 cases. J Thorac Dis. 2019; 11(1):123-130.

94.   Rahman NM, Mishra EK, Davies HE et al. Clinically important factors influencing the diagnostic measurement of pleural fluid pH and glucose. Am J Respir Crit Care Med. 2008 Sep 1;178(5):483-90.

95.   Porcel JM, Azzopardi M, Koegelenberg CF et al. The diagnosis of pleural effusions. Expert Rev Respir Med. 2015; 9(6):801-815.

96.   Krenke R, Nasilowski J, Korczynski P. Incidence and aetiology of eosinophilic pleural effusion. Eur Respir J. 2009 Nov; 34(5):1111-7.

97.   Rubins JB, Rubins HB. Etiology and prognostic significance of eosinophilic pleural effusions. A prospective study. Chest. 1996 Nov;110(5):1271-4.

98.   Kalomenidis I, Light RW. Eosinophilic pleural effusions. Curr Opin Pulm Med. 2003 Jul;9(4):254-60.

99.   Haraguchi T, Tashiro H, Takahashi K et al. Idiopathic eosinophilic pleurisy: A practical diagnostic approach. Respir Med Case Rep. 2021 May 20;33:101430.

100.   Maskell NA, Butland RJ; Pleural Diseases Group, Standards of Care Committee, British Thoracic Society. BTS guidelines for the investigation of a unilateral pleural effusion in adults. Thorax. 2003; 58 (suppl 2): ii8-ii17.

101.   Arnold DT, De Fonseka D, Perry S et al. Investigating unilateral pleural effusions: the role of cytology. Eur Respir J. 2018 Nov 8; 52(5):1801254.

102.   Porcel JM, Esquerda A, Bielsa S. Diagnostic performance of adenosine deaminase activity in pleural fluid: a single-center experience with over 2100 consecutive patients. Eur J Intern Med. 2010 Oct;21(5):419-23

103.   Janda S, Swiston J. Diagnostic accuracy of pleural fluid NT-pro-BNP for pleural effusions of cardiac origin: a systematic review and meta-analysis. BMC Pulm Med. 2010;10:58.

104.   Han YQ, Yan L, Li P et al. A Study Investigating Markers in PLeural Effusion (SIMPLE): a prospective and double-blind diagnostic study. BMJ Open. 2019 Aug 1; 9(8):e027287.

105.   Maskell N, Gleeson F, Davies R. Standard pleural biopsy versus CT-guided cutting-needle biopsy for diagnosis of malignant disease in pleural effusions: a randomised controlled trial. Lancet 2003; 361: 1326–1330

106.   Qureshi NR, Gleeson FV. Imaging of pleural disease. Clin Chest Med 2006; 27: 193–213.

107.   Bhatnagar R, Corcoran JP, Maldonado F. Advanced medical interventions in pleural disease. Eur Respir Rev. 2016 Jun; 25(140):199-213.

108.   Bueno C.E, Clement M.G, Castro B.C. Cytologic and bacteriologic analysis of fluid and pleural biopsy specimens with Cope's needle. Study of 414 patients. Arch. Intern. Med. 1990;150:1190–1194

109.   Diacon AH, Van de Wal BW, Wyser C, Smedema JP, Bezuidenhout J, Bolliger CT, Walzl G. Diagnostic tools in tuberculous pleurisy: a direct comparative study. Eur Respir J. 2003 Oct;22(4):589-91.

110.   Rahman NM, Ali NJ, Brown G, et al. Local anaesthetic thoracoscopy: British Thoracic Society pleural disease guideline 2010. Thorax 2010; 65: ii54–ii60.

111.   Marel M, Zrůstová M, Stasný B, Light RW. The incidence of pleural effusion in a well-defined region. Epidemiologic study in central Bohemia. Chest. 1993 Nov;104(5):1486-9

112.   Roger VL. Epidemiology of heart failure. Circ Res. 2013 Aug 30; 113(6):646-59.

113.   Croft JB, Giles WH, Pollard RA et al. Heart failure survival among older adults in the United States: a poor prognosis for an emerging epidemic in the Medicare population. Arch Intern Med.1999 Mar 8; 159(5):505-10.

114.   Merlo J, Ostergren PO, Broms K. Survival after initial hospitalisation for heart failure: a multilevel analysis of patients in Swedish acute care hospitals. J Epidemiol Community Health.2001 May; 55(5):323-9.

115.   Stewart S, MacIntyre K, Capewell S, McMurray JJ. Heart failure and the aging population: an increasing burden in the 21st century? Heart.2003Jan; 89(1):49-53.

116.   Siirilä-Waris K, Lassus J, Melin J,Peuhkurinen K, Nieminen MS, Harjola V-P.Characteristics, outcomes, andpredictors of 1-year mortality in patientshospitalized for acute heart failure. EurHeart J. 2006; 27(24):3011-3017.

117.   Lombardi C, Peveri G, Cani D, et al. In-hospital and long-term mortality for acute heart failure: analysis at the time of admission to the emergency department. ESC Heart Fail. 2020; 7(5):2650-2661.

118.   Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. Eur Heart J. 2012 Jul;33(14):1750-7.

119.   Ercan S, Davutoglu V, Altunbas G, et al. Prognostic role of incidental pleural effusion diagnosed during echocardiographic evaluation. Clin Cardiol 2014; 37:115–118

120.   Rahimi K, Bennett D, Conrad N, et al. Risk prediction in patients with heart failure: a systematic review and analysis. JACC Heart Fail. 2014 Oct;2(5):440-6.

121.   Duflos C, Solecki K, Galinier M. Conception and bicentric validation of the proSCANNED score, a simplified bedside prognostic score for Heart Failure patients. Sci Rep. 2021 Mar 17; 11(1):6179.

122. Morales-Rull JL, Bielsa S, Conde-Martel A et al. Pleural effusions in acute decompensated heart failure: Prevalence and prognostic implications. Eur J Intern Med 2018 ; 52 : 49 – 53

123. Kataoka H, Takada S. The role of thoracic ultrasonography for evaluation of patients with decompensated chronic heart failure. J Am Coll Cardiol. 2000 May; 35(6):1638-46.

124. Wiener-Kronish JP, Matthay MA, Callen PW. Relationship of pleural effusions to pulmonary hemodynamics in patients with congestive heart failure. Am Rev Respir Dis 1985; 132: 1253–1256

125. Thomas L, Marwick TH, Popescu BA. Left Atrial Structure and Function, and Left Ventricular Diastolic Dysfunction: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019 Apr 23;73(15):1961-1977.

126. Rajyaguru C, Kalra A, Samim A et al. Increased E/A Ratio is a Risk Factor for the Formation of Pleural Effusion in Heart Failure. Lung. 2020 Feb;198(1):229-233

127. Walker S, Maskell N. Identification and management of pleural effusions of multiple aetiologies. Curr Opin Pulm Med 2017; 23: 339 – 45.

128. Majid A, Kheir F, Fashjian M, et al. Tunneled pleural catheter placement with and without talc poudrage for treatment of pleural effusions due to congestive heart failure. Ann Am Thorac Soc 2016; 13: 212–216.

129. Freeman RK, Ascioti AJ, Dake M, et al. A propensity-matched comparison of pleurodesis or tunneled pleural catheter for heart failure patients with recurrent pleural effusion. Ann Thorac Surg 2014; 97: 1872–1877

130. Frost N, Ruwwe-Glösenkamp C, Raspe M, et al. Indwelling pleural catheters for non-malignant pleural effusions: report on a single centre's 10 years of experience. BMJ Open Respir Res. 2020; 7(1):e000501.

131. Walker S, Shojaee S. Nonmalignant pleural effusions: are they as benign as we think? Eur Respir Monogr 2020; 87: 218-231

132. Llorens P, Javaloyes P, Masip J et al. Prognostic value of chest radiographs in patients with acute heart failure: the Radiology in Acute Heart Failure (RAD-ICA) study. Emergencias. 2019 Oct; 31(5):318-326.

133. Kataoka H. Ultrasound pleural effusion sign as a useful marker for identifying heart failure worsening in established heart failure patients during follow-up. Congest Heart Fail. 2012 Sep-Oct; 18(5):272-7.

134. Davutoglu V, Yildirim C, Kucukaslan H,et al. Prognostic value of pleural effusion,CA-125 and NT-proBNP in patients with acute decompensated heart failure.Kardiol Pol. 2010;68(7):771-778

135.   Kinasewitz GT, Keddissi JI. Hepatic hydrothorax. Curr Opin Pulm Med. 2003 Jul; 9(4):261-5.

136.   Kamath S, Sunder A (July 26, 2021) Hepatic Hydrothorax in the Absence of Ascites: A Diagnostic Challenge. Cureus 13(7): e16650.

137.   Strauss RM, Boyer TD. Hepatic hydrothorax. Semin Liver Dis. 1997; 17 (3):227-32.

138.   Gurung P, Goldblatt M, Huggins JT et al. Pleural fluid analysis and radiographic, sonographic, and echocardiographic characteristics of hepatic hydrothorax. Chest. 2011 Aug; 140(2):448-453.

139.   Singh A, Bajwa A, Shujaat A. Evidence-based review of the management of hepatic hydrothorax. Respiration. 2013; 86(2):155-73.

140.   Bintcliffe OJ, Lee GY, Rahman NM, Maskell NA. The management of benign non-infective pleural effusions. Eur Respir Rev. 2016 Sep; 25(141):303-16.

141.   Dhanasekaran R, West JK, Gonzales PC. Transjugular intrahepatic portosystemic shunt for symptomatic refractory hepatic hydrothorax in patients with cirrhosis. Am J Gastroenterol 2010;105(3):635

142.   Copelan A, Kapoor B, Sands M. Transjugular intrahepatic portosystemic shunt: indications, contraindications, and patientwork-up. Semin Intervent Radiol. 2014; 31(3):235

143.   Kniese C, Diab K, Ghabril M. Pleural Catheters in Hepatic Hydrothorax: A Single-Center Series of Outcomes and Complications. Chest. 2019 Feb; 155(2):307-314.

144.   Liu LU, Haddadin HA, Bodian CA, et al. Outcome analysis of cirrhotic patients undergoing chest tube placement. Chest 2004; 126:142-148.

145.   Soin S, Sher N, Saleem N. Spontaneous bacterial empyema: an elusive diagnosis in a patient with cirrhosis. BMJ Case Rep 2018; 2018: bcr-2018-224810.

146.   Aujayeb A, Jackson K, Johnston R, et al. A difficult pleural effusion in a cirrhotic patient. Breathe 2020; 16: 200049.

147.   Badillo, R.; Rockey, D.C. Hepatic Hydrothorax: Clinical Features, Management, and Outcomes in 77 Patients and Review of the Literature. Medicine 2014, 93, 135–142.

148.   Hung TH, Tseng CW, Tsai CC. The long-term outcomes of cirrhotic patients with pleural effusion. Saudi J Gastroenterol. 2018; 24(1):46-51.

149.   Matei, D.; Craciun, R.; Crisan, D.; et al. Hepatic Hydrothorax—An Independent Decompensating Event Associated with Long-Term Mortality in Patients with Cirrhosis. J. Clin. Med. 2021, 10, 3688.

150.   Hasan M, Sutradhar I, Gupta RD, Sarker M: Prevalence of chronic kidney disease in South Asia: a systematic review. BMC Nephrol. 2018, 19:291.

151.   Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: global dimension and perspectives. Lancet.2013;382(9888):260-72.

152.   Eknoyan G, Lameire N, Eckardt K, Kasiske B, Wheeler D, Levin A, et. al: KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2013, 3:5-14.

153.   Berger HW, Rammohan G, Neff MS, Buhain WJ: Uremic pleural effusion: a study in 14 patients on chronic dialysis. Ann Intern Med. 1975, 82:362-4.

154.   Bakirci T, Sasak G, Ozturk S, Akcay S, Sezer S, Haberal M: Pleural effusion in long-term hemodialysis patients. In. Transplantation proceedings. 2007, 39:889-91

155.   Rashid-Farokhi F, Pourdowlat G, Nikoonia MR. Uremic pleuritis in chronic hemodialysis patients. Hemodial Int. 2013 Jan; 17(1):94-100.

156.   Maher JF. Uremic pleuritis. Am J Kidney Dis. 1987 Jul;10(1):19-22.

157.   Nomoto Y, Suga T, Nakajima K et al. Acute hydrothorax in continuous ambulatory peritoneal dialysis--a collaborative study of 161 centers. Am J Nephrol. 1989; 9(5):363-7.

158.   Jabbar A, Qureshi R, Nasir K, et al. (October 10, 2021) Transudative and Exudative Pleural Effusion in Chronic Kidney Disease Patients: A Prospective Single-Center Study. Cureus 13(10): e18649.

159.   Jenkins, P. and Shelp, W. (1974) Recurrent pleural transudate in the nephrotic syndrome. A new approach to treatment. JAMA 230:587–588.

160.   Potechin R, Amjadi K, Srour N. Indwelling pleural catheters for pleural effusions associated with end-stage renal disease: a case series. Ther Adv Respir Dis. 2015 Feb;9(1):22-7.

161.   Jagasia MH, Cole FH, Stegman MH. Video-assisted talc pleurodesis in the management of pleural effusion secondary to continuous ambulatory peritoneal dialysis: a report of three cases. Am J Kidney Dis. 1996 Nov; 28(5):772-4.

162.   Tang S, Chui WH, Tang AW et al. Video-assisted thoracoscopic talc pleurodesis is effective for maintenance of peritoneal dialysis in acute hydrothorax complicating peritoneal dialysis. Nephrol Dial Transplant. 2003 Apr;18(4):804-8.

163.   Kwan BC, Chow KM, Pang WF. Unexplained exudative pleural effusion in chronic peritoneal dialysis patients. Perit Dial Int. 2010 Sep-Oct; 30(5):534-40.

164.   Hamada S, Sano T, Nagatani Y, Tsukino M. Pleural effusion negatively impacts survival of patients undergoing maintenance hemodialysis. Pulmonology. 2019 Jan-Feb;25(1):58-60.

165.   Rogers CJ, DeVries K. Journal of Medieval Military History: Volume VIII. Boydell and Brewer; 2010.

166.   Falguera M, Carratalà J, Bielsa S et al. Predictive factors, microbiology and outcome of patients with parapneumonic effusion. Eur Respir J. 2011 Nov; 38(5):1173-9.

167.   Light RW. Parapneumonic effusions and empyema. Proc Am Thorac Soc. 2006;3(1):75-80.

168.   Finley C, Clifton J, Fitzgerald JM, Yee J. Empyema: an increasing concern in Canada. Can Respir J. 2008; 15(2):85-89.

169.   Grijalva CG, Zhu Y, Nuorti JP. Emergence of parapneumonic empyema in the USA. Thorax.2011 Aug; 66(8):663-8.

170.   Burgos J, Falcó V, Pahissa A. The increasing incidence of empyema. Curr Opin Pulm Med. 2013 Jul; 19(4):350-6.

171.   Cargill TN, Hassan M, Corcoran JP et al. A systematic review of comorbidities and outcomes of adult patients with pleural infection. Eur Respir J. 2019 Oct 1; 54(3):1900541.

172.   Menzies SM, Rahman NM, Wrightson JM et al. Blood culture bottle culture of pleural fluid in pleural infection.Thorax. 2011 Aug; 66(8):658-62.

173.   Maskell NA, Batt S, Hedley EL, et al. The bacteriology of pleural infection by genetic and standard methods and its mortality significance. Am J Respir Crit Care Med. 2006 Oct 1; 174(7):817-23.

174.   Chen CH, Hsu WH, Chen HJ et al. Different bacteriology and prognosis of thoracic empyemas between patients with chronic and end-stage renal disease. Chest. 2007 Aug; 132(2):532-9.

175.   Foster S, Maskell N. Bacteriology of complicated parapneumonic effusions. Curr Opin Pulm Med. 2007 Jul; 13(4):319-23.

176.	Meyer CN, Rosenlund S, Nielsen J, Friis-Møller A. Bacteriological aetiology and antimicrobial treatment of pleural empyema. Scand J Infect Dis. 2011 Mar; 43(3):165-9.

177.	Tucker TA, Jeffers A, Boren J, et al. Organizing empyema induced in mice by Streptococcus pneumoniae: effects of plasminogen activator inhibitor-1 deficiency. Clin Transl Med. 2016; 5(1):17.

178.	Popowicz N, Idell S, Lee YCG. Pathogenesis of pleural infection: A complex warfare. Respirology. 2018 Jan; 23(1):8-9.

179.	Bedawi EO, Hassan M, McCracken D, Rahman NM. Pleural infection: a closer look at the etiopathogenesis, microbiology and role of antibiotics. Expert Rev Respir Med. 2019 Apr; 13(4):337-347.

180.	Zeillemaker A.M., Diepersloot R.J., Leguit P. Mesothelial Cell Activation by Micro-Organisms. Sepsis 3. 1999. 285–291.

181.	Idell S, Girard W, Koenig KB, et al. Abnormalities of pathways of fibrin turnover in the human pleural space. Am. Rev. Respir. Dis.1991; 144:187–194.

182.	Aleman C, Alegre J, Monasterio J, et al. Association between inflammatory mediators and the fibrinolysis system in infectious pleural effusions. Clin. Sci. 2003; 105: 601–607.

183.	Light RW, MacGregor MI, Ball WC, et al. Diagnostic significance of pleural fluid pH and PCO2. Chest. 1973; 64:591–596.

184.	Sahn SA, Reller LB, Taryle DA, et al. The contribution of leukocytes and bacteria to the low pH of empyema fluid. Am. Rev. Respir. Dis. 1983; 128:811–815.

185.	Sasse SA, Jadus MR, Kukes GD. Pleural fluid transforming growth factor-beta1 correlates with pleural fibrosis in experimental empyema. Am. J. Respir. Crit. Care Med. 2003; 168:700–705.

186.	Mutsaers SE, Kalomenidis I, Wilson NA, et al. Growth factors in pleural fibrosis. Curr Opin Pulm Med. 2006; 12:251–258.

187.	Civen R, Jousimies-Somer H, Marina M et al. A retrospective review of cases of anaerobic empyema and update of bacteriology. Clin Infect Dis. 1995 Jun;20 Suppl 2:S224-9.

188.	Dyrhovden R, Nygaard RM, Patel R et al. The bacterial aetiology of pleural empyema. A descriptive and comparative metagenomic study. Clin Microbiol Infect. 2019 Aug; 25(8):981-986.

189.	Lindstrom ST, Kolbe J. Community acquired parapneumonic thoracic empyema: predictors of outcome. Respirology. 1999 Jun; 4(2):173-9.

190. Chen KY, Hsueh PR, Liaw YS et al. A 10-year experience with bacteriology of acute thoracic empyema: emphasis on Klebsiella pneumoniae in patients with diabetes mellitus. Chest. 2000 Jun; 117(6):1685-9.

191. Ahmed RA, Marrie TJ, Huang JQ. Thoracic empyema in patients with community-acquired pneumonia. Am J Med. 2006 Oct; 119(10):877-83.

192. Tsang KY, Leung WS, Chan VL. Complicated parapneumonic effusion and empyema thoracis: microbiology and predictors of adverse outcomes. Hong Kong Med J. 2007 Jun; 13(3):178-86.

193. Marks DJ, Fisk MD, Koo CY et al. Thoracic empyema: a 12-year study from a UK tertiary cardiothoracic referral centre. PLoS One. 2012; 7(1):e30074.

194. Park CK, Oh HJ, Choi HY et al. Microbiological Characteristics and Predictive Factors for Mortality in Pleural Infection: A Single-Center Cohort Study in Korea. PLoS One. 2016 Aug 16; 11(8):e0161280.

195. Lin YT, Chen TL, Siu LK et al. Clinical and microbiological characteristics of community-acquired thoracic empyema or complicated parapneumonic effusion caused by Klebsiella pneumoniae in Taiwan. European Journal of Clinical Microbiology & Infectious Diseases 2010 Aug; 29(8):1003-1010.

196. Hassan M, Cargill T, Harriss E et al. The microbiology of pleural infection in adults: a systematic review. Eur Respir J. 2019 Oct 1;54(3):1900542.

197. Boyanova L, Vladimir Djambazov, Gergova G, et al. Anaerobic microbiology in 198 cases of pleural empyema: a Bulgarian study. Anaerobe. 2004; 10:261–267.

198. Brims FJ, Lansley SM, Waterer GW, Lee YC. Empyema thoracis: new insights into an old disease. Eur Respir Rev. 2010 Sep; 19(117):220-8.

199. Iliopoulou M, Skouras V, Psaroudaki Z et al. Bacteriology, antibiotic resistance and risk stratification of patients with culture-positive, community-acquired pleural infection. J Thorac Dis. 2021 Feb; 13(2):521-532.

200. Davies CWH, Gleeson FV, Davies RJO. BTS guidelines for the management of pleural infection Thorax 2003; 58:ii18-ii28.

201. Corcoran JP, Wrightson JM, Belcher E, et al. Pleural infection: past, present, and future directions. The Lancet Respiratory Medicine. 2015;3:563–577

202. Ferrer A, Osset J, Alegre J et al. Prospective clinical and microbiological study of pleural effusions. Eur J Clin Microbiol Infect Dis. 1999 Apr; 18(4):237-41.

203.   Heffner JE, Brown LK, Barbieri C. Pleural fluid chemical analysis in parapneumonic effusions: a meta-analysis. Am J Respir Crit Care Med. 1995; 151(6):1700-1708.

204.   Jiménez Castro D, Díaz Nuevo G, Sueiro A et al. Pleural fluid parameters identifying complicated parapneumonic effusions. Respiration. 2005 Jul-Aug; 72(4):357-64.

205.   Porcel JM. Distinguishing complicated from uncomplicated parapneumonic effusions. Curr Opin Pulm Med. 2015 Jul; 21(4):346-51.

206.   Dixon G, Lama-Lopez A, Bintcliffe OJ et al. The role of serum procalcitonin in establishing the diagnosis and prognosis of pleural infection. Respir Res. 2017;18(1):30.

207.   Arnold DT, Hamilton FW, Elvers KT et al. Pleural Fluid suPAR Levels Predict the Need for Invasive Management in Parapneumonic Effusions. Am J Respir Crit Care Med. 2020 Jun 15; 201(12):1545-1553.

208.   Kiropoulos TS, Kostikas K, Oikonomidi S et al. Acute phase markers for the differentiation of infectious and malignant pleural effusions. Respir Med. 2007 May; 101(5):910-8.

209.   Skouras V, Boultadakis E, Nikoulis D et al. Prognostic value of C-reactive protein in parapneumonic effusions. Respirology. 2012 Feb;17(2):308-14.

210.   Kogan Y, Sabo E, Odeh M. Diagnostic Value of C-Reactive Protein in Discrimination between Uncomplicated and Complicated Parapneumonic Effusion. Diagnostics (Basel). 2020 Oct 15;10(10):829.

211.   Daniil ZD, Zintzaras E, Kiropoulos T et al. Discrimination of exudative pleural effusions based on multiple biological parameters. Eur Respir J. 2007 Nov;30(5):957-64.

212.   Perlepe G, Varsamas C, Petinaki E et al. Discrimination of Exudative Pleural Effusions Based on Pleural Adenosine Deaminase (ADA)-C-Reactive Protein (CRP) Levels, and Their Combination: An Observational Prospective Study. J Pers Med. 2021 Aug 30;11(9):864.

213.   Ferreiro L, Lado-Baleato Ó, Suárez-Antelo J, et al. Diagnosis of infectious pleural effusion using predictive models based on pleural fluid biomarkers. Ann Thorac Med. 2019; 14(4):254-263.

214.   Watanabe, N., Ishii, T., Kita, N. et al. The usefulness of pleural fluid presepsin, C-reactive protein, and procalcitonin in distinguishing different causes of pleural effusions. BMC Pulm Med 18, 176 (2018).

[111]

215.   Lin MC, Chen YC, Wu JT et al. Diagnostic and prognostic values of pleural fluid procalcitonin in parapneumonic pleural effusions. Chest. 2009 Jul; 136(1):205-211.

216.   Porcel JM, Vives M, Cao G et al. Biomarkers of infection for the differential diagnosis of pleural effusions. Eur Respir J. 2009 Dec; 34(6):1383-9.

217.   Saraya T, Ohkuma K, Koide T et al. A novel diagnostic method for distinguishing parapneumonic effusion and empyema from other diseases by using the pleural lactate dehydrogenase to adenosine deaminase ratio and carcinoembryonic antigen levels. Medicine (Baltimore). 2019 Mar;98(13):e15003.

218.   Tobin CL, Lee YC. Pleural infection: what we need to know but don't. Curr Opin Pulm Med. 2012 Jul; 18(4):321-5.

219.   Sundaralingam A, Banka R, Rahman NM. Management of Pleural Infection. Pulm Ther. 2020 Dec 9:1–16.

220.   Sibley CD, Peirano G, Church DL. Molecular methods for pathogen and microbial community detection and characterization: current and potential application in diagnostic microbiology. Infect Genet Evol. 2012; 12(3):505-521.

221.   Franchetti L, Schumann DM, Tamm M, Jahn K, Stolz D. Multiplex bacterial polymerase chain reaction in a cohort of patients with pleural effusion. BMC Infect Dis. 2020 Feb 1;20(1):99.

222.   Psallidas I, Kanellakis NI, Bhatnagar R et al. A Pilot Feasibility Study in Establishing the Role of Ultrasound-Guided Pleural Biopsies in Pleural Infection (The AUDIO Study). Chest. 2018 Oct; 154(4):766-772.

223.   Evans AL, Gleeson FV. Radiology in pleural disease: state of the art. Respirology. 2004;9(3):300-312

224.   Chen KY, Liaw YS, Wang HC, et al. Sonographic septation: a useful prognostic indicator of acute thoracic empyema. J Ultrasound Med 2000; 19: 837–843.

225.   Idell S, Rahman NM. Intrapleural Fibrinolytic Therapy for Empyema and Pleural Loculation: Knowns and Unknowns. Ann Am Thorac Soc. 2018 May; 15(5):515-517.

226.   Wait MA, Sharma S, Hohn J, Dal Nogare A. A randomized trial of empyema therapy. Chest. 1997 Jun; 111(6):1548-51.

227.   Bedawi, E.O., George, V. & Rahman, N.M. A New Approach to Pleural Infection: Let It Be? Curr Pulmonol Rep 8, 112–122 (2019).

228. Teixeira LR, Sasse SA, Villarino MA, et al. Antibiotic levels in empyemic pleural fluid. Chest. 2000; 117:1734–1739.

229. Nwiloh J, Freeman H, McCord C. Malnutrition: an important determinant of fatal outcome in surgically treated pulmonary suppurative disease. J Natl Med Assoc. 1989 May; 81(5):525-9.

230. Ferguson AD, Prescott RJ, Selkon JB, et al. The clinical course and management of thoracic empyema. QJM 1996; 89:285–289.

231. Juan Pablo, Uribe Alvaro, Ayala Fayez et al. Early chest tube insertion (<24 hours) decreases treatment failure among patients with complicated parapneumonic effusion and empyema. Chest 2020

232. Porcel JM, Valencia H, Bielsa S. Factors influencing pleural drainage in parapneumonic effusions. Rev Clin Esp. 2016 Oct; 216(7):361-366.

233. Colice GL, Curtis A, Deslauriers J et al. Medical and surgical treatment of parapneumonic effusions: an evidence-based guideline. Chest. 2000 Oct; 118(4):1158-71.

234. Rahman NM, Maskell NA, Davies CW et al. The relationship between chest tube size and clinical outcome in pleural infection. Chest. 2010 Mar; 137(3):536-43.

235. Bedawi EO, Hassan M, Rahman NM. Recent developments in the management of pleural infection: A comprehensive review. Clin Respir J. 2018 Aug; 12(8):2309-2320.

236. Piccolo F, Popowicz N, Wong D. Intrapleural tissue plasminogen activator and deoxyribonuclease therapy for pleural infection. J Thorac Dis. 2015 Jun; 7(6):999-1008.

237. Mehta HJ, Biswas A, Penley AM et al. Management of Intrapleural Sepsis with Once Daily Use of Tissue Plasminogen Activator and Deoxyribonuclease. Respiration. 2016; 91(2):101-6.

238. McClune JR, Wilshire CL, Gorden JA et al. Safety and Efficacy of Intrapleural Tissue Plasminogen Activator and DNase during Extended Use in Complicated Pleural Space Infections. Can Respir J. 2016; 2016:9796768.

239. Majid A, Kheir F, Folch A et al. Concurrent Intrapleural Instillation of Tissue Plasminogen Activator and DNase for Pleural Infection. A Single-Center Experience. Ann Am Thorac Soc. 2016 Sep; 13(9):1512-8.

240. Idell S, Florova G, Shetty S et al. Precision-guided, Personalized Intrapleural Fibrinolytic Therapy for Empyema and Complicated Parapneumonic Pleural Effusions: The Case for the Fibrinolytic Potential. Clin Pulm Med. 2017 Jul;24(4):163-169.

241. Kheir F, Thakore S, Mehta H et al. Intrapleural Fibrinolytic Therapy versus Early Medical Thoracoscopy for Treatment of Pleural Infection. Randomized Controlled Clinical Trial. Ann Am Thorac Soc. 2020 Aug;17(8):958-964.

242. Scarci M, Abah U, Solli P et al. EACTS expert consensus statement for surgical management of pleural empyema. Eur J Cardiothorac Surg. 2015 Nov; 48(5):642-53.

243. Shen KR, Bribriesco A, Crabtree T et al. The American Association for Thoracic Surgery consensus guidelines for the management of empyema. J Thorac Cardiovasc Surg. 2017 Jun; 153(6):e129-e146.

244. Redden MD, Chin TY, van Driel ML. Surgical versus non-surgical management for pleural empyema. Cochrane Database Syst Rev. 2017; 3(3):CD010651.

245. Bilgin M, Akcali Y, Oguzkaya F. Benefits of early aggressive management of empyema thoracis. ANZ J Surg. 2006 Mar; 76(3):120-2.

246. Muhammad MI. Management of complicated parapneumonic effusion and empyema using different treatment modalities. Asian Cardiovasc Thorac Ann. 2012 Apr;20(2):177-81.

247. Nayak R, Brogly SB, Lajkosz K. Outcomes of Operative and Nonoperative Treatment of Thoracic Empyema: A Population-Based Study. Ann Thorac Surg. 2019 Nov; 108(5):1456-1463.

248. A randomised controlled trial of the feasibility of early administration of clot-busting medication through a chest tube versus early surgery in pleura infection (ISRCTN18192121).

249. Fitzgerald DB, Waterer GW, Read CA et al. Steroid therapy and outcome of parapneumonic pleural effusions (STOPPE): Study protocol for a multicenter, double-blinded, placebo-controlled randomized clinical trial. Medicine (Baltimore). 2019 Oct; 98(43):e17397.

250. Bender JM, Ampofo K, Sheng X. Parapneumonic empyema deaths during past century, Utah. Emerg Infect Dis. 2009 Jan; 15(1):44-8.

251. Søgaard M, Nielsen RB, Nørgaard M et al. Incidence, length of stay, and prognosis of hospitalized patients with pleural empyema: a 15-year Danish nationwide cohort study. Chest. 2014 Jan; 145(1):189-192.

252. Rahman NM, Kahan BC, Miller RF, et al. A clinical score (RAPID) to identify those at risk for poor outcome at presentation in patients with pleural infection. Chest 2014; 145:848–855.

[114]

253.   Wong D, Yap E. Pleural infection in a New Zealand centre: high incidence in Pacific people and RAPID score as a prognostic tool. Intern Med J. 2016 Jun;46 (6):703-9.

254.   Touray S, Sood RN, Lindstrom D et al. Risk Stratification in Patients with Complicated Parapneumonic Effusions and Empyema Using the RAPID Score. Lung. 2018 Oct; 196(5):623-629.

255.   White HD, Henry C, Stock EM. Predicting Long-Term Outcomes in Pleural Infections. RAPID Score for Risk Stratification. Ann Am Thorac Soc. 2015 Sep; 12(9):1310-6.

256.   Corcoran JP, Psallidas I, Gerry S et al. Prospective validation of the RAPID clinical risk prediction score in adult patients with pleural infection: the PILOT study. Eur Respir J. 2020 Nov 26; 56(5):2000130.

257.   Porcel JM. Dual intracavitary therapy for pleural infections: leaving reluctance behind. The European Respiratory Journal. 2019 Aug; 54(2).

258.   Bibby AC, Dorn P, Psallidas I et al. ERS/EACTS statement on the management of malignant pleural effusions. Eur Respir J. 2018 Jul 27; 52(1):1800349.

259.   Chen Y, Mathy NW, Lu H. The role of VEGF in the diagnosis and treatment of malignant pleural effusion in patients with non small cell lung cancer (Review). Mol Med Rep. 2018 Jun; 17(6):8019-8030.

260.   Roberts ME, Neville E, Berrisford RG. Management of a malignant pleural effusion: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010 Aug; 65 Suppl 2:ii32-40.

261.   Lui M. M. S., Fitzgerald D. B., Lee Y. C. G. Phenotyping malignant pleural effusions. Current Opinion in Pulmonary Medicine. 2016. vol. 22, no. 4, pp. 350–355,

262.   Havelock T, Teoh R, Laws D, Gleeson F; BTS Pleural Disease Guideline Group. Pleural procedures and thoracic ultrasound: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010 Aug;65 Suppl 2:ii61-76.

263.   Feller-Kopman DJ, Reddy CB, DeCamp MM et al. Management of Malignant Pleural Effusions. An Official ATS/STS/STR Clinical Practice Guideline. Am J Respir Crit Care Med. 2018 Oct 1; 198(7):839-849.

264.   Clive AO, Kahan BC, Hooper CE, et al. Predicting survival in malignant pleural effusion: development and validation of the LENT prognostic score. Thorax 2014; 69:1098–1104.

265.   Psallidas I, Kanellakis NI, Gerry S et al. Development and validation of response markers to predict survival and pleurodesis success in patients with

malignant pleural effusion (PROMISE): a multicohort analysis. Lancet Oncol. 2018 Jul; 19(7):930-939.

266.   Zhang X, Yi FS, Shi HZ. Predicting Survival for Patients with Malignant Pleural Effusion: Development of the CONCH Prognostic Model. Cancer Manag Res. 2021 Jun 14;13: 4699-4707.

267.   Molina S, Martinez-Zayas G, Sainz PV et al. Breast and Lung Effusion Survival Score Models: Improving Survival Prediction in Patients With Malignant Pleural Effusion and Metastasis. Chest. 2021 Sep;160(3):1075-1094.

268.   Psallidas I, Kalomenidis I, Porcel JM, et al. Malignant pleural effusion: from bench to bedside. Eur Respir Rev. 2016 Jun; 25(140):189-98.

269.   Sahn SA. Pleural diseases related to metastatic malignancies. European Respiratory Journal Aug 1997, 10 (8) 1907-1913;

270.   Stathopoulos GT, Kollintza A, Moschos C et al. Tumor necrosis factor-α promotes malignant pleural effusion. Cancer Res. 2007; 67:9825–9834.

271.   Cui R, Takahashi F, Ohashi R, et al. Osteopontin is involved in the formation of malignant pleural effusion in lung cancer. Lung Cancer. 2009; 63:368–374.

272.   Moschos C, Psallidas I, Kollintza A et al. The angiopoietin/Tie2 axis mediates malignant pleural effusion formation. Neoplasia. 2009; 11:298–304.

273.   Economidou F., Margaritopoulos G., Antoniou K. M. The angiogenetic pathway in malignant pleural effusions: Pathogenetic and therapeutic implications. Exp. Ther. Med. 1, 3–7 (2010).

274.   Psallidas I, Stathopoulos GT, Maniatis NA, et al. Secreted phosphoprotein-1 directly provokes vascular leakage to foster malignant pleural effusion. Oncogene. 2012 Feb 27.

275.   Chernow B, Sahn SA. Carcinomatous involvement of the pleura. An analysis of 96 patients. Am J Med. 1977; 63(5): 695-702.

276.   Ferreiro L, Porcel JM, Valdés L. Diagnosis and Management of Pleural Transudates. Arch Bronconeumol. 2017 Nov;53(11):629-636.

277.   Zarogoulidis K, Zarogoulidis P, Darwiche K, et al. Malignant pleural effusion and algorithm management. J Thorac Dis. 2013 Sep; 5 Suppl 4(Suppl 4):S413-9.

278.   Thomas J.M., Musani A. I. Malignant pleural effusions: a review. Clin Chest Med. 2013. 34, 459–471.

279.   Swiderek J., Morcos S., Donthireddy V. et al. Prospective study to determine the volume of pleural fluid required to diagnose malignancy. Chest. 2010; vol. 137, no. 1, pp. 68–73.

280.   Scherpereel, P. Astoul, P. Baas et al. Guidelines of the European respiratory society and the European society of thoracic surgeons for the management of malignant pleural mesothelioma. European Respiratory Journal. 2010; vol. 35, no. 3, pp. 479–495.

281.   Newman A, Bratman S et al. An ultra sensitive method for quantitating circulating tumour DNA with broad patient coverage. Nat Med 2014;20:548–54

282.   Karachaliou N, Mayo-de las Casas C, Queralt C, et al. Association of EGFR L858R mutation in circulating free DNA with survival in the EURTAC trial. JAMA Oncol 2015; 1: 149–157.

283.   Porcel JM, Vives M, Esquerda A. Use of panel of tumor markers in pleural fluid for the differential diagnosis of benign and malignant effusions. Chest. 2004; 126(6):1757-1763.

284.   Wang S, Tian S, Li Y, et al. Development and validation of a novel scoring system developed from a nomogram to identify malignant pleural effusion. EBioMedicine. 2020; 58:102924.

285.   Hallifax RJ., Corcoran JP., Ahmed A. et al. Physician based ultrasound-guided biopsy for diagnosing pleural disease. Chest. 2014; vol. 146, no. 4, pp. 1001–1006.

286.   Metintas M, Ak G, Dundar E, et al. Medical thoracoscopy vs CT scan-guided Abrams pleural needle biopsy for diagnosis of patients with pleural effusions: a randomized, controlled trial. Chest. 2010 Jun; 137(6):1362-8.

287.   Medford, Y. Awan, A. Marchbank, et al. Diagnostic and therapeutic performance of video-assisted thoracoscopic surgery (VATS) in investigation and management of pleural exudates. The Annals of Royal College of Surgeons of England. 2008; 90(7):597–600.

288.   Lentz RJ, Lerner AD, Pannu JK et al. Routine monitoring with pleural manometry during therapeutic large-volume thoracentesis to prevent pleural-pressure-related complications: a multicentre, single-blind randomised controlled trial. Lancet Respir Med. 2019 May; 7(5):447-455.

289.   Putnam JB Jr, Walsh GL, Swisher SG. Outpatient management of malignant pleural effusion by a chronic indwelling pleural catheter. Ann Thorac Surg. 2000 Feb; 69(2):369-75.

290.   Freeman RK, Ascioti AJ, Mahidhara RS. A propensity-matched comparison of pleurodesis or tunneled pleural catheter in patients undergoing

diagnostic thoracoscopy for malignancy. Ann Thorac Surg. 2013 Jul;96(1):259-63: discussion 263-4.

291.   Srour N, Amjadi K, Forster A, Aaron S. Management of malignant pleural effusions with indwelling pleural catheters or talc pleurodesis. Can Respir J. 2013;20(2):106-110.

292.   Dipper A, Jones HE, Bhatnagar R et al. Interventions for the management of malignant pleural effusions: a network meta-analysis. Cochrane Database Syst Rev. 2020 Apr 21; 4(4):CD010529.

293.   Maskell NA, Lee YC, Gleeson FV et al. Randomized trials describing lung inflammation after pleurodesis with talc of varying particle size. Am J Respir Crit Care Med. 2004 Aug 15;170(4):377-82.

294.   Janssen JP, Collier G, Astoul P et al. Safety of pleurodesis with talc poudrage in malignant pleural effusion: a prospective cohort study. Lancet. 2007 May 5; 369(9572):1535-1539.

295.   Fysh ETH, Wrightson JM, Lee YCG, Rahman NM. Fractured indwelling pleural catheters. Chest. 2012 Apr;141(4):1090-1094.

296.   Tremblay A, Mason C, Michaud G. Use of tunnelled catheters for malignant pleural effusions in patients fit for pleurodesis. Eur Respir J. 2007 Oct;30(4):759-62.

297.   Iyer NP, Reddy CB, Wahidi MM, et al. Indwelling Pleural Catheter versus Pleurodesis for Malignant Pleural Effusions. A Systematic Review and Meta-Analysis. Ann Am Thorac Soc. 2019 Jan;16(1):124-131.

298.   Wrightson JM, Fysh E, Maskell NA, Lee YC. Risk reduction in pleural procedures: sonography, simulation and supervision. Curr Opin Pulm Med. 2010 Jul;16(4):340-50.

299.   Fysh ETH, Tremblay A, Feller-Kopman D et al. Clinical outcomes of indwelling pleural catheter-related pleural infections: an international multicenter study. Chest. 2013 Nov;144(5):1597-1602.

300.   Puri V, Pyrdeck TL, Crabtree TD et al. Treatment of malignant pleural effusion: a cost-effectiveness analysis. Ann Thorac Surg. 2012 Aug; 94(2):374-9; discussion 379-80.

301.   Muruganandan S, Azzopardi M, Fitzgerald DB et al. Aggressive versus symptom-guided drainage of malignant pleural effusion via indwelling pleural catheters (AMPLE-2): an open-label randomised trial. Lancet Respir Med. 2018 Sep;6(9):671-680.

302. Wahidi MM, Reddy C, Yarmus L et al. Randomized Trial of Pleural Fluid Drainage Frequency in Patients with Malignant Pleural Effusions. The ASAP Trial. Am J Respir Crit Care Med. 2017 Apr 15;195(8):1050-1057

303. A randomised study of the relative benefits of combined indwelling pleural catheter (IPC) and talc pleurodesis therapy or video-assited thoracoscopic surgery (VATS) in the management of patients with malignant pleural effusion (AMPLE-3) ACTRN12618001013257.

304. Sivakumar P, Douiri A, West A et al. OPTIMUM: a protocol for a multicentre randomised controlled trial comparing Out Patient Talc slurry via Indwelling pleural catheter for Malignant pleural effusion vs Usual inpatient Management. BMJ Open. 2016 Oct 18; 6(10):e012795.

305. Niho S, Kubota K, Yoh K, et al. Clinical outcome of chemoradiation therapy in patients with limited-disease small cell lung cancer with ipsilateral pleural effusion. J Thorac Oncol 2008; 3: 723–727

306. Qi N, Li F, Li X, et al. Combination use of paclitaxel and avastin enhances treatment effect for the NSCLC patients with malignant pleural effusion. Medicine (Baltimore) 2016; 95: e5392

307. Lin JB, Lai FC, Li X, et al. Sequential treatment strategy for malignant pleural effusion in non-small cell lung cancer with the activated epithelial grow factor receptor mutation. J Drug Target 2017; 25: 119–124.

308. Temel JS, Greer JA, Muzikansky A et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med. 2010 Aug 19; 363(8):733-42.

309. Heffner JE, Nietert PJ, Barbieri C. Pleural fluid pH as a predictor of survival for patients with malignant pleural effusions. Chest 2000; 117:79–86.

310. Bielsa S, Salud A, Martinez M, et al. Prognostic significance of pleural fluid data in patients with malignant effusion. Eur J Intern Med 2008; 19:334–339.

311. Pilling JE, Dusmet ME, Ladas G, Goldstraw P. Prognostic factors for survival after surgical palliation of malignant pleural effusion. J Thorac Oncol 2010;5: 1544–1550.

312. Anevlavis S, Kouliatsis G, Sotiriou I, et al. Prognostic factors in patients presenting with pleural effusion revealing malignancy. Respiration 2014;87:311–316.

313. Kasapoglu US, Arınç S, Gungor S, et al. Prognostic factors affecting survival in nonsmall cell lung carcinoma patients with malignant pleural effusions. ClinRespir J 2015.

[119]

314.   Lee YS, Nam HS, Lim JH, et al. Prognostic impact of a new score using neutrophil-to-lymphocyte ratios in the serum and malignant pleural effusion in lung cancer patients. BMC Cancer. 2017; 17(1):557.

315.   Shi XY, Yi FS, Wang Z, Qiao X, Zhai K. Prognostic value of a new score using serum alkaline phosphatase and pleural effusion lactate dehydrogenase for patients with malignant pleural effusion. Thorac Cancer. 2020 Feb; 11(2):320-328.

316.   Qiao X, Zhang ZR, Shi XY, Yi FS. Total Protein-Chloride Ratio in Pleural Fluid Independently Predicts Overall Survival in Malignant Pleural Effusion at the First Diagnosis. Front Oncol. 2022 Jan 10;11:777930.

317.   Lehnert P, Lange T, Møller CH, et al. Acute Pulmonary Embolism in a National Danish Cohort: Increasing Incidence and Decreasing Mortality. Thromb Haemost 2018;118:539-46.

318.   Lampropoulos IC, Raptis DG, Daniil Z et al. Temporal trends in pulmonary embolism prevalence in Greece during 2013-2017. BMC Public Health. 2021 Mar 21;21(1):559.

319.   Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 1999; 353:1386-9.

320.   Shiraev TP, Omari A, Rushworth RL. Trends in pulmonary embolism morbidity and mortality in Australia. Thromb Res 2013;132:19-25

321.   Porcel JM, Madroñero AB, Pardina M et al. Analysis of pleural effusions in acute pulmonary embolism: radiological and pleural fluid data from 230 patients. Respirology. 2007 Mar; 12(2):234-9.

322.   Liu M, Cui A, Zhai ZG, Guo XJ, et al. Incidence of pleural effusion in patients with pulmonary embolism. Chin Med J (Engl). 2015 Apr 20; 128(8):1032-6.

323.   Choi SH, Cha SI, Shin KM et al. Clinical Relevance of Pleural Effusion in Patients with Pulmonary Embolism. Respiration. 2017; 93(4):271-278.

324.   Zhang J, Zhou H, Aili A, Wang M, Shen Y, Yi Q. Prevalence and clinical significance of pleural effusion in patients with acute pulmonary embolism: a retrospective study. J Thorac Dis. 2021; 13(2):541-551.

325.   Hooper C, Laurence I, Harvey J et al. The role of CT pulmonary angiography in the investigation of unilateral pleural effusions. Respiration. 2014; 87(1):26-31.

326.   Jackson K, Aujayeb A. Pleural Effusions in Pulmonary Emboli: A Single Centre Experience. Cureus. 2020 Dec 6; 12(12):e11942.

327.   Findik S. Pleural effusion in pulmonary embolism. Curr Opin Pulm Med. 2012 Jul; 18(4):347-54.

328.   Light RW. Pleural effusion in pulmonary embolism. Semin Respir Crit Care Med. 2010 Dec; 31(6):716-22.

329.   Zhou X, Zhang Z, Zhai Z, et al. Pleural effusions as a predictive parameter for poor prognosis for patients with acute pulmonary thromboembolism. J Thromb Thrombolysis 2016; 42:432-40.

330.   Olgun Yıldızeli Ş, Kasapoğlu US, Arıkan H, et al. Pleural effusion as an indicator of short term mortality in acute pulmonary embolism. Tuberk Toraks 2018; 66:185-96.

331.   Levy O, Fux D, Bartsikhovsky T, Vosko S, Tishler M, Copel L. Clinical relevance of bilateral pleural effusion in patients with acute pulmonary embolism. Intern Med J. 2020 Aug; 50(8):938-944.

332.   World Health Organization. 2020 Global tuberculosis report.

333.   Centres for Disease Control and Prevention. Reported Tuberculosis in the United States, 2017. Atlanta, US Department of Health and Human Services, 2018.

334.   Korea Centers for Disease Control and Prevention. Annual report on the notified tuberculosis in Korea 2017. Cheongju, Korea Centers for Diseases Control and Prevention, 2018.

335.   Karstaedt AS. Extrapulmonary tuberculosis among adults: experience at Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa. S Afr Med J 2013; 104: 22–24.

336.   Porcel JM. Tuberculous pleural effusion. Lung 2009; 187: 263–270.

337.   Mitra DK, Sharma SK, Dinda AK, et al. Polarized helper T cells in tubercular pleural effusion: phenotypic identity and selective recruitment. Eur J Immunol 2005; 35: 2367–2375.

338.   Ruan SY, Chuang YC, Wang JY et al. Revisiting tuberculous pleurisy: pleural fluid characteristics and diagnostic yield of mycobacterial culture in an endemic area. Thorax. 2012 Sep;67(9):822-7

339.   Candela A, Andujar J, Hernandez L, et al. Functional sequelae of tuberculous pleurisy in patients correctly treated. Chest 2003; 123: 1996–2000.

340.   Valdés L, Alvarez D, San José E et al. Tuberculous pleurisy: a study of 254 patients. Arch Intern Med. 1998 Oct 12;158(18):2017-21.

341.   Andreu J, Cáceres J, Pallisa E, et al. Radiological manifestations of pulmonary tuberculosis. Eur J Radiol 2004; 51:139–149

[121]

342.   Ko JM, Park HJ, Cho DG, et al. CT differentiation of tuberculous and non-tuberculous pleural infection, with emphasis on pulmonary changes. Int J Tuberc Lung Dis 2015; 19: 1361–1368.

343.   Bolliger CT, de Kock MA. Influence of a fibrothorax on the flow/volume curve. Respiration 1988; 54: 197–200.

344.   Light RW. Update on tuberculous pleural effusion. Respirology 2010; 15: 451–458

345.   Diacon AH, Van de Wal BW, Wyser C et al. Diagnostic tools in tuberculous pleurisy: a direct comparative study. Eur Respir J. 2003 Oct;22(4):589-91.

346.   Lewinsohn DM, Leonard MK, LoBue PA et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. Clin Infect Dis. 2017 Jan 15; 64(2):111-115.

347.   Skouras VS, Kalomenidis I. Pleural fluid tests to diagnose tuberculous pleuritis. Curr Opin Pulm Med. 2016 Jul;22(4):367-77

348.   Arnold DT, Bhatnagar R, Fairbanks LD, et al. Pleural fluid adenosine deaminase (pfADA) in the diagnosis of tuberculous effusions in a low incidence population. PLoS One. 2015;10(2):e0113047

349.   Skouras VS, Magkouta SF, Psallidas I, et al. Interleukin-27 improves the ability of adenosine deaminase to rule out tuberculous pleural effusion regardless of pleural tuberculosis prevalence. Infect Dis (Lond) 2015; 47: 477-83.

350.   Valdés L, San José E, Ferreiro L, et al. Interleukin 27 could be useful in the diagnosis of tuberculous pleural effusions. Respir Care 2014; 59: 399-405.

351.   Yang X, Zhang J, Liang Q et l. Use of T-SPOT.TB for the diagnosis of unconventional pleural tuberculosis is superior to ADA in high prevalence areas: a prospective analysis of 601 cases. BMC Infect Dis. 2021 Jan 4;21(1):4.

352.   Liu SF, Liu JW, Lin MC. Characteristics of patients suffering from tuberculous pleuritis with pleural effusion culture positive and negative for Mycobacterium tuberculosis, and risk factors for fatality. Int J Tuberc Lung Dis. 2005 Jan; 9(1):111-5.

353.   Shu CC, Wang JT, Wang JY et al. In-hospital outcome of patients with culture-confirmed tuberculous pleurisy: clinical impact of pulmonary involvement. BMC Infect Dis. 2011 Feb 21; 11:46.

354. Bielsa S, Acosta C, Pardina M et al. Tuberculous Pleural Effusion: Clinical Characteristics of 320 Patients. Arch Bronconeumol. 2019 Jan; 55(1):17-22.

355. World Health Organisation. Guidelines for treatment of drug susceptible tuberculosis and patient care. Geneva, World Health Organization, 2017.

356. Canete C, Galarza I, Granados A, et al. Tuberculous pleural effusion: experience with six months of treatment with isoniazid and rifampicin. Thorax 1994; 49: 1160–1161

357. Bouayad Z, Aichane A, Trombati N, et al. Treatment of pleural tuberculosis with a short 4-month regimen: preliminary results. Tuber Lung Dis 1995; 76: 367–369

358. Long R, Barrie J, Peloquin CA. Therapeutic drug monitoring and the conservative management of chronic tuberculous empyema: case report and review of the literature. BMC Infect Dis 2015; 15: 327.

359. Sharma SK, Ryan H, Khaparde S, et al. Index-TB guidelines: guidelines on extrapulmonary tuberculosis for India. Indian J Med Res 2017; 145: 448–463.

360. Ryan H, Yoo J, Darsini P. Corticosteroids for tuberculous pleurisy. Cochrane database Syst Rev 2017; 3:CD001876.

361. Chung C-L, Chen C-H, Yeh C-Y, et al. Early effective drainage in the treatment of loculated tuberculous pleurisy.Eur Respir J 2008; 31: 1261–1267.

362. Cases Viedma E, Lorenzo Dus MJ, Gonzalez-Molina A, et al. A study of loculated tuberculous pleural effusions treated with intrapleural urokinase. Respir Med 2006; 100: 2037–2042.

363. Xiong Y, Gao X, Zhu H, et al. Role of medical thoracoscopy in the treatment of tuberculous pleural effusion. J Thorac Dis 2016; 8: 52–60.

364. Bagheri R, Haghi SZ, Dalouee MN, et al. Effect of decortication and pleurectomy in chronic empyema patients. Asian Cardiovasc Thorac Ann 2016; 24: 245–249.

365. Chen B, Zhang J, Ye Z, et al. Outcomes of video-assisted thoracic surgical decortication in 274 patients with tuberculous empyema. Ann Thorac Cardiovasc Surg 2015; 21: 223–228.

366. Imazio M, Hoit BD. Post-cardiac injury syndromes. An emerging cause of pericardial diseases. Int J Cardiol 2013;168:648

367. Adler, Y., Charron, P., Imazio, M. et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases. European heart journal, 36(42), 2921–2964.

[123]

368. Van Osch D, Nathoe HM, Jacob KA, et al. Determinants of the postpericardiotomy syndrome: a systematic review. Eur J Clin Invest. 2017; 47 (6):456–467.

369. Lehto J, Kiviniemi T. Postpericardiotomy syndrome after cardiac surgery. Ann Med. 2020 Sep;52(6):243-264.

370. Imazio M, Trinchero R, Brucato A, et al. COPPS Investigators. COlchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS): a multicentre, randomized, double-blind, placebo-controlled trial. Eur Heart J. 2010 Nov;31(22):2749-54.

371. Lehto J, Gunn J, Karjalainen P, et al. Incidence and risk factors of postpericardiotomy syndrome requiring medical attention: The Finland postpericardiotomy syndrome study. J Thorac Cardiovasc Surg 2015;149:1324

372. Bielsa S, Corral E, Bagüeste P, Porcel JM. Characteristics of Pleural Effusions in Acute Idiopathic Pericarditis and Post-Cardiac Injury Syndrome. Ann Am Thorac Soc. 2016 Feb;13(2):298-300.

373. Paull DE, Delahanty TJ, Weber FJ, et al. Thoracoscopic talc pleurodesis for recurrent, symptomatic pleural effusion following cardiac operations. Surg Laparosc Endosc Percutan Tech. 2003; 13(5): 339–344.

374. Light RW. Pleural effusions following cardiac injury and coronary artery bypass graft surgery. Semin Respir Crit Care Med. 2001 Dec;22(6):657-64.

375. Light RW. Pleural effusions after coronary artery bypass graft surgery. Curr Opin Pulm Med. 2002 Jul;8(4):308-11.

376. Sadikot RT, Rogers JT, Cheng DS et al. Pleural fluid characteristics of patients with symptomatic pleural effusion after coronary artery bypass graft surgery. Arch Intern Med. 2000 Sep 25; 160(17):2665-8.

377. Lee YC, Vaz MA, Ely KA, et al. Symptomatic persistent post-coronary artery bypass graft pleural effusions requiring operative treatment: clinical and histologic features. Chest. 2001 Mar; 119(3):795-800.

378. Ip H, Sivakumar P, McDermott EA et al. Multidisciplinary approach to connective tissue disease (CTD) related pleural effusions: a four-year retrospective evaluation. BMC Pulm Med. 2019 Aug 27; 19(1):161.

379. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet2016; 388: 2023–2038

380. Balbir-Gurman A, Yigla M, Nahir AM, et al. Rheumatoid pleuraleffusion. Semin Arthritis Rheum 2006; 35: 368–378

[124]

381.   Sahn SA, Kaplan RL, Maulitz RM, et al. Rheumatoid pleurisy. Observations on the development of low pleural fluid pH andglucose level. Arch Intern Med 1980; 140: 1237–1238.

382.   Schneider F, Gruden J, Tazelaar HD, et al. Pleuropulmonarypathology in patients with rheumatic disease. Arch Pathol LabMed 2012; 136: 1242–1252

383.   Tsokos GC. Systemic lupus erythematosus. N Engl J Med 2011;365: 2110–2121.

384.   Keane MP, Lynch JP 3rd, Pleuropulmonary manifestations of systemic lupus erythematosus. Thorax 2000; 55: 159–166.

385.   Smith PR, Nacht RI. Drug-induced lupus pleuritis mimicking pleural space infection. Chest. 1992 Jan;101(1):268-9.

386.   Good JT, Jr., King TE, Antony VB, et al. Lupus pleuritis. Clinicalfeatures and pleural fluid characteristics with special referenceto pleural fluid antinuclear antibodies. Chest 1983; 84:714–718.

387.   Spagnolo P, Cordier JF, Cottin V. Connective tissue diseases,multimorbidity and the ageing lung. Eur Respir J 2016; 47:1535–1558.

388.   Cervera R, Khamashta MA, Font J, et al. Morbidity and mortalityin systemic lupus erythematosus during a 10-year period: acomparison of early and late manifestations in a cohort of 1,000 patients. Medicine (Baltimore) 2003; 82: 299–308

389.   Browne GW, Pitchumoni CS. Pathophysiology of pulmonary complications of acute pancreatitis. World J Gastroenterol. 2006 Nov 28;12(44):7087-96.

390.   Kumar P, Gupta P, Rana S. Thoracic complications of pancreatitis. JGH Open. 2018; 3(1):71-79.

391.   Sontakke A, Tayade BO. Case series of pancreatic pleural effusion with pancreatico-pleural fistula. JIACM 2014;15:245-8

392.   Uchiyama T, Suzuki T, Adachi A, Hiraki S, Iizuka N. Pancreatic pleural effusion: Case report and review of 113 cases in Japan. Am J Gastroenterol 1992;87:387-91

393.   Light RW. Exudative pleural effusions secondary to gastrointestinal diseases. Clin Chest Med. 1985 Mar;6(1):103-11.

394.   Johnson CD, Abu-Hilal M. Persistent organ failure during the first week as a marker of fatal outcome in acute pancreatitis. Gut. 2004 Sep; 53(9):1340-4.

395.   Polyzogopoulou E, Bikas C, Danikas D, Koutras A, Kalfarentzos F, Gogos CA. Baseline hypoxemia as a prognostic marker for pulmonary complications and outcome in patients with acute pancreatitis. Dig Dis Sci. 2004 Jan;49(1):150-4

396.   Raghu MG, Wig JD, Kochhar R et al. Lung complications in acute pancreatitis. JOP. 2007 Mar 10; 8(2):177-85.

397.   Ocampo C, Silva W, Zandalazini H et al. Pleural effusion is superior to multiple factor scoring system in predicting acute pancreatitis outcome. Acta Gastroenterol Latinoam. 2008 Mar; 38(1):34-42.

398.   Skouras V, Kalomenidis I. Chylothorax: diagnostic approach. Curr Opin Pulm Med. 2010 Jul;16(4):387-93.

399.   Garcia-Pachon E, Padilla-Navas I. Urinothorax: case report and review of the literature with emphasis on biochemical diagnosis. Respiration 2004;71(5):533–6. 16.

400.   Dimitriadis G, Tahmatzopoulos A, Kampantais S, et al. Unilateral urinothorax can occur contralateral to the affected kidney. Scand J Urol Nephrol 2012.

401.   Stark DD, Shanes JG, Baron RL, et al. Biochemical features of urinothorax. Arch Intern Med 1982; 142(8):1509–11

402.   Meigs JV. Fibroma of the ovary with ascites and hydrothorax; Meigs' syndrome. Am J Obstet Gynecol. 1954 May;67(5):962-85.

403.   Timmerman D, Moerman P, Vergote I. Meigs' syndrome with elevated serum CA 125 levels: two case reports and review of the literature. Gynecol Oncol. 1995 Dec;59(3):405-8.

404.   Krenke R, Maskey-Warzechowska M, Korczynski P, et al. Pleural Effusion in Meigs' Syndrome-Transudate or Exudate? : Systematic Review of the Literature. Medicine (Baltimore). 2015; 94(49):e2114.

405.   Zannad F, Mebazaa A, Juilliere Y, et al.Clinical profile, contemporary management and one-year mortality inpatients with severe acute heart failuresyndromes: The EFICA study. Eur J HeartFail. 2006;8(7):697-705

406.   Muntwyler J, Abetel G, Gruner C,Follath F. One-year mortality amongunselected outpatients with heart failure.Eur Heart J. 2002;23(23):1861-1866.

407.   Goodkin DA, Bragg-Gresham JL, Koenig KG et al. Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the United States: the Dialysis Outcomes and Practice Patterns Study (DOPPS). J Am Soc Nephrol. 2003 Dec; 14(12):3270-7.

408.   Said A, Williams J, Holden J, et al. Modelf or end stage liver disease score predicts mortality across a broad spectrum of liverdisease. J Hepatol. 2004; 40(6):897-903.

409.   Moy MP, Levsky JM, Berko NS, et al. A new, simple method for estimating pleural effusion size on CT scans. Chest 2013; 143(4):1054–1059.

410.   Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985 Oct; 13 (10):818-29.

411.   Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA. 2001 Oct 10; 286(14):1754-8.

412.   Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

413.   Hasley PB, Albaum MN, Li YH, et al. Do pulmonary radiographic findings at presentation predict mortality in patients with community-acquired pneumonia? Arch Intern Med 1996; 156:2206–2212

414.   Kim J, Park JS, Cho YJ, et al. Predictors of prolonged stay in patients with community-acquired pneumonia and complicated parapneumonic effusion. Respirology 2016;21(1):164-71

415.   Tu CY, Hsu WH, Hsia TC, Chen HJ, Chiu KL, Hang LW, et al. The changing pathogens of complicated parapneumonic effusions or empyemas in a medical intensive care unit. Intensive Care Med. (2006) 32:570–6.

416.   Koma Y, Inoue S, Oda N et al. Clinical characteristics and outcomes of patients with community-acquired, health-care-associated and hospital-acquired empyema. Clin Respir J. 2017 Nov; 11(6):781