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ΜΑΡΚΑΤΗΣ ΕΛΕΥΘΕΡΙΟΣ
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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)»

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ΕΥΧΑΡΙΣΤΙΕΣ

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

Ιδιαίτερη μνεία αξίζει ο Διευθυντής της Πνευμονολογικής κλινικής του Γενικού Νοσοκομείου Κέρκυρας κ. Ηλίας Παπανικολάου για την καθοριστική συμβολή του στη σύλληψη της ιδέας και τη συνολική επίβλεψη της μελέτης.

Ευχαριστώ τη σύντροφο της ζωής μου Αγάπη Κουρομπλή για την υπομονή και στήριξή της, τον γιο μας Απόστολο που αποτελεί πηγή έμπνευσης, τους γονείς και την αδελφή μου για τα ανεκτίμητα ηθικά εφόδια που παρείχαν στη ζωή μου.

Επίσης, εκφράζω την ευγνωμοσύνη μου στη συνάδελφο κ. Φαίη Περλεπέ για τη σημαντική βοήθειά της με τα δεδομένα και τον συνάδελφο κ. Δημήτριο Αρβανίτη για τη ανεκτίμητη βοήθειά του στη στατιστική ανάλυση.

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Αφιερωμένο στην μνήμη των ασθενών μας που έφυγαν από τη ζωή

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ΠΕΡΙΕΧΟΜΕΝΑ

ΣΕΛ

ΠΕΡΙΕΧΟΜΕΝΑ 5

INTRODUCTION 9

GENERAL PART .....……11

CHAPTER 1 GENERAL FOR PLEURAL CAVITY AND PLEURAL EFFUSION

1.1 Embryology and anatomy of pleural cavity…….**12**

1.2 Physiology of pleural cavity…….....**13**

1.3 Pleural effusion formation……..**13**

1.4 Pathophysiologic effects of pleural effusion…….....**15**

CHAPTER 2 DIAGNOSTIC APPROACH TO PLEURAL EFFUSION

2.1 Initial approach…….**16**

2.2 Imaging…….....**17**

2.3 Thoracentesis and pleural fluid analysis…….....**20**

2.4 Invasive interventions…….**23**

CHAPTER 3 MAIN CAUSES OF PLEURAL EFFUSIONS

3.1 Heart failure……**28**

3.2 Hepatic hydrothorax……..**31**

3.3 Kidney failure……..…**33**

3.4 Pleural infection

Institutional Repository - Library & Information Centre - University of Thessaly
15/10/2023 05:03:51 EEST - 167.114.118.212

3.4.1 Epidemiology……..... ***35***

3.4.2 Pathogenesis/ microbiology…….. ***35***

3.4.3 Diagnosis ……..***39***

3.4.4 Management……***41***

3.4.5 Prognosis……..…***45***

3.5 Malignant pleural effusions

3.5.1 General……..***46***

3.5.2 Pathogenesis……....***47***

3.5.3 Diagnostic approach……....***48***

3.5.4 Management……***52***

3.5.5 Prognosis……..***57***

3.6 Pulmonary embolism……**59**

3.7 Tuberculous pleuritis……**60**

3.8 Post cardiac injury ……**63**

3.9 Connective tissue diseases ……**64**

3.10 Less common causes…….. **66**

CHAPTER 4 MORTALITY AMONG PATIENTS WTH PLEURAL EFFUSION……..69

SPECIFIC PART .....……..70

CHAPTER 5 METHODS……...71

CHAPTER 6 STATISTICAL ANALYSIS……72

Institutional Repository - Library & Information Centre - University of Thessaly
15/10/2023 05:03:51 EEST - 167.114.118.212

CHAPTER 7 RESULTS……73

CHAPTER 8 DISCUSSION…….86

CHAPTER 9 CONCLUSIONS……90

ABSTRACT…….91

ΠΕΡΙΛΙΨΗ……..93

REFERENCES .....……96

Institutional Repository - Library & Information Centre - University of Thessaly
15/10/2023 05:03:51 EEST - 167.114.118.212

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15/10/2023 05:03:51 EEST - 167.114.118.212

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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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.

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15/10/2023 05:03:51 EEST - 167.114.118.212

GENERAL PART

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15/10/2023 05:03:51 EEST - 167.114.118.212

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]**.

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15/10/2023 05:03:51 EEST - 167.114.118.212

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

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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].**

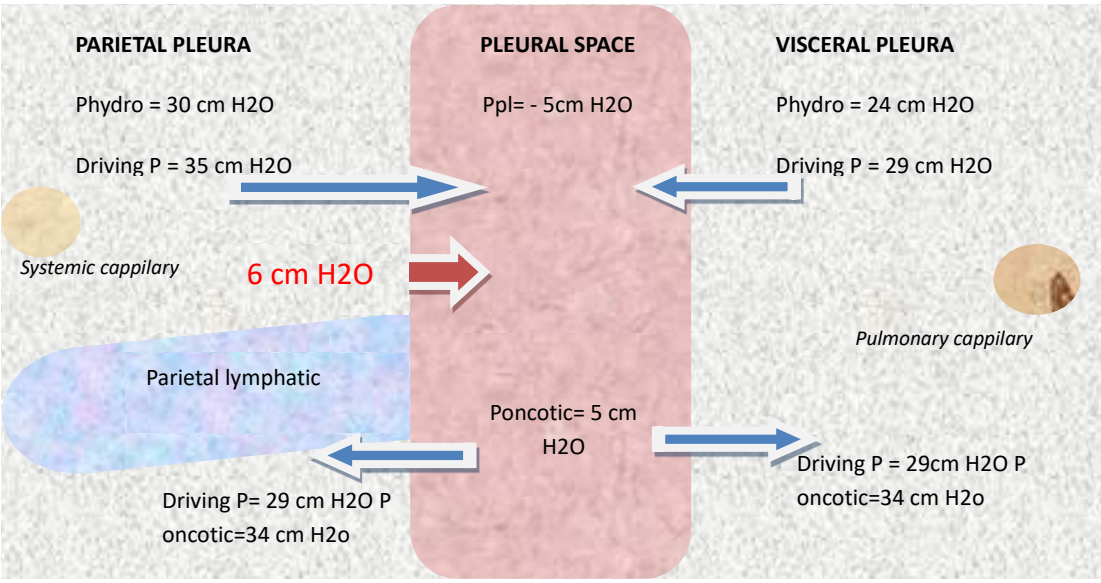

Figure 1] The physiological pleural fluid turnover

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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].**

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15/10/2023 05:03:51 EEST - 167.114.118.212

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,

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15/10/2023 05:03:51 EEST - 167.114.118.212

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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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,

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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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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,

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15/10/2023 05:03:51 EEST - 167.114.118.212

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].**

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15/10/2023 05:03:51 EEST - 167.114.118.212

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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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-

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15/10/2023 05:03:51 EEST - 167.114.118.212

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].**

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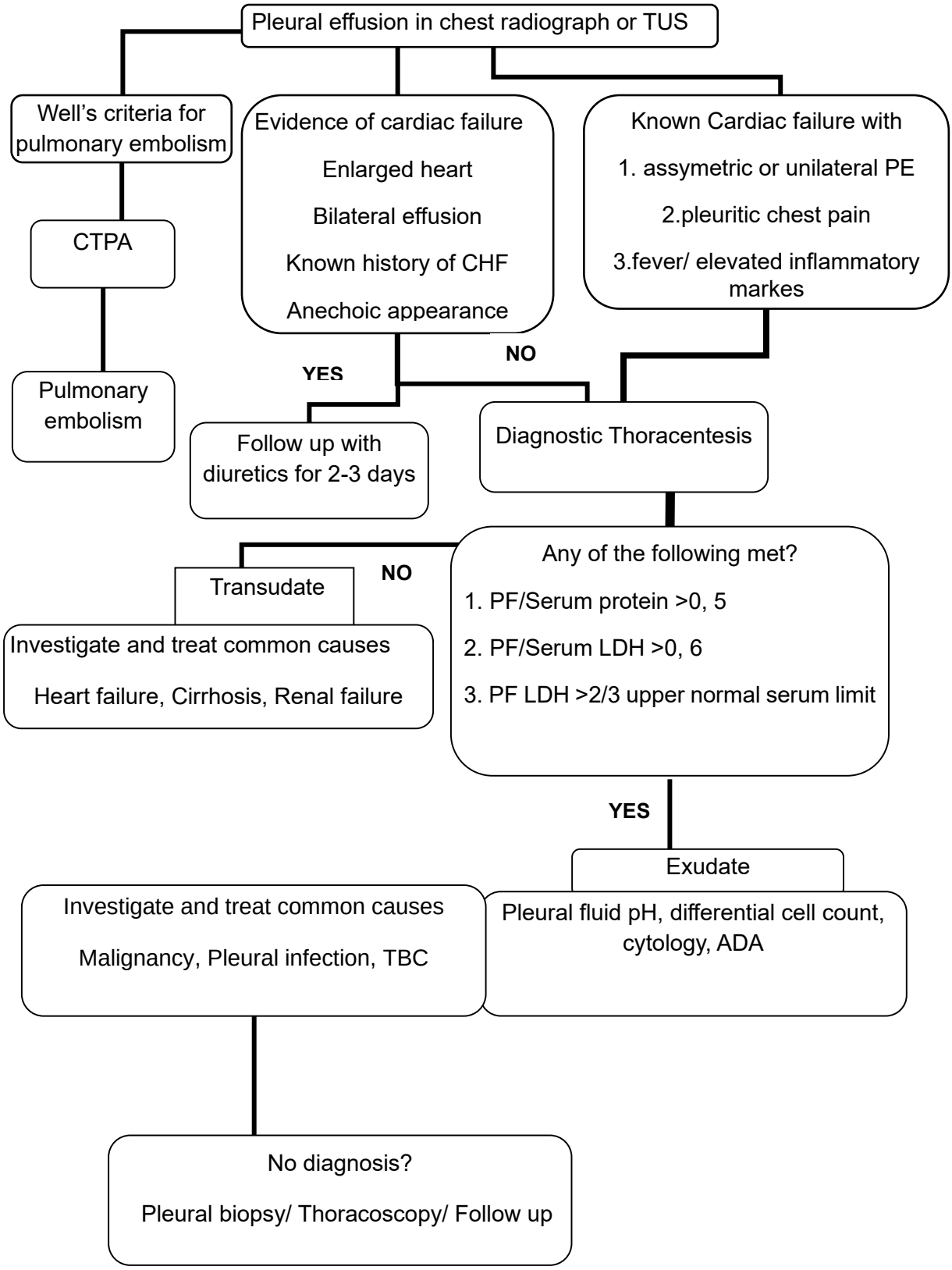

Figure 2] Initial approach to a patient with pleural effusion

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15/10/2023 05:03:51 EEST - 167.114.118.212

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 **Pulmonary Embolism**	**200,000** **150,000**	**Cirrhosis** **Gastrointestinal disease**	**50,000** **25,000**
		Tuberculosis	**2,500**

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

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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]

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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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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].**

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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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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].**

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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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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].**

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15/10/2023 05:03:51 EEST - 167.114.118.212

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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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).**

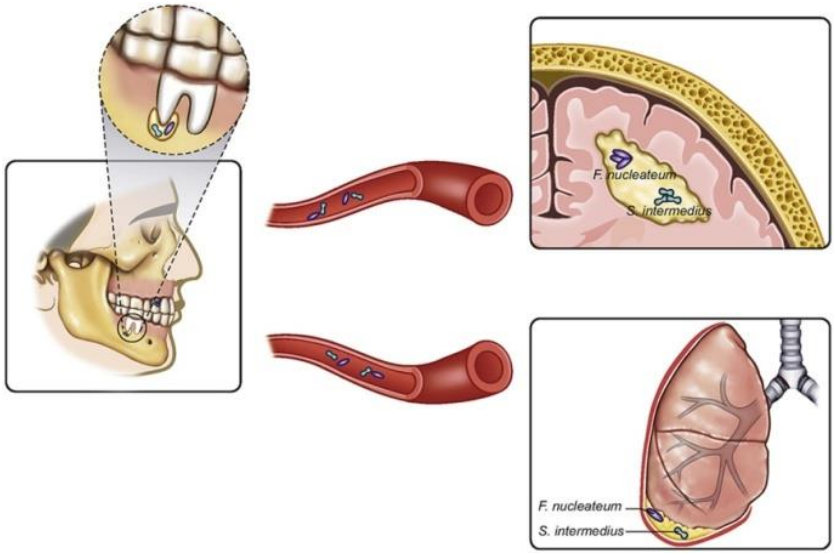

Figure 3] '' Primary empyema'' [188].

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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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]

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15/10/2023 05:03:51 EEST - 167.114.118.212

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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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],**

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15/10/2023 05:03:51 EEST - 167.114.118.212

[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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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].**

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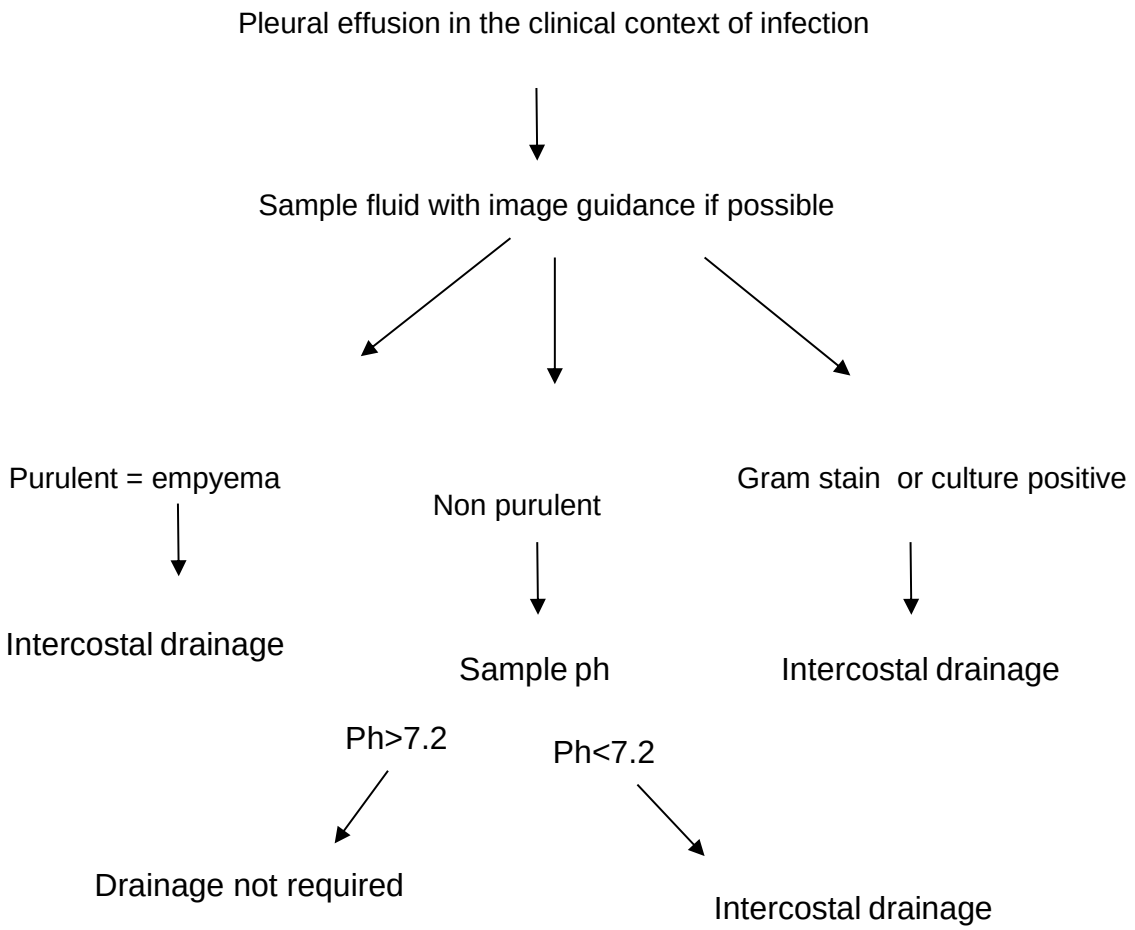

Figure 4] Algorithm for the initial approach to a pleural infection

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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].**

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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].**

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15/10/2023 05:03:51 EEST - 167.114.118.212

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].**

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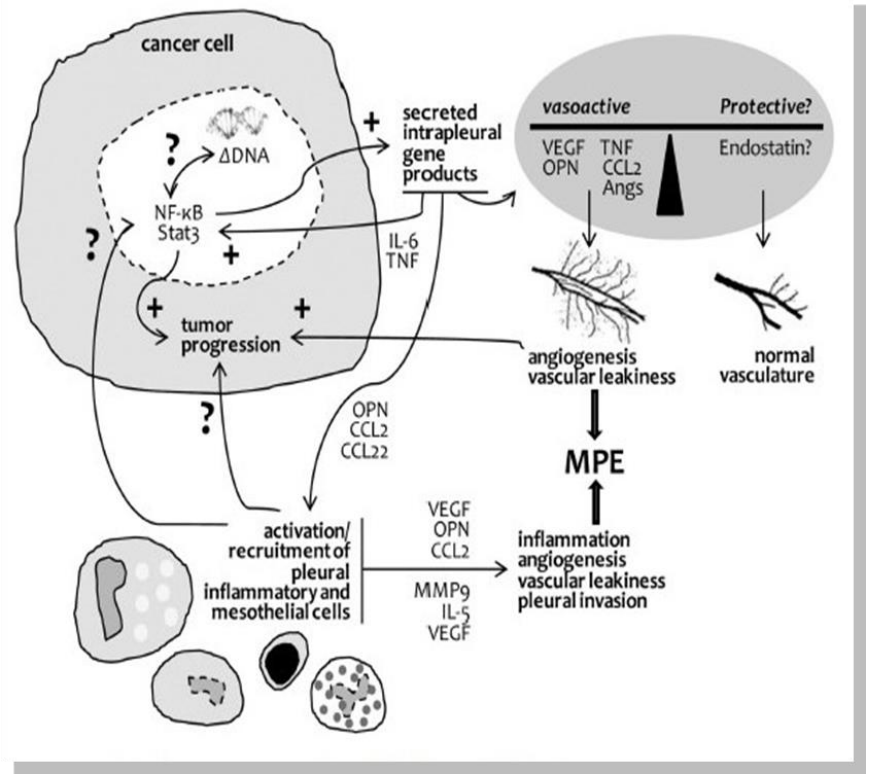

Figure 5] Tumor–host interactions in pathogenesis of MPE [8].

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

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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

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

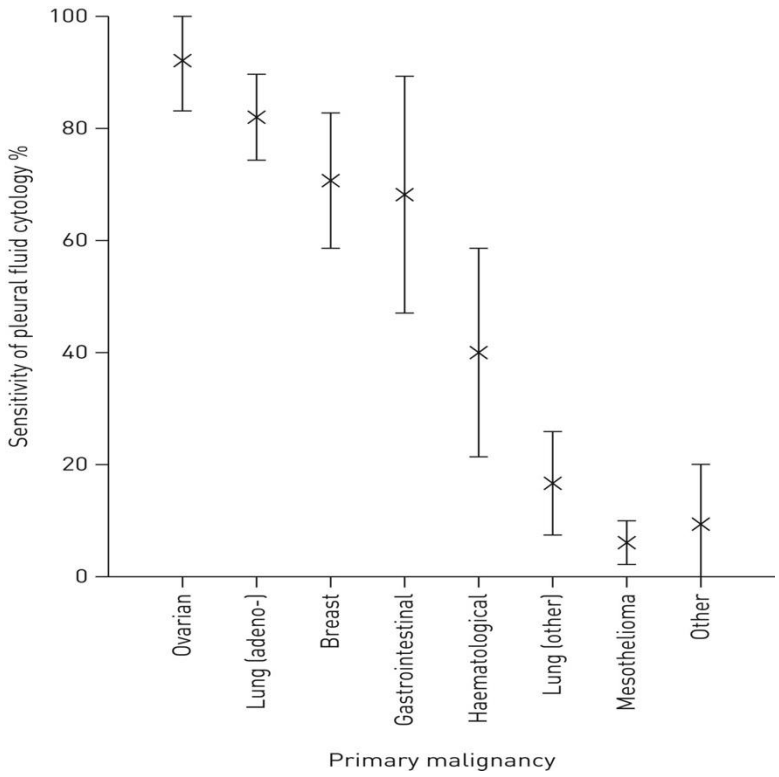

Figure 6] Sensitivity of pleural fluid cytology by malignancy [101]

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

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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].**

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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).

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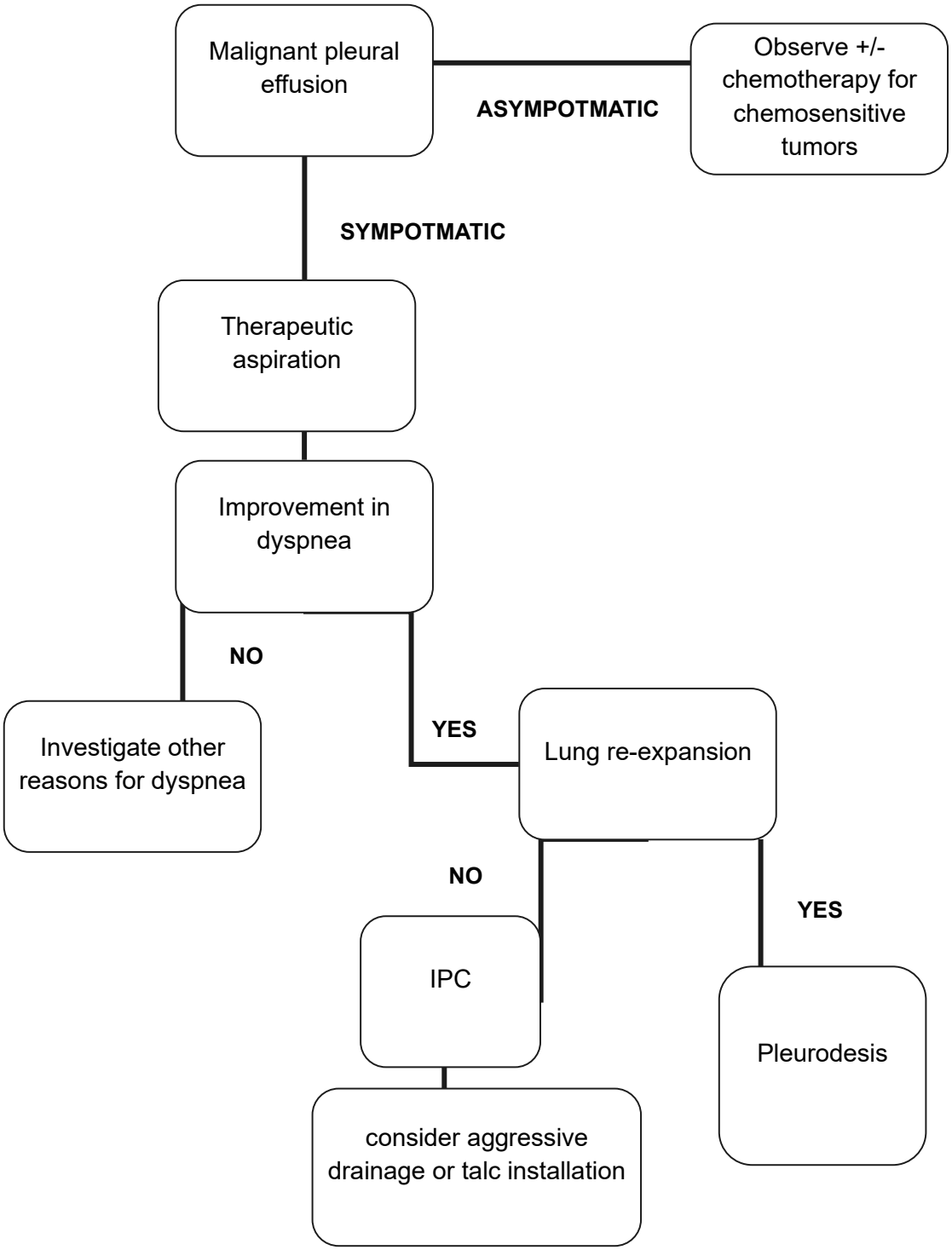

Figure 7] Algorithm for the management of malignant pleural effusion

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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.

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15/10/2023 05:03:51 EEST - 167.114.118.212

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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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
E ECOG PS	0 1 2 3-4	0 1 2 3
N neutrophil-to-lymphocyte ratio	<9 >9	0 1
T Tumor type	Mesothelioma Hematological malignancy Breast cancer Gynecological cancer Renal cancer Lung cancer Another tumor	0 1 2

Risk categories	Score
Low risk	**0-1**
Moderate risk	**2-4**
High risk	**5-7**

Table 7] LENT prognostic score for MPE [264]

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15/10/2023 05:03:51 EEST - 167.114.118.212

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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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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15/10/2023 05:03:51 EEST - 167.114.118.212

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].**

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15/10/2023 05:03:51 EEST - 167.114.118.212

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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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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15/10/2023 05:03:51 EEST - 167.114.118.212

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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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].**

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15/10/2023 05:03:51 EEST - 167.114.118.212

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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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.

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15/10/2023 05:03:51 EEST - 167.114.118.212

SPECIFIC PART

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15/10/2023 05:03:51 EEST - 167.114.118.212

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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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.

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15/10/2023 05:03:51 EEST - 167.114.118.212

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 etiologies	13	Pulmonary embolism	24 (4.72%)
		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).

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15/10/2023 05:03:51 EEST - 167.114.118.212

	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.

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15/10/2023 05:03:51 EEST - 167.114.118.212

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%.

Institutional Repository - Library & Information Centre - University of Thessaly
15/10/2023 05:03:51 EEST - 167.114.118.212

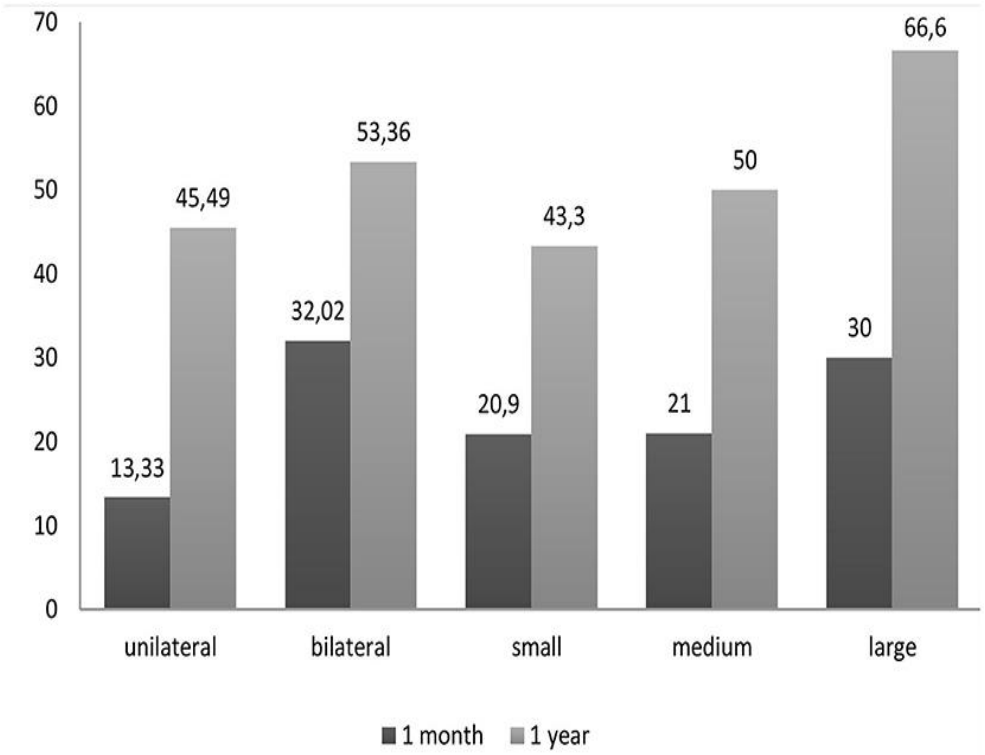

Figure 8] Percent mortality based on the distribution and size of the PE

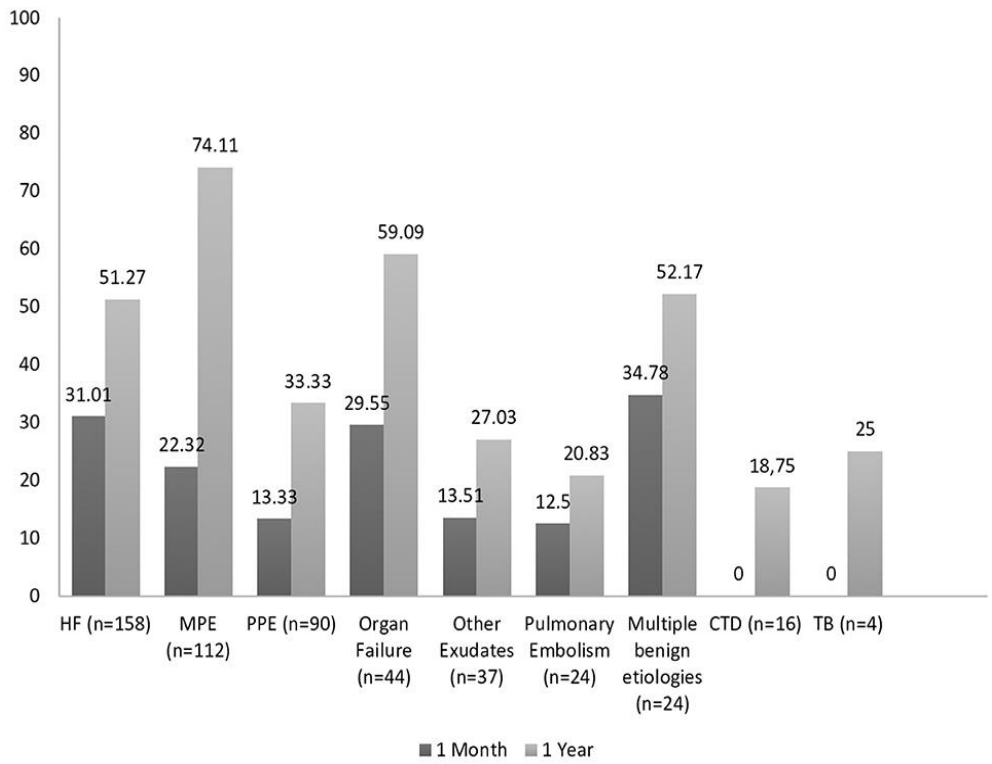

Figure 9] Percent mortality based on the diagnosis of the PE

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15/10/2023 05:03:51 EEST - 167.114.118.212

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).

Institutional Repository - Library & Information Centre - University of Thessaly
15/10/2023 05:03:51 EEST - 167.114.118.212

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.

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15/10/2023 05:03:51 EEST - 167.114.118.212

Sofa score	OR	95% CIs	*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.

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15/10/2023 05:03:51 EEST - 167.114.118.212

1 month	OR	95% CIs	*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% CIs**	***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.

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15/10/2023 05:03:51 EEST - 167.114.118.212

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; CIs, confidence intervals.

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

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15/10/2023 05:03:51 EEST - 167.114.118.212

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.

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15/10/2023 05:03:51 EEST - 167.114.118.212

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.

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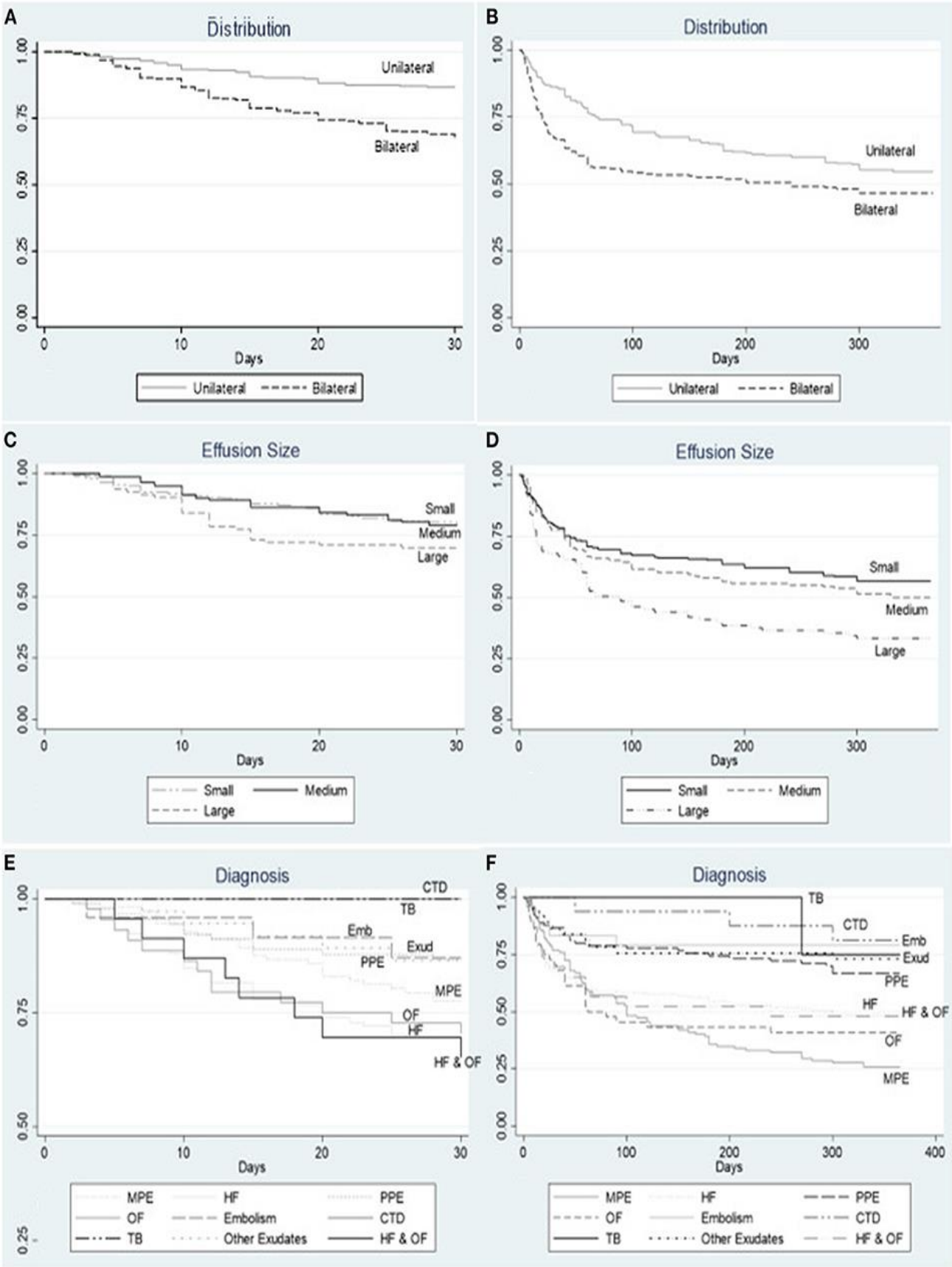

Figure 10] Kaplan Meier survival curves

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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

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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

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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.

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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

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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.

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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.

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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.

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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

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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

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η κακοήθεια μακροπρόθεσμα. Οι διιδρωματικές συλλογές πιθανώς σχετίζονται με χειρότερα αποτελέσματα.

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