“A DESCRIPTIVE STUDY ON ROLE OF PLEURAL FLUID C-REACTIVE PROTEIN IN PLEURAL EFFUSIONS”

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For the Award of the Degree of

M.D. GENERAL MEDICINE – BRANCH I

Submitted by

Registration Number: 200120102006

GOVERNMENT KILPAUK MEDICAL COLLEGE

CHENNAI

MAY 2023

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DECLARATION

I solemnly declare that this dissertation **"A DESCRIPTIVE STUDY ON ROLE OF PLEURAL FLUID C-REACTIVE PROTEIN IN PLEURAL EFFUSIONS"** was prepared by me at Government Kilpauk Medical College and Hospital, Chennai, under the guidance and supervision of ***Prof. Dr. P.PARANTHAMAN M.D,*** Professor and HOD of General Medicine, Department of General Medicine, Government Kilpauk Medical College and Hospital, Chennai. This dissertation is submitted to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai** in partial fulfilment of the University regulations for the award of the degree of **M.D. Branch I (General Medicine).**

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DEPARTMENT	: DEPT OF GENERAL MEDICINE GOVERNMENT KILPAUK MEDICAL COLLEGE, CHENNAI

The request for an approval from the Institutional Ethics Committee (IEC) was considered on the IEC meeting held on **07/07/2022** at Government Kilpauk Medical College, Chennai-10.

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Dr.G.BHARANI DHARAN

Place: Chennai- 10

Date: 16.12.2022

LIST OF ABBREVIATIONS

PE	Pleural effusion
TB	Tuberculosis
ICU	Intensive care unit
LDH	Lactate dehydrogenase
ADA	Adenosine deaminase
CRP	C reactive protein
ANS	Autonomic nervous system
PF	Pleural fluid

TABLE OF CONTENTS

1. ABSTRACT

Background: The pleural cavity, also known as the pleural effusion, is where fluid collects between both the parietal and visceral pleura which can develop independently or as a result of another parenchymal disease, such as an infection, cancer, or inflammatory diseases. The use of pleural fluid CRP in diagnosing exudative pleural effusion has been the subject of numerous studies undertaken all over the world. However, there are only a few studies with small samples that are available from India, so this study was done to determine the effectiveness of pleural fluid CRP as a biomarker for differentiating between exudative and transudative pleural effusions.

Methods: A observational study was done in a tertiary care centre among 88 patients with pleural effusion to determine their CRP levels. The data were analyzed using descriptive and inferential statistics of CRP in pleural effusion to differentiate exudative and transudative effusion.

Results: The pleural fluid CRP level was higher in exudative than transudative effusion. The AUC was 0.995 in the differentiation of exudative from transudative effusion (cut off value 43.4) using Pleural fluid CRP levels.

Conclusion: The pleural fluid CRP was a potential biomarker in differentiating exudative from transudative effusions.

Key words: Pleural effusion, CRP, exudative, transudative, biomarker

2. INTRODUCTION

Background

The pleural cavity, also known as the pleural effusion, is where fluid collects between both the parietal and visceral pleura. It can develop independently or as a result of another parenchymal disease, such as an infection, cancer, or inflammatory diseases. One of the main factors contributing to pulmonary mortality rates is pleural effusion. (1)

There are more than 50 known causes of pleural effusion (PE). (2) Nearly half of instances are caused by congestive heart failure, with pneumonia, pulmonary emboli, and cancer coming in as the next three most common causes. (3)The distribution of the causes, however, primarily depends on the population under investigation. For instance, the prevalence of tuberculous pleural effusion is expected to be constant with respect to the overall number of TB cases (14.3%-19.3%), while the prevalence of pleural effusion among ICU patients is projected to be 22.19+ 17%. Although the microbial epidemiology of parapneumonic effusions varies from pneumonia with such a greater proportion of anaerobic bacteria, the incidence of these effusions is also rising steadily. (4) More than 60% of tuberculous pleural effusions frequently strike people between the ages of 15 and 44. Males experience tuberculous pleural effusions more frequently than females. The gender ratio is roughly 3:2, and developing tuberculous pleural

effusions are frequent in underdeveloped nations where TB infection is ubiquitous. (5)

Chest radiographs are helpful in determining whether an effusion is present. The quantity of effusion affects the effusion findings. It takes at least 200 ml of fluid to completely obliterate the costophrenic angle, often known as the meniscus indication of a pleural effusion, on an upright posteroanterior (PA) view. However, a lateral view can diagnose this indication in 50 ml of fluid. When pleural effusion is suspected, a chest ultrasound is more accurate and helpful. It also aids in thoracentesis planning. Thoracentesis is required in all cases of unilateral effusion in adults to identify the origin of the pleural fluid. (6)

The first step in treating pleural effusion is figuring out if it is exudative or transudative. At least one of Light's criteria—pleural fluid protein divided by serum protein greater than 0.5, pleural fluid lactate dehydrogenase divided by serum LDH greater than 0.6, or pleural fluid LDH greater than two-thirds of the upper limit of normal serum LDH—must be met for an exudative pleural effusion.(7) Transudative pleural effusions, however, are exempt from all of the requirements. (8)Fluid pH, fluid protein, albumin, ADA and LDH, fluid glucose, fluid triglyceride, fluid cell count differential, fluid gramme stain and culture, and fluid cytology are often used assays on the pleural fluid to identify the aetiology.(9)

Local variables that affect the generation and absorption of pleural fluid lead to exudative pleural effusion. Extensive diagnostic testing is necessary to identify the local aetiology of the effusion if the pleural effusion is exudative. In India, malignancy, empyema, parapneumonic effusion, and tuberculosis (TB) are the most typical causes of exudative pleural effusion.

The acute-phase protein known as C-reactive protein (CRP) is primarily produced by the liver's hepatocytes in response to a variety of stimuli, including bacterial infections, inflammation, cancer, and pulmonary emboli. Tillett and Francis made the C-reactive protein (CRP) discovery in 1930. The term "CRP" originated from the discovery of a substance in the serum of patients with acute inflammation that reacted with the pneumococcus capsule's "c" carbohydrate antigen. (10)

An increased C-reactive protein can be caused by many different things. These illnesses might have an infectious or non-infectious genesis, and they encompass both acute and chronic conditions. However, noticeably increased CRP levels are typically related to an infectious cause (an example of pathogen-associated molecular pattern recognition).(9) CRP increases can also be brought on by trauma (alarmin response). About 90% of the time, bacterial infections are linked with extremely high CRP values, greater than 50 mg/dL. CRP has been utilised as a prognostic factor in numerous studies for both acute and chronic diseases, such as hepatitis C (11), dengue (12), and malaria (13).

CRP level measurement is a clinically useful organ disease screening test, severity index, and therapeutic response indicator. Since the CRP in the pleural fluid may be attributed to enhanced blood diffusion as a result of inflammatory capillary leakage, the pleural fluid CRP is likely to represent serum CRP levels.

Justification

Exudative pleural effusions are currently being further evaluated using pleural fluid cell count and differentials, glucose level, adenosine deaminase (ADA), fluid GeneXpert for Mycobacterium tuberculosis (MTb), fluid culture, and cytology. The sensitivity and specificity of the above-mentioned tests, however, cannot be relied upon. Pleural fluid cultures offer unmistakable proof of parapneumonic effusion and empyema, although they are time-consuming and only 60% positive.(14) The false-negative rate for pleural fluid cytology is unusually high. Consequently, a number of novel biomarkers are being investigated to develop a quick and affordable way to distinguish between exudative pleural effusions.

The use of pleural fluid CRP in diagnosing exudative pleural effusion has been the subject of numerous studies undertaken all over the world. However, there are only a few studies with small samples that are available from India, where the typical causes of exudative effusion are different from those in Western nations. Given this, a study was done to determine the effectiveness of pleural fluid CRP

as a biomarker for differentiating between the exudative and transudative pleural effusions.

3. AIMS AND OBJECTIVES

AIM

- To determine the role of pleural fluid C – reactive protein in pleural effusion and its aetiology.

OBJECTIVES

- To determine the role of pleural fluid C – reactive protein in pleural effusion.
- To assess the diagnostic value of pleural fluid C – reactive protein in pleural effusion differentiating exudative from transudative effusion.
- To evaluate the position of CRP in the diagnostic algorithm of pleural effusion.

HYPOTHESIS

- **Null hypothesis**
    - There was no role of CRP in pleural effusion

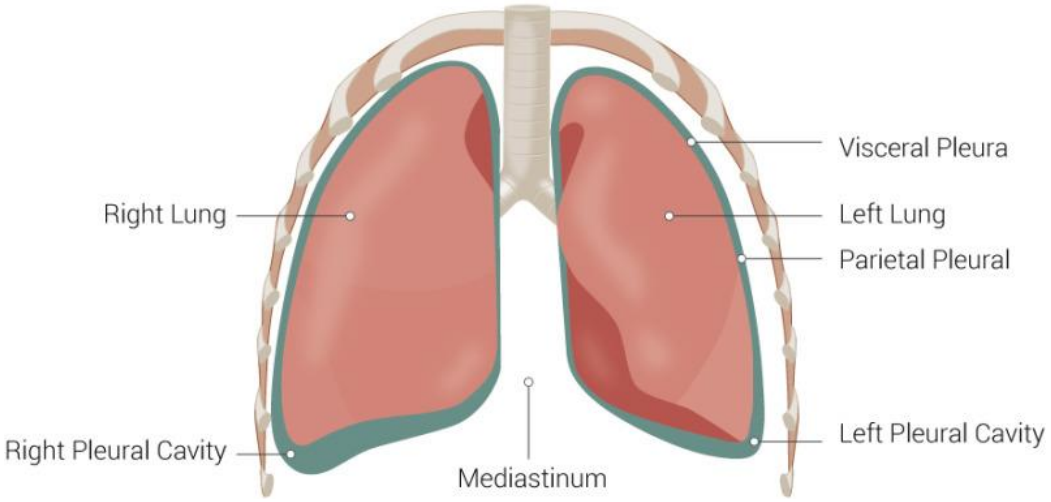
4. REVIEW OF LITERATURE

Literature reviewed and discussed in following headings

- Anatomy and Physiology
- Pleural effusion
- C reactive protein
- Studies representing the diagnostic value of pleural fluid CRP in differentiating exudative from transudative effusion

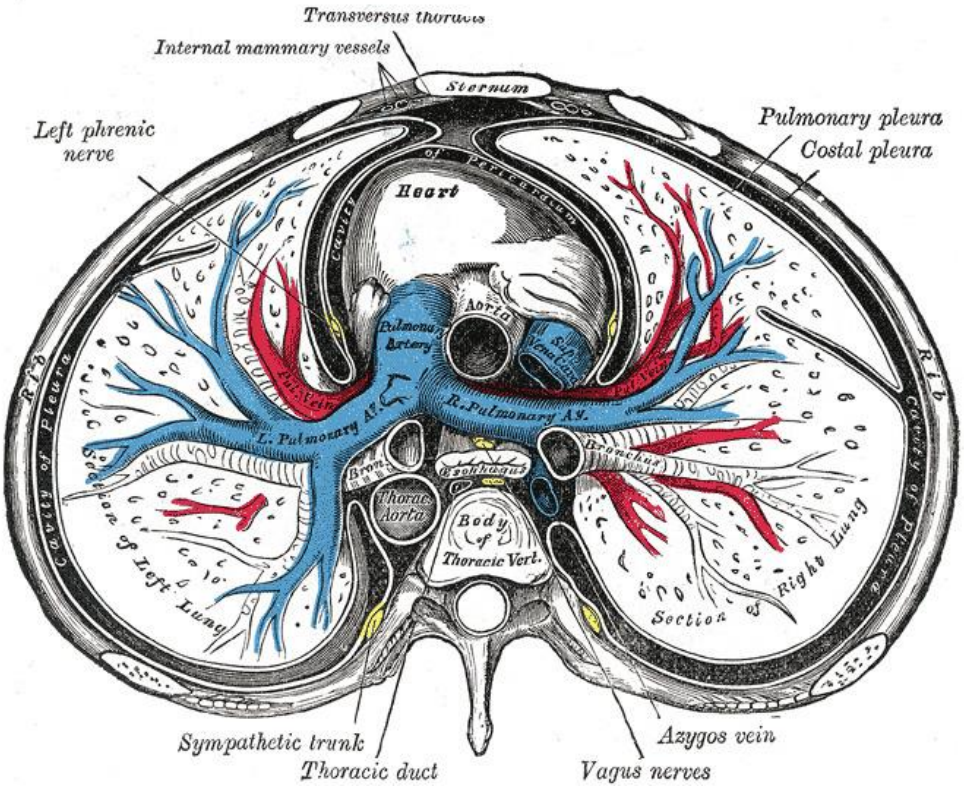
ANATOMY OF PLEURA

A pleura is a serous membrane with two layers of membranous tissue that folded back on itself to produce a pleural sac.(15) The parietal pleura, which connects to the chest wall, is the name of the outer layer. The lungs, blood arteries, nerves, and bronchi are all covered by the inner layer, which is known as the visceral pleura. The right and left pleural cavities are not connected anatomically.



Picture 1: Pleural cavity

The bronchial circulation supplies blood to the visceral pleura, while the intercostal arteries feed blood to the parietal pleura. (16) The diaphragmatic component of the parietal pleura is supplied by the phrenic nerve, whereas the costal and cervical regions are innervated by the intercostal nerve. The only part of the pleura that is capable of feeling pain is the parietal pleura. The visceral pleura lacks sensory innervation and derives its nerve supply from the autonomic nervous system (ANS). (17)



Picture 2: Cross section of pleura

PHYSIOLOGY OF PLEURAL FLUID

Between the parietal and visceral pleura lies a space known as the pleural cavity. There is a minor quantity of serous fluid in the area, and it serves two important purposes. Throughout lung inflation and deflation, the serous fluid constantly hydrates the pleural surface and facilitates their sliding over one another. The visceral and parietal pleura are drawn together by surface tension, which is produced by the serous fluid. Through this mechanism, the thoracic cavity will be able to enlarge during inspiration. The amount of fluid in the pleural cavity in healthy people is roughly 0.3 mL/kg.

Total white blood cell count in normal pleural fluid is 1.716 x 10(3) cells per millilitre (-1). Various cell counts: 75% macrophages, 23% lymphocytes, 1% to 2% of mesothelial cells, 1% of neutrophils, and 0% of eosinophils. It is noteworthy that smokers have slightly higher neutrophil percentages than nonsmokers.(18)

The lymphatic system continuously removes pleural fluid through the stomata in the parietal pleura, while it is also continuously created either by parietal circulation in the form of bulk flow. The pleural space in a healthy person has a small volume (10–20 mL) and a moderate total protein (below 1.5 g/dL).

At the parietal pleural level, a pressure gradient allows pleural fluid to pass from systemic microvessels into the extrapleural interstitium and then into the pleural space. The majority (about 75%) of the pleural cavity drainage is provided by the lymphatics, while little is absorbed through the visceral pleura. The lymphatic vessels emerge as stomata immediately onto the surface of a parietal pleura. Under normal circumstances, there is minimal pleural fluid drainage from the visceral pleura.

As a physiological reaction to the buildup of pleural fluid or even other fluid inside the pleural space, the rate of reabsorption may increase. Before extra fluid starts to build up in the pleural space, the absorption rate can rise by around 40 times the average reference rate. Significant pleural fluid buildup typically

suggests excess pleural fluid production, lymphatic obstruction, or another source of fluid, such as bleeding.

PLEURAL EFFUSION

The pleural cavity, also known as the pleural effusion, is where fluid collects between both the parietal and visceral pleura. It can develop independently or as a result of another parenchymal disease, such as an infection, cancer, or inflammatory diseases. One of the main factors contributing to pulmonary illness and death is pleural effusion. (1)

Pathophysiology

Changes in fluid and solute balance lead to pleural effusions, and the mechanism underlying these changes determines whether the effusion is exudative (increased protein concentration) or transudative (lower protein content). Exudate, which is fluid that seeps around the capillary cells and is brought on by inflammation, and transudate, which is fluid that is forced through the capillary as a result of high intracellular pressure. A transudate effusion leads to an imbalance between both the hydrostatic and oncotic pressure inside the capillaries. An exudative effusion is a change in the local inflammatory elements that cause a buildup of pleural fluid.

The rate of pleural fluid production is higher than the rate of reabsorption, which leads to a formation of fluid in the pleural space. When the maximal lymph

flow is exceeded, exudative effusion develops, which has a larger protein concentration than typical. Exudate develops when the systemic capillaries' enhanced protein permeability leads to a rise in the concentration of pleural liquid protein. Exudative pleural effusions are typically brought on by inflammatory conditions, cancer, granulomatous diseases like tuberculosis or coccidioidomycosis, collagen vascular disorders, and infections like pneumonia.

Hypooncotic fluid (lower protein content) results from an increase in both capillary and mesothelial water permeability, and transudate develops if filtration surpasses the maximal lymph reabsorption through the parietal stomata. Transudative pleural effusions can arise as a result of starvation, cirrhosis, nephrotic syndrome, and congestive heart failure. The final three circumstances are a result of hypoalbuminemia, which lowers colloid oncotic pressure.

Increased capillary permeability brought on by the release of cytokines and inflammatory mediators from the platelet-rich thrombi may be the cause of the localised pleural fluid effusion that is found after a pulmonary embolism.

Symptoms

- Dyspnea
- Chest pain
- Cough

Physical examination

For a physical examination to produce good results, the pleural cavity must contain at least 500 ml of fluid. More than 1500 ml of fluid has been found to accumulate in the pleural space when there is significant tachypnea, significantly reduced chest expansion, absence of tactile fremitus, absence of breath sounds, contralateral tracheal or mediastinal shift (Trail's sign, tracheal deviation), bulging intercostal spaces, and presence of egophony. (19)

Inspection: a predominance of abdominal breathing, asymmetrical chest wall expansion, tracheal shift, intercostal fullness, Trail's sign, scars from prior thoracocentesis or biopsies.

Percussion: Typically, dullness is seen in percussion. The percussion sound has always been described as dull and woody. Direct percussion, which has mostly been displaced by the digitodigital style of percussion, is thought to have been invented by Joseph Leopold Auenbrugger. It is preferred to pound on the sufferer when they are sitting up. Although this specific physical characteristic may be difficult to distinguish in bilateral pleural effusion, Auenbrugger and Forbes claim that dullness is a need for detecting pleural effusion.

Auscultation: On auscultation, there are fewer or no breath sounds. In dry pleurisy, a pleural rub is frequently audible.

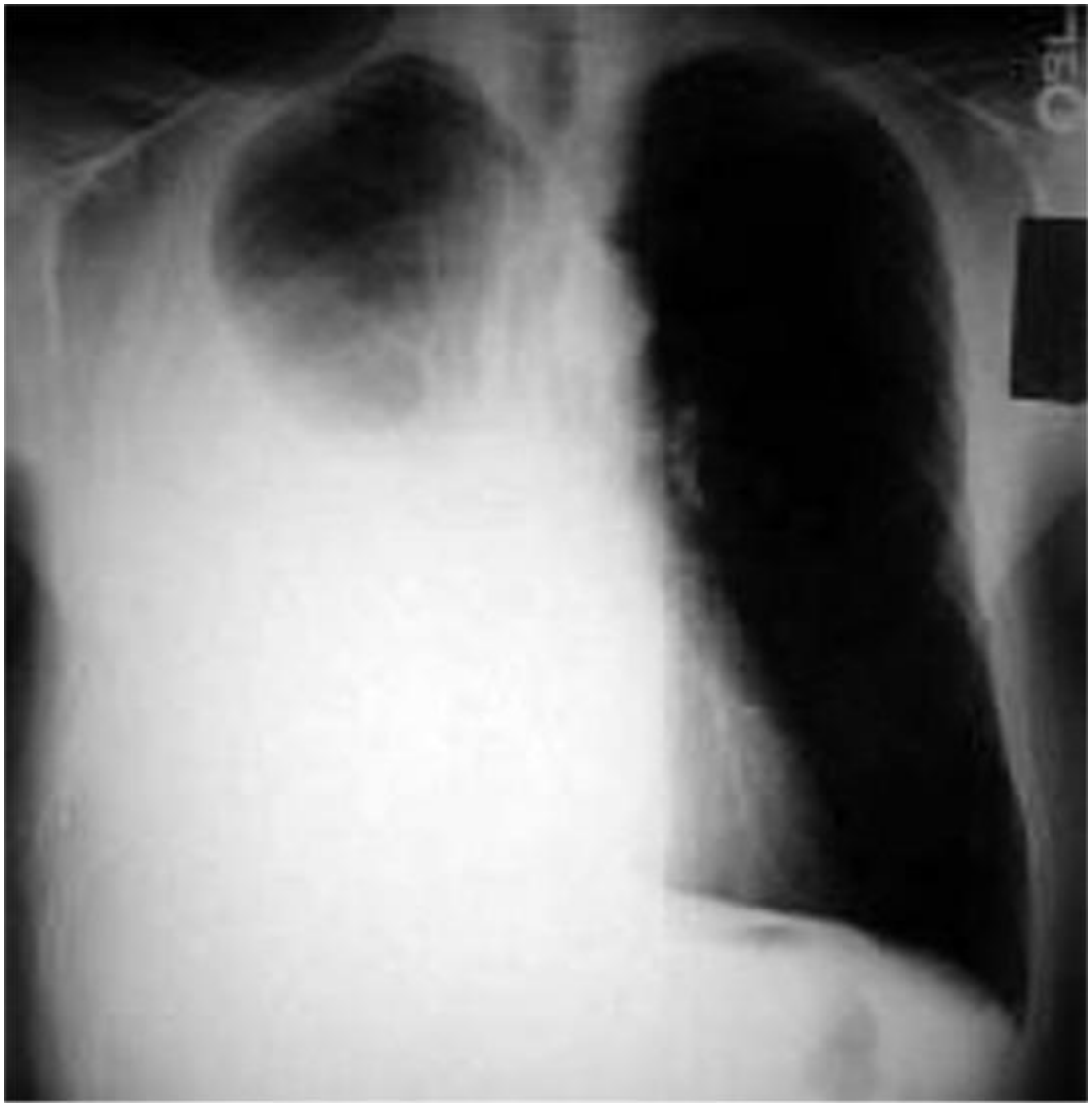
Egophony (E to A change): Voice's tonality shifting from E to A (but not pitch or volume). They typically produce a high-pitched nasal sound that Laennec likened to a goat bleating. It is distinguished by the suddenness and intensity

with which it manifests; it often covers a relatively small area on one side of the chest. Before reaching a definitive diagnosis, make sure the opposite side of the body has not experienced a comparable change in sound. The underlying principle is that as fluid builds up, high-frequency noises are better transmitted and low-frequency sounds are filtered out.

Whispering pectoriloquy: The term "pectoriloquy" refers to the voice's enhanced resonance as it travels into the lungs. When putting a stethoscope and over patient's chest, a whispered sound is audible. Just at the upper border of both the pleural effusion, egophony and whispered pectoriloquy are audible.

Evaluation

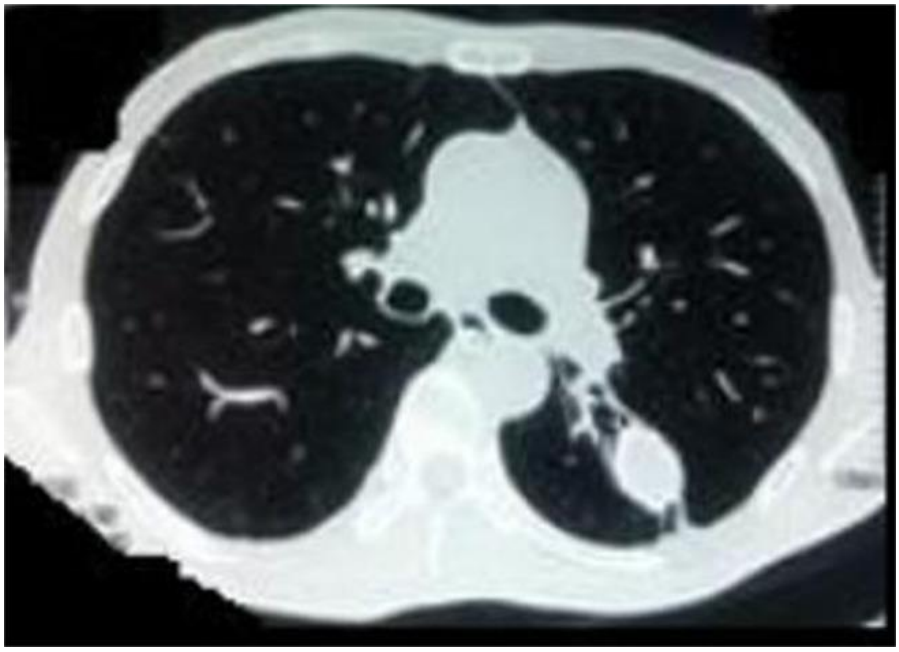
- Plain chest x-ray: Pleural effusion can easily be identified by conventional radiography. These pleural-based densities' uniformity points to pleural fluid loculation.



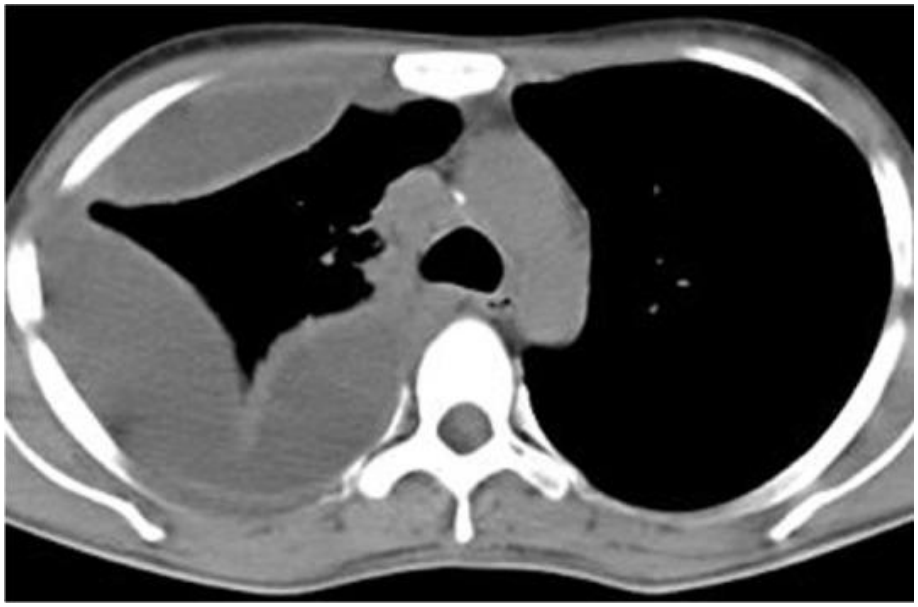
Picture 3: Chest Xray PA view with Ellis S-shaped curve

- Chest ultrasound: Ultrasonography aids in thoracentesis guiding and the detection of free or loculated pleural effusions.
- Chest computed tomography (CT): A CT scan with intravenous contrast is beneficial for people with empyema or loculated effusion. It is easier to see the pleural surfaces and find pleural fluid loculations with radiographic contrast. A split pleura sign—a thickening of the visceral and parietal pleura and a considerable separation of the pleural surfaces—

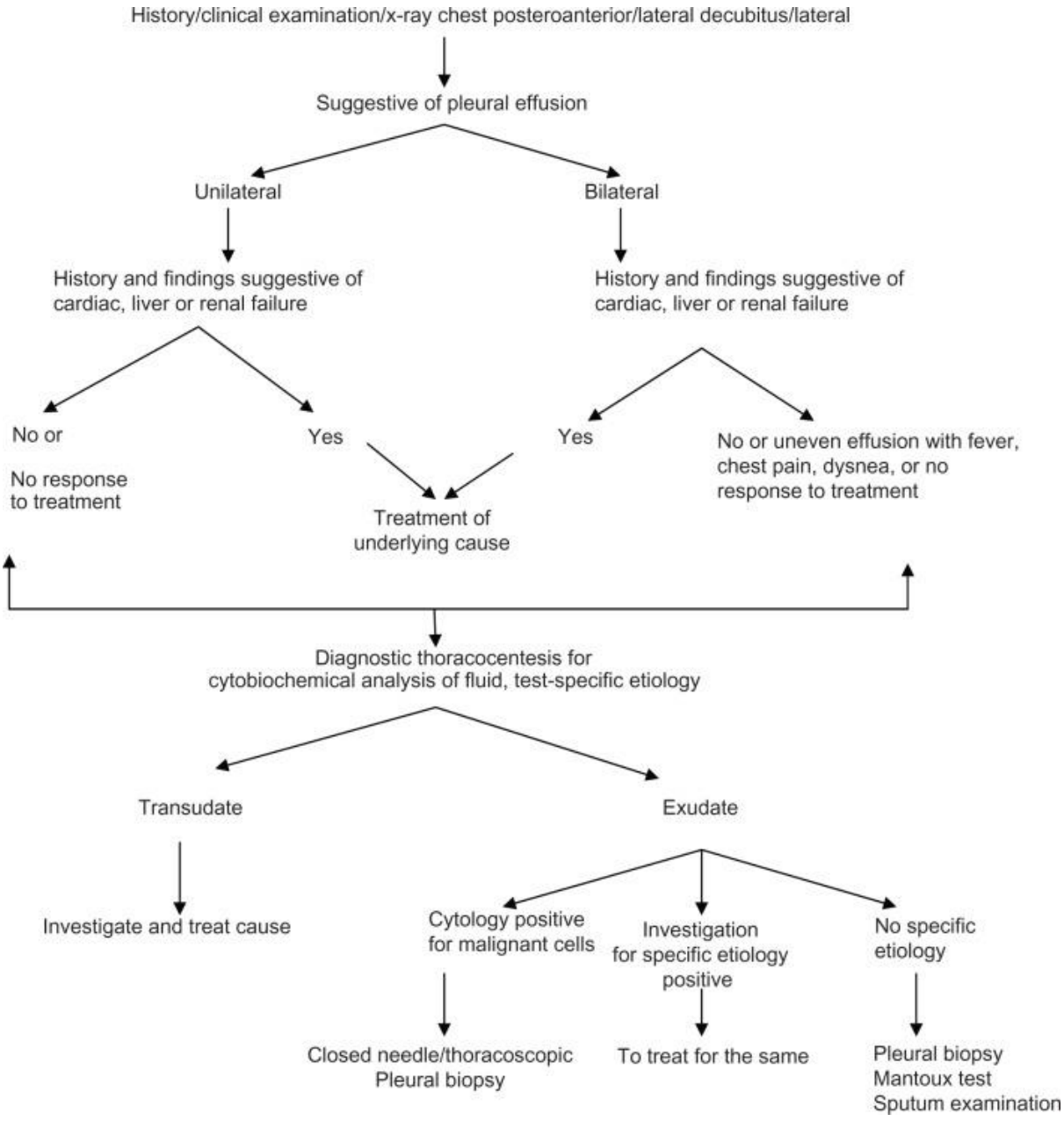
indicates the existence of empyema. Using CT, underlying parenchymal abnormalities can be found.



Picture 4: CT chest - comet tail sign



Picture 5: Contrast-enhanced CT: split pleural sign



Pleural fluid analysis

A treatment called a thoracentesis is used to drain fluid or air from the thoracic cavity for either diagnostic or therapeutic purposes. Thoracentesis is also referred to as needle thoracostomy, pleural tap, needle decompression, and thoracocentesis. Immediately following the delivery of local anaesthetic, a

cannula, or hollow needle, is inserted into the thorax. (20) The pleural space is reached by inserting a needle through the chest wall.(21)

To ensure that pleural aspiration is aseptic, sterile gloves, a sterile environment, skin sterilising solution, and a clean dressing are required. A 21G (green) needle is required for a straightforward diagnostic pleural aspiration. To get a sample, a 50 ml syringe is all that is required. This most frequently takes the form of an intravenous cannula joined to a three-way tap, tubing, and syringe. If needed, an underwater seal can be used for sampling or disposal. (21) Before starting any activity, a thoracic ultrasonography should be performed.

The preferred location for the procedure is on the affected side, either in the posterior midscapular line if the patient is sitting or standing, or in the midaxillary line if the patient is lying on their back. (22)

Directly parallel to the skin, insert the needle, catheter on a syringe, or prefabricated catheter. To progress the catheter through the skin and soft tissue smoothly while using a catheter kit, it may be advantageous to cut a tiny nick in the skin using an 11-blade scalpel. When inserting a needle or catheter, apply negative pressure to the syringe until you feel a decrease of resistance and can get a continuous flow of fluid. To find unauthorised entrance into a vessel or other structure, this is crucial. Put the catheter in the thoracic cavity before the needle. If doing a diagnostic tap, after collecting enough fluid in the syringe for fluid analysis, remove the needle. If not, connect the collecting tube to the stopcock on

the needle or the catheter. Use gravity feed or serial syringe draw with a three-way stop-cock to drain larger amounts of liquids into a plastic drainage bag. Remove the catheter after the desired volume of fluid has been drained and maintain pressure to halt any bleeding from the catheter's insertion site.

Pleural fluid analysis

- Microbiology: Gram stain and culture and sensitivity
- Biochemical tests: total protein, lactate dehydrogenase and glucose.
- Pleural fluid total and differential count

Biomarkers of pleural effusion

Acute decompensated heart failure is characterised by a high PF concentration of the amino-terminal segment of probrain natriuretic peptide (>1500 pg/ml). Three helpful biomarkers—adenosine deaminase, interferon, and interleukin-27—can be used to diagnose tuberculous pleurisy, but only the first is well-established in clinical practise. There are three types of diagnostic PF biomarkers for cancer: soluble protein-based, immunocytochemical, and nucleic acid-based. Carcinoembryonic antigen (CEA), carbohydrate antigen 15-3, and mesothelin are a few examples of soluble indicators that are just suggestive and not conclusive of cancer. (23)

There is little evidence to support the advantage of novel biomarkers of infection over conventional pleural biochemistries in identifying complicated

parapneumonic pleural effusions from uncomplicated parapneumonic pleural effusions (e.g., C-reactive protein, procalcitonin, STREM-1).(24)

PF results	Common causes
Low glucose and/or high LDH	Pleural infection, MPE, rheumatoid effusion, oesophageal rupture, lupus pleuritis and, at times, TPE
High protein levels	Exudative effusion and any aetiology, very high levels are often caused by TB
Very low protein (<15 g/dL)	Dural leak, urinothorax, entrapped lung
Lymphocyte predominance	TPE, lymphoma, post cardiac bypass graft, renal or liver failure, rheumatoid arthritis, rarely PPE
Neutrophil predominance	PPE, early TPE, less commonly due to pulmonary embolism or pancreatitis
Eosinophil predominance	MPE, idiopathic and PPE

Picture 6: Differential diagnosis of pleural fluid results

Light's criteria

According to a study published in 1972 by Dr. Richard Light, it is possible to distinguish between transudative and exudative effusions using biochemical data.

Although the criteria have a lower specificity, making it more likely that a transudate may be mistaken for an exudate than vice versa, any one of them being present indicates an exudative effusion with a 94.7% accuracy. This is crucial so that exudative effusion causes like MPE become less likely to go unnoticed.

Pleural fluid is classified as a transudate or exudate based on modified Light's criteria. **Pleural** fluid is considered an exudative **effusion** if at least one of the criteria is met.

1. **Pleural** fluid protein/serum protein ratio of more than 0.5
2. **Pleural** fluid lactate dehydrogenase (LDH)/serum LDH ratio of more than 0.6
3. **Pleural** fluid LDH is more than two-thirds of the upper limits of normal laboratory value for serum LDH.

Common causes of transudates include illnesses such congestive left heart failure, nephrotic syndrome, liver cirrhosis, hypoalbuminemia causing malnutrition, and the start of peritoneal dialysis that change the hydrostatic or oncotic pressures in the pleural space.

Exudates can be caused by inflammatory diseases such pancreatitis, lupus, and rheumatoid arthritis, cancer, lung infections like pneumonia or TB, and malignancy.

Exudate or transudate pulmonary embolism, drug-induced pleural effusion (e.g., methotrexate, amiodarone, phenytoin, dasatinib, generally exudate), post-radiotherapy esophageal rupture, and ovarian hyperstimulation syndrome (exudate) are a few less frequent causes of pleural effusion.

Tuberculous pleural effusion

Pathogenesis

A number of variables work together to cause fluid to build up in the pleural area as a result of mycobacterium tuberculosis (Mtb) infection. The initial inflammatory response to the antigen leads to an increase in capillary permeability, enabling an influx of proteins, and the protein content within the fluid in contribute effectively a higher rate of pleural fluid formation. (25)The provoking component is the rupture of a subpleural caseous focus, which results in entry of Mtb antigen into to the pleural space. (26)The lymphatic stomata in the parietal pleura are blocked by inflammatory pleuritis, which slows the removal of pleural fluid.(27)

A patient may experience different phases of the cellular component of the inflammatory response. Most frequently, a rapid influx of polymorphonuclear leucocytes, especially neutrophils, characterizes the early response to pleural damage by Mtb. This is followed by the infiltration of macrophages, a protracted immunological response driven by lymphocytes, the release of adenosine deaminase (ADA), and the development of pleural granulomas.(28)

The majority of the lymphocytes are T-helper cells, and the presence of high amounts of gamma interferon (IFN-), interleukin 12 (IL-12), and other related cytokines promotes a T-helper type 1 (Th1) response. Compartmentalization is the word used to describe the fact that the fluid in a tuberculous effusion has a noticeably higher number of Th1 cells than serum or peripheral blood.

The paucibacillary nature of these effusions and low yield on Mtb culture are thought to be caused by the evolution of a strong Th1 response to the Mtb infection, which led to compartmentalization of the pleural fluid and effective containment of Mtb bacilli. This, in part, led to early studies concluding that tuberculous effusions were always delayed hypersensitivity reactions rather than true pleural infection. Evidence that guinea pigs sensitised to a pure protein derivative generated an exudative pleural effusion in response to the delivery of Mtb antigen to the pleural space, which was later inhibited by the administration of anti-lymphocyte serum, provided support for this notion.(29)

Clinical features

Common symptoms of TB effusions include unilateral pleuritic chest discomfort (75%), cough (70%), fever (85%), night sweats (50%), dyspnea (50%), and weight loss (25–85%). TB effusions often appear as acute to subacute diseases. Only moderate symptoms are present in a tiny percentage of people. The HIV-positive group typically exhibits concomitant disseminated TB, lymphadenopathy, and hepatosplenomegaly more commonly, as well as a longer illness duration, milder chest pain, and a greater risk of systemic symptoms like weight loss and night sweats.(30)

Complications

TB empyema

It results from persistent active pleural infection, which causes neutrophil infiltration, the formation of a purulent effusion (that may have loculations), and eventually, widespread pleural thickening and calcification. Occasionally, an infection known as empyema necessitans, which can drain into the skin through fistulae, spreads through the parietal pleura into the chest wall.

Chylothorax

a lipid effusion dominated by triglycerides and chylomicrons

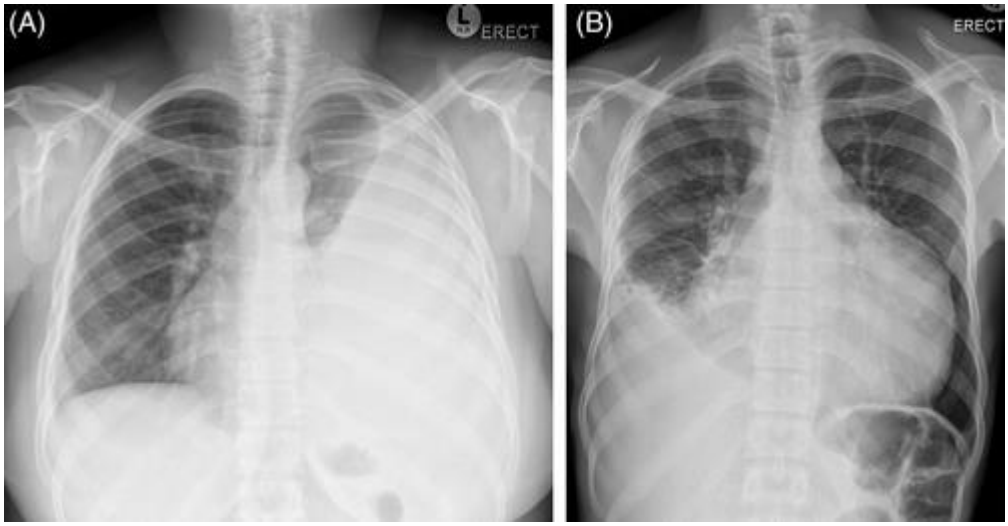
Pseudochylothorax

a lipid effusion with a high concentration of cholesterol

Evaluation

Chest radiography

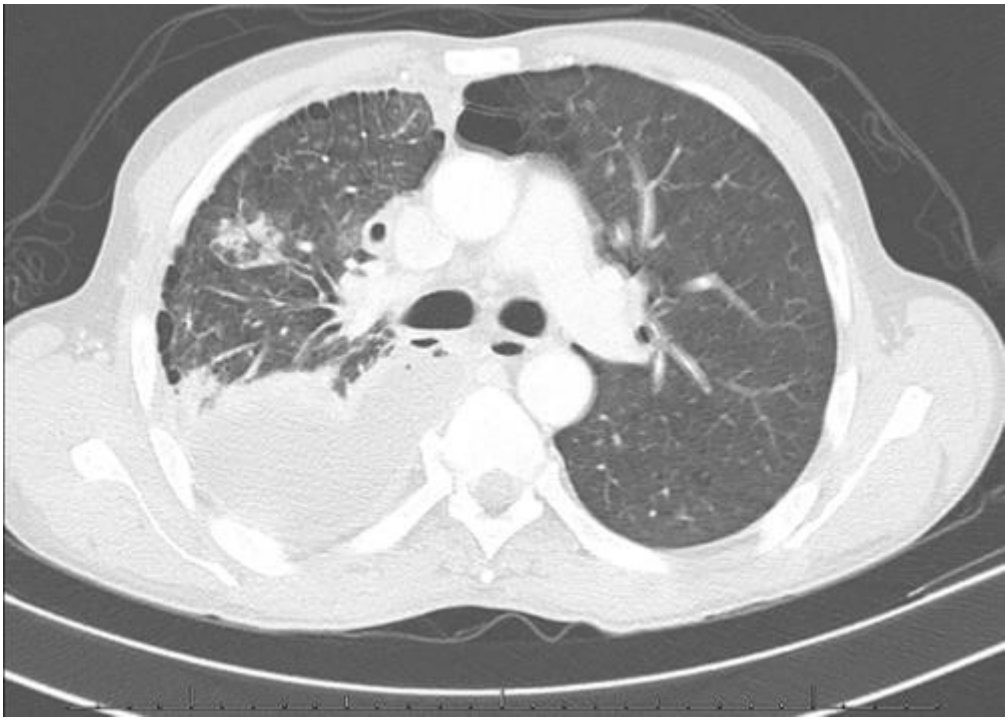
TB effusions frequently occur unilaterally, without favouring one side over the other, and range widely in size. On chest imaging, persistent pleural thickening and lung encasement are two potential long-term consequences.



Picture 7: Uncomplicated pleural effusion - TB

CT tomography

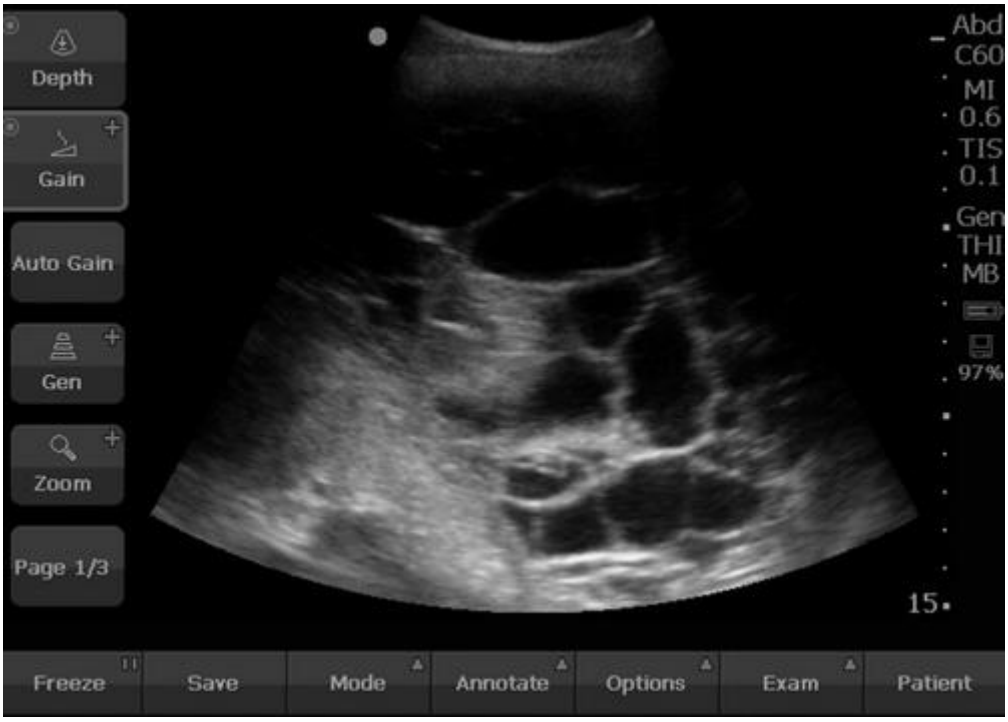
The most prevalent findings were micronodules in the subpleural and peribronchovascular interstitium, and interlobular septal thickening.(31) The pretty standard CT scan of a patient with a TB pleural effusion demonstrates diffuse thickening of both the visceral and parietal pleura, separated by fluid (the "split pleura" sign). (32)



Picture 8: CT Right sided pleural effusion

Transthoracic ultrasound

Transthoracic ultrasonography is largely used to direct investigations and therapies in tuberculous effusions, increasing yield and enhancing safety. Otherwise non-specific ultrasound observations could include free-flowing anechoic effusions, complicated echogenic effusions, and effusions with septations or loculations.(33)



Picture 9: septated effusion secondary to pleural tuberculosis

Malignant pleural effusion

The presence of cancerous cells there in pleural fluid defines a malignant pleural effusion. (34) (35)According to the American Joint Committee on Malignancy TNM staging system, the presence of MPE indicates the systemic spread of cancer and is currently staged as M1a illness.(36) It has been determined that the presence of malignant cells in pleural wash fluid in patients who do not also have a pleural effusion is a sign of micro-metastatic disease and is linked to a greater recurrence risk and shorter life. (37)The tumour may affect the parietal and visceral pleura directly or through blood-borne dissemination. While secondary dissemination from the visceral pleura may affect the parietal pleura, direct seeding has also been seen.

Etiology

An MPE can be produced by almost any malignancy. Lung cancer in males and breast cancer in women are the most frequent etiologies of MPE, together accounting for around 75% of all MPEs. In decreasing order of occurrence, other cancers linked to MPE include lymphoma, ovarian cancer, gastrointestinal cancer, and mesothelioma. Around 7% of cases of these cancers occur in conjunction with an unidentified underlying disease. Paramalignant pleural effusions are pleural effusions that develop in the presence of an underlying cancer but do not show signs of malignancy in the fluid or pleural surface. These effusions may develop as a result of systemic or localised tumour effects, side effects of cancer treatment, or concomitant nonmalignant illness. (38) (39)

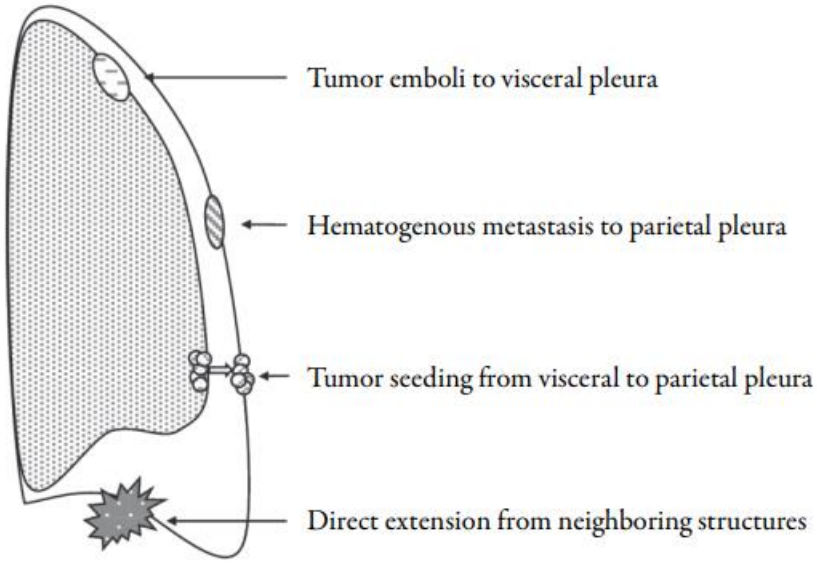
Pathophysiology

A disruption of the Starling forces, which control and direct fluid biomechanics in the pleural space, is thought to be the pathogenesis.

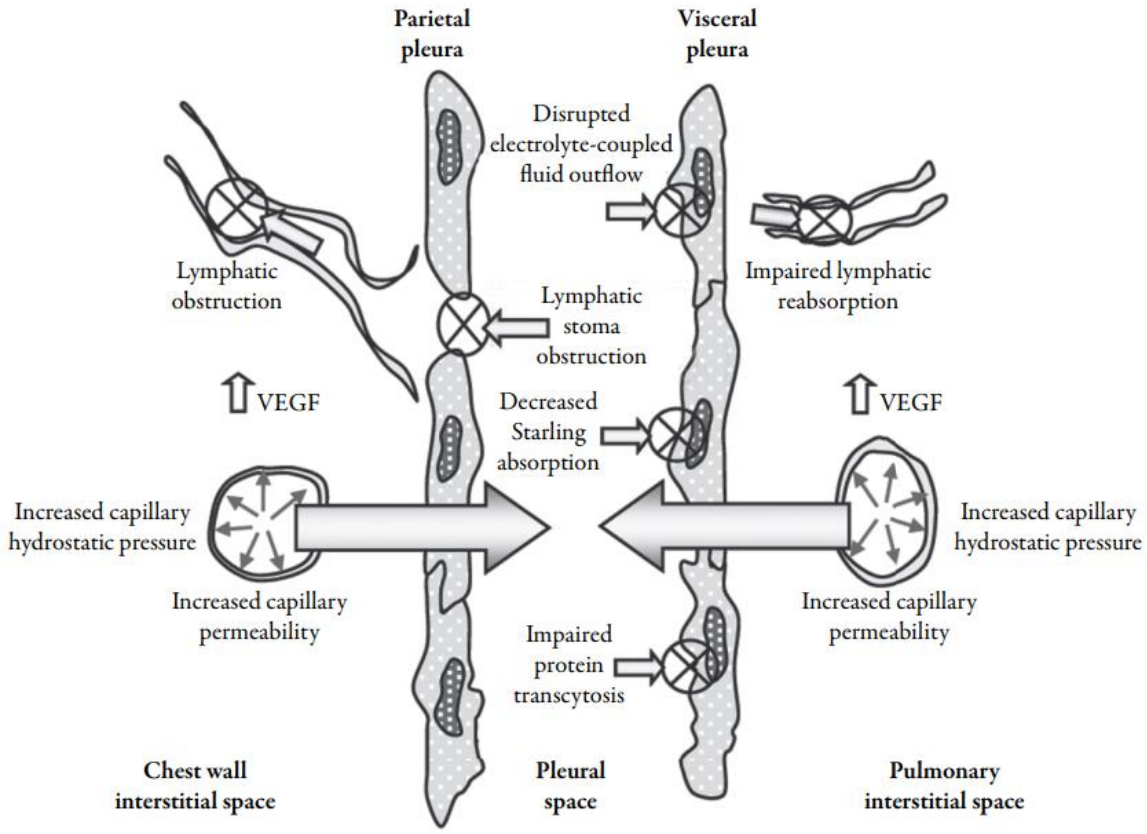
Lymphatic veins in the parietal pleura control absorption, whereas pleural fluid production is controlled by the difference in hydrostatic and oncotic pressure between both the pulmonary circulation and pleural space.

A blockage of the stomata inside the parietal pleura or metastatic involvement of the hilar and mediastinal lymph nodes has been hypothesised as the cause of

the failure to drain its fluid from the pleural space, which may result in an accumulation of extra fluid.



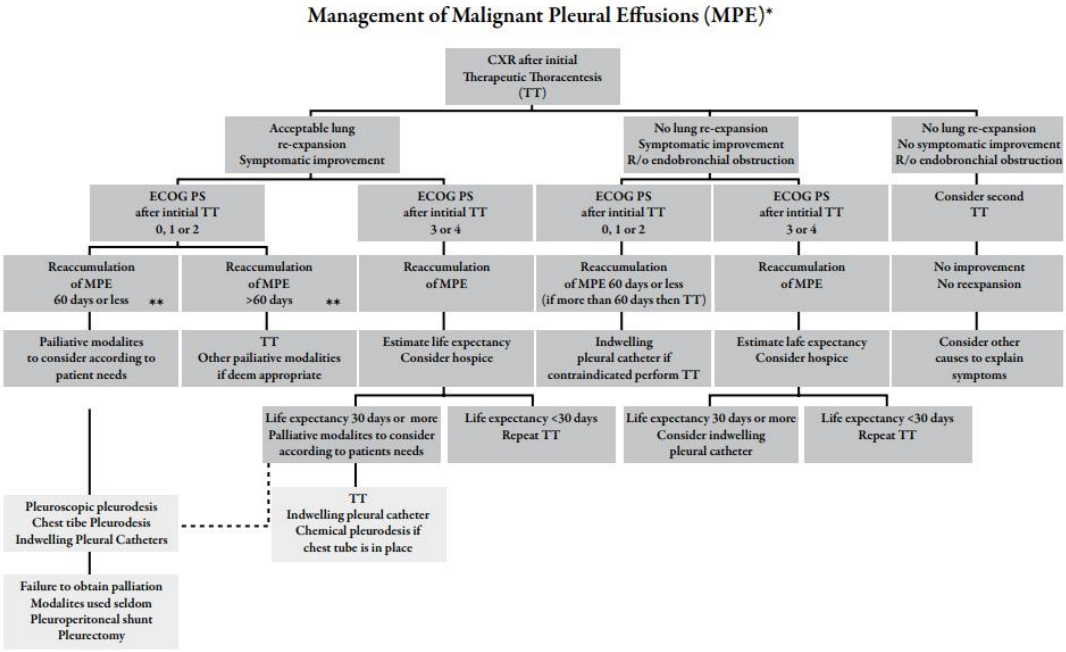
Picture 10: Pleural involvement in malignancy



Picture 11: Mechanisms of impaired transpleural flow resulting in accumulation of fluid(40)

The close proximity of microvessels to the pleural surface as well as the existence of stomata located between mesothelial cells are two characteristics of the human parietal pleura that explain its function in the creation and elimination of pleural liquid and protein in normal condition. Pleural fluid must be produced more often because of greater hydrostatic pressure, reduced oncotic or pleural pressure, enhanced microvascular permeability, or peritoneal-pleural movements for it to accumulate in disease. The rate of development must outpace lymphatic clearance, which could be hindered by malignant infiltration or slowed down by hydrostatic factors. (41)

Management



Parapneumonic effusion

An ipsilateral lung infection, most commonly pneumonia, is referred to as a parapneumonic effusion when there is an accumulation of exudative pleural fluid. The majority of bacterial infections are linked to pneumonic effusions. (42)

complicated parapneumonic effusions brought on by bacterial pleural invasion. Pleural fluid has a pH below 7.20 and there is a lowered glucose level in this kind of parapneumonic effusion. Fluid from difficult parapneumonic effusions does not grow in cultures, which may be due to quick bacterial clearance from the pleural space or a low bacterial concentration. The fluid is referred to as complex since a solution requires drainage.

Exudative, neutrophilic parapneumonic effusions that are not complicated. Gram stain and culture results are negative, the pH is over 7.20, and the glucose level is above 60 mg/dl.(43)

When there is open pus in the pleural space or Gram stain or a positive culture show that the pleural fluid is infected with bacteria, this condition is known as empyema thoracis. (44)

Stages

Exudative stage: In this stage, proinflammatory cytokines like interleukin 8 (IL-8) and tumour necrosis factor-alpha cause increased capillary permeability, which leads to an accumulation of fluid in the pleural space (TNF-a). In this early stage, neutrophils typically predominate in the clear exudative fluid that makes up the pleural fluid. At this stage, the pleural fluid is a straightforward parapneumonic effusion, which typically goes away on its own once pneumonia has been adequately treated with antibiotics. This stage follows the development of pneumonia by 2 to 5 days.

If proper care is not given, the fibrinopurulent stage may occur. In this stage, the pleural cavity develops fluid loculations as a result of the deposition of fibrin clots and fibrin membranes. This stage takes roughly 5 to 10 days following pneumonia onset.

Fibrin membranes are transformed into a thick, non-elastic pleural peel during the organising stage, which causes the trapped lung to have restrictive respiratory dysfunction. It might take this stage two to three week to develop.

Evaluation

- Plain chest x-ray: Pleural effusion can easily be identified by conventional radiography. These pleural-based densities' uniformity points to pleural fluid loculation.
- Chest ultrasound: Ultrasonography aids in thoracentesis guiding and the detection of free or loculated pleural effusions.
- Chest computed tomography (CT): A CT scan with intravenous contrast is beneficial for people with empyema or loculated effusion. It is easier to see the pleural surfaces and find pleural fluid loculations with radiographic contrast. A split pleura sign—a thickening of the visceral and parietal pleura and a considerable separation of the pleural surfaces—indicates the existence of empyema. Using CT, underlying parenchymal abnormalities can be found.

Special scenarios

Trapped lung

The term "trapped lung" is used to define an advanced stage of lung pathogenesis in a patient who has previously had of malignant pleural effusion.

This stage is characterised by the lung's inability to fully expand, the visceral pleura's failure to attach to the parietal pleura, and the persistence of a hollow cavity. (45)

Persistent air leaks

After an ultrasound-guided thoracentesis, there is a minor (3 to 4 percent) however significant risk of developing a pneumothorax.(46) A tiny percentage of people who experience pneumothorax will need to have a chest tube inserted. A buildup of air bubbles inside the drainage bag attached towards the chest drain indicates the presence of an air leak. An air leak is deemed persistent if it continues for more than five to seven days after a chest tube has been inserted. The underlying cause could be a bronchopleural fistula or alveolar pleural fistulous connection between both the sterile pleural space and the tracheobronchial tree. (47)

Septated Pleural Effusion

Fluids from an effusion that are fibrin-rich can cause pockets to form. (48)

Malignant Eosinophilic Pleural effusion

MEPE is characterised by the presence of exudative effusion and histological confirmation of malignancy, as well as by the presence of more than 10% of eosinophils inside the differential white blood cell counts during the initial thoracentesis. (49)

Hemorrhagic malignant Pleural Effusion

This happens between 47% and 50% of the time. A significant degree of dyspnea, a greater frequency of chest discomfort, a decline in general physical health, the presence of a substantial effusion, and thickening due to a parietal pleural effusion are typical symptoms of HMPE. (50)

C REACTIVE PROTEIN

The liver produces CRP, a pentameric protein whose concentration increases in the presence of inflammation. CRP is an acute-phase reactant protein which is mainly activated by the action of IL-6 on the gene in charge of CRP transcription during in the acute phase of an inflammatory or viral event. Tillett and Francis made the discovery of C-reactive protein (CRP) in 1930.(51) Because it was initially discovered to be a substance in the blood of patients suffering from acute inflammation that responded with "c" carbohydrate antigen of the pneumococcus capsule, the name CRP was born. (10)

Both pro- and anti-inflammatory effects can be attributed to CRP. By interacting with phosphocholine, phospholipids, histone, chromatin, and fibronectin, it aids in the detection and removal of invading infections and injured cells. To speed up the elimination of cellular debris, injured or apoptotic cells, and foreign pathogens, it can activate the traditional complement pathway as well as phagocytic cells via Fc receptors. (52)

An increased C-reactive protein can be caused by many different things. These illnesses might have an infectious or non-infectious genesis, and they encompass both acute and chronic conditions. However, noticeably increased CRP levels are typically related to an infected cause (an example of pathogen-associated molecular pattern recognition). CRP increases can also be brought on by trauma (alarmin response). Smaller elevations are (53) linked to a wider range of etiologies, from periodontal disease to sleep disorders.

Serum level CRP

- 0.3 mg/dL or less: Normal (level seen in most healthy adults).
- Normal or slight rise between 0.3 and 1.0 mg/dL (can be seen in obesity, pregnancy, depression, diabetes, common cold, gingivitis, periodontitis, sedentary lifestyle, cigarette smoking, and genetic polymorphisms).
- Moderate elevation, between 1.0 and 10.0 mg/dL (Systemic inflammation such as RA, SLE, or other autoimmune diseases, malignancies, myocardial infarction, pancreatitis, bronchitis).
- Greater than 10.0 mg/dL: Significant rise (Acute bacterial infections, viral infections, systemic vasculitis, major trauma).
- 50.0 mg/dL or more: severe elevation (Acute bacterial infections).

CRP and Pleural effusion

CRP plays an important part in the evaluation of pneumonia since it is elevated in the serum and plasma of individuals with pneumonia.

In order to distinguish exudates from transudates and to distinguish PPEs from other exudates, such as those related to neoplastic conditions, higher pleural effusion CRP levels may offer a valuable, quick, practical, and accurate technique. (54)

Recent research has suggested that pleural CRP is a more sensitive and specific biomarker than serum CRP for the differential diagnosis of pleural effusions. Due to its 1000-fold increase in response to infection and the favourable association between serum and pleural CRP levels, CRP can be regarded as a good option. The local pleural cells' production of IL-6 and TNF initiates the stimulation of CRP synthesis in the liver. Because the existence of CRP in the pleural fluid may be caused by enhanced migration from the blood as a result of inflammatory capillary leaks, the pleural fluid CRP levels are most likely to match the serum levels. Additionally, a number of studies demonstrated that circulating CRP may "leak" into the pleural cavity, and elevated pleural CRP may serve as a potential biomarker for pleural infection.

STUDIES REPRESENTING THE DIAGNOSTIC VALUE OF PLEURAL FLUID CRP IN DIFFERENTIATING EXUDATIVE FROM TRANSUDATIVE EFFUSION

The Chinese meta-analysis by Li D et al(55) includes 18 publications. The following estimations provide a summary of the diagnostic performance of pleural CRP for PPE (parapneumonic effusion): sensitivity (0.80), specificity

(0.82), PLR (4.51), NLR (0.25), DOR (18.26), and AUC (0.88). The diagnostic accuracy of serum CRP in PPE was 0.79. The following diagnostic indicators for pleural CRP were used to distinguish between complicated PPE (CPPE) and uncomplicated PPE: sensitivity (0.65), specificity (0.85), PLR (4.26), NLR (0.41), DOR (10.38), and AUC (0.83). Serum and pleural CRP both contribute to the diagnosis of PPE, albeit only slightly. Pleural CRP levels can also help distinguish between CPPE and straightforward PPE. However, additional biomarker testing should be used to evaluate the CRP assay results.

Angeles RR et al(56) meta-analysis found that Nine data points were combined to generate an SROC including an AUC of 0.91. We determined an ideal cut-off of 21.9 mg/dL, with either a sensitivity of 0.91 (0.73 to 0.98) or a specificity of 0.82 (results above the cut-off are classed as TPE) (0.7 to 0.9). A test for separating TPE (Tuberculous pleural effusion) from MPE (Malignant pleural effusion) that is reasonably accurate is the p-CRP determination.

Turay UY et al in a study at Turkey found that Sixteen individuals were included in transudate group and 81 patients in the exudate group based on the light criteria utilised. Pleural fluid CRP levels and the ratio of pleural fluid to serum were both substantially lower in the transudate group (P=0.009) than in the exudate group, which included 35 patients with neoplastic effusions, 10 patients with chronic non-specific pleurisy, 19 patients with tuberculous pleurisy, 16 patients with parapneumonic effusion, and one patient with Dressler syndrome.

The CRP levels in the parapneumonic effusion subgroup (mean 89 +/- 16.3) were significantly higher than those in the other subgroups, other exudate of neoplastic effusion, tuberculous pleurisy, chronic non-specific effusion, and the transudate group (P0.0001; P0.0001; P0.0004 and P0.0001, respectively) when these subgroups were compared. In the parapneumonic effusion grouping compared to the neoplastic sample, the ratio between pleural fluid and serum CRP was substantially greater (P0.0002; 6.6 +/- 2.7 and 1 +/- 0.2, respectively). A high sensitivity (93.7%), specificity (76.5%), and positive predictive value of 98.4% were observed for pleural fluid CRP levels > 30 mg.

Rismantab et al(57) in a research stated that According to Light's criteria, 61 patients (36.1%) and 108 patients (63.9%) had exudative pleural effusion and transudative pleural effusion, respectively. Participants with in exudative and transudative categories had CRP levels in their pleural fluid that were, respectively, 13.3±37.1 and 3.5±4.3mg/dl (p=0.008). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the 3.31 mg/dl cut-off point of CRP level for pleural effusion were 96.3%, 72.1%, 86%, and 91.7%, respectively. According to the findings of this study, it may be possible to distinguish between exudative and transudative pleural effusions based on the concentration of CRP in the effusion fluid.

Basso et al(58) study at Italy described that the sensitivity of CRP was 92.5% and specificity was 71.9%.

Chierakal N et al(59) study found that 148 patients had lymphocytic exudative pleural effusions; of them, 60 had MPE (malignant pleural effusion), 55 had TBP (tuberculous pleuritis), and 33 had non-specific pleuritis. Compared to the MPE group, the TBP group's pleural fluid and serum CRP levels were considerably higher (54.58± 4.50 mg/L and 106.93±9.54 mg/L vs. 12.66±3.52 mg/L and 49.66±8.84 mg/L, respectively, P 0.001). In comparison to the MPE group, the TBP group had a considerably greater ratio of pleural fluid to serum CRP. The optimal cut-off value of ≥30 mg/dL for pleural fluid CRP used to have a sensitivity of 72% with 93% specificity, while the cut-off value of 0.45 for the ratio of pleural fluid to serum CRP had a sensitivity of 60% and 89% specificity.

Chen S C et al(54) study found that In comparison to UPPE [uncomplicated parapneumonic effusion] (3.9 mg/dl), pleural CRP was considerably greater in CPPE [complicated parapneumonic effusion] (11.6 mg/dl) and empyema (12.2 mg/dl). Sensitivity, specificity, and area under the receiver-operating characteristic curve (AUC) for the diagnosis of CPPE and empyema with a cutoff value for pleural CRP of 8.7 mg/dl were 0.80, 0.97, and 0.94, respectively.

Elsammak M et al(60) study found that In comparison to patients with malignant or transudative effusion, those with tuberculous effusion exhibited significantly greater serum CRP effusion and effusion/serum ratios of CRP.

Izhakian S et al(61) study found that with the following means for the four groups, the pleural CRP levels significantly distinguished them (p 0.001):

parapneumonic effusion, 5.38±4.85 mg/dL; lung transplant, 2.77±2.66 mg/dL; malignancy, 1.19±1.51 mg/dL; and heart failure, 0.57±0.81 mg/dL. The cut-off value for pleural fluid CRP to distinguish parapneumonic effusions from the other 3 groups was 1.38 mg/dL. 84.2%, 71.5%, 37%, and 95%, respectively, were the sensitivity, specificity, positive predictive value, and negative predictive value. Pleural effusion Parapneumonic effusions can be distinguished from other exudative effusions using CRP levels. A pleural effusion from congestive heart failure is likely to be indicated by CRP values below 0.64 mg/dL, while levels above 1.38 mg/dL are suggestive of an infectious origin.

Makwana et al(62) study found that CRP levels in pleural fluid varied significantly between groups in our study (p 0.001). In comparison to tuberculous and malignant effusions, pleural fluid CRP was considerably higher in the groups with empyema and parapneumonic effusions. The ideal cut-off value for distinguishing between parapneumonic effusion and tuberculous effusion was CRP 47.4 mg/dl, which produced 87.5% sensitivity and 92.5% specificity. Pleural fluid CRP was found to be a highly accurate marker for identifying malignancy in parapneumonic effusion (cut-off value 49.2 mg/dl, 75% sensitivity, and 85.7% specificity) and parapneumonic plus empyema in tuberculous effusion plus malignant effusion (cut-off value 47.4 mg/dl, 84.6% sensitivity, and 90.8% specificity). CRP levels in pleural fluid can be used as an extra tool in the

exudative effusion differential diagnosis. It notably distinguishes tuberculous and malignant effusions from parapneumonic effusions and empyema.

Rismantab et al(57) found 169 participants with pleural effusion signed up for the research in total. According to Light's criteria, 61 patients (36.1%) and 108 patients (63.9%) had exudative pleural effusion and transudative pleural effusion, respectively. Patients in the exudative and transudative groups had CRP levels in their pleural fluid that were, respectively, 13.3±37.1 and 3.5±4.3mg/dl (p=0.008). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the 3.31 mg/dl cut-off point of CRP level for pleural effusion were 96.3%, 72.1%, 86%, and 91.7%, respectively. According to the findings of our investigation, it may be possible to distinguish between exudative and transudative pleural effusions based on the concentration of CRP in the effusion fluid.

Mohammed et al(63) in a study found that In TBPE and MPE, respectively, the mean values of p-CRP were 36.51 3.91 and 26.39 7.57 mg/dl, with a strongly significant difference (P=0.001). Sensitivity and specificity reached 89.47 and 80.00% for p-CRP and 15.79 and 100.00%, correspondingly, for s-CRP when cutoff values of 31.6 and 43.3 mg/l were used. The p-area CRP's under the receiver operating characteristic curve was 0.888, outperforming the s- CRP's (0.525). The diagnostic process for individuals with pleural effusion benefits

greatly by the assessment of CRP levels with in pleural fluid. A helpful supplementary test that may help distinguish between MPE and TBPE is p-CRP.

Gabhale et al(64) research stated that The malignant group's pleural fluid CRP level was significantly lower than that of the infectious parapneumonic group, followed by the chronic non-specific inflammatory group and tubercular patients. For the distinction between tubercular and non-tubercular effusions, ROC analysis of pleural fluid CRP shown good sensitivity (97.05%), specificity (71.76%), NPV of 95.31%, and PPV of 80.48%. At a cutoff level of 90.8 mg/l, sensitivity, specificity, NPV, and PPV of CRP for pleural effusion distinction between parapneumonic and non-parapneumonic conditions (tubercular, chronic non-specific inflammation, malignant, and others) were all 100%. It offers the biggest Area under Curve, which is 1.000. When employed as a diagnostic tool, pleural fluid CRP can help distinguish between acute and chronic inflammation as well as between infectious and non-infectious inflammation. A CRP result of more than 30 mg/l virtually completely rules out malignancy. With great sensitivity and adequate specificity, pleural fluid CRP can be employed as a diagnostic biomarker for the differential diagnosis of parapneumonic pleural effusion.

5. MATERIAL AND METHODS

5.1 Study Design:

- Prospective observational study

5.2 Study Area:

- Department of General Medicine, Govt Kilpauk Medical College.Royapettah Hospital – tertiary care centres

5.3 Study Duration:

- Six months (April 2022 - November 2022)

5.4 Study Population:

- Patients aged more than eighteen years with Pleural effusion

5.5 Inclusion Criteria:

- Aged more than eighteen years
- Both gender
- All cases of pleural effusion irrespective of etiology with radiological evidence for diagnostic thoracocentesis.

- Participants willing to give consent for participation in this study.

5.6 Exclusion Criteria:

- Pregnant and lactating women
- Mentally ill who were unable to give consent
- Rib fractures
- Conditions contraindicated for performing a diagnostic thoracocentesis
- Participants not willing to give consent.

5.7 Sampling Technique:

- Simple random sampling

5.8 Sample Size:

- Sample size was calculated by using the formula

$$n = \frac{Z^2{}_{1-\alpha/2}\ S^2}{L^2}$$

n = required sample size

S = Standard deviation (the average pleural fluid CRP of the exudative group was 42 ±19.07 mg/L based on Pankaj K et al(65) study)

L = absolute precision (4%)

80% power and 95% confidence interval

The sample size was estimated to be 88.

5.9 Study Instruments:

- A semi structured questionnaire
- Stethoscope
- Manual sphygmomanometer
- Thermometer
- Pleural fluid aspiration needle

5.10 Operational Definition:

- Pleural effusion
    - The pleural cavity, also known as the pleural effusion, is where fluid collects between the parietal and visceral pleura.(1)
- C reactive protein
    - The liver produces CRP, a pentameric protein whose concentration increases during response to inflammation. CRP seems to be an acute-phase reactant protein that is mainly activated by the action of

IL-6 on the gene in charge of CRP transcription as during acute phase of an inflammatory or viral event.(10)

5.11 Data Collection:

- After obtaining informed written consent, data was gathered from participants using an interview method and a semi-structured questionnaire based on inclusion criteria. The baseline demographics, clinical and laboratory parameters were recorded, and they were subjected to diagnostic thoracocentesis. The pleural fluid was withdrawn and sent for analysis.

5.12 Measurement of Variables:

- Dependent variable
    - C reactive protein was measured as a continuous variable
- Independent variable
    - Age was a continuous variable expressed in numbers
    - Gender was a categorical variable (male/female)
    - BMI was measured as a continuous variable
    - Symptoms was included as categorical variable

- Laboratory values like hemoglobin, total count, platelet count. ESR, LDH and serum protein were measured.
- Sputum – gram staining, AFB and culture & sensitivity results included as continuous variable.
- Pleural fluid biomarkers glucose, protein, LDH, ADA, pleural fluid protein ratio, pleural fluid LDH ratio and CRP were recorded.
- Pleural effusion - gram staining, AFB and culture & sensitivity results included as continuous variable.
- Type of pleural effusion was included as categorical variable based on Light criteria. (exudative/transudative)
- Diagnosis were included as categorical variable.

5.13 Data Analysis:

- Data was entered in Microsoft excel 2019 and analysed by SPSS (Statistical Package of Social Sciences) version 21. The variables were analysed by using descriptive and inferential statistics.
- The data of continuous variables obeying normal distribution and nonnormal distribution were represented by "mean ± standard deviation (x ± s)" and "median (lower quartile, upper quartile) (M (P25p75)), respectively. Continuous variables that obey normal distribution were

tested by t-test, and continuous variables that do not obey normal distribution are tested by nonparametric rank sum test (Wilcoxon).

- The categorical variables were expressed by percentage and the chi-squared test was used for comparison between groups. All the statistics were tested by a two-sided test, with a p-value less than 0.05 considered to be statistically significant. All confidence intervals (CI) were set to 95%.

5.14 Ethical Issues:

- The study protocol was presented to the Institutional ethics board for the permit of the study
- Informed oral consent was obtained from the participants before the start of the study.

6. RESULTS

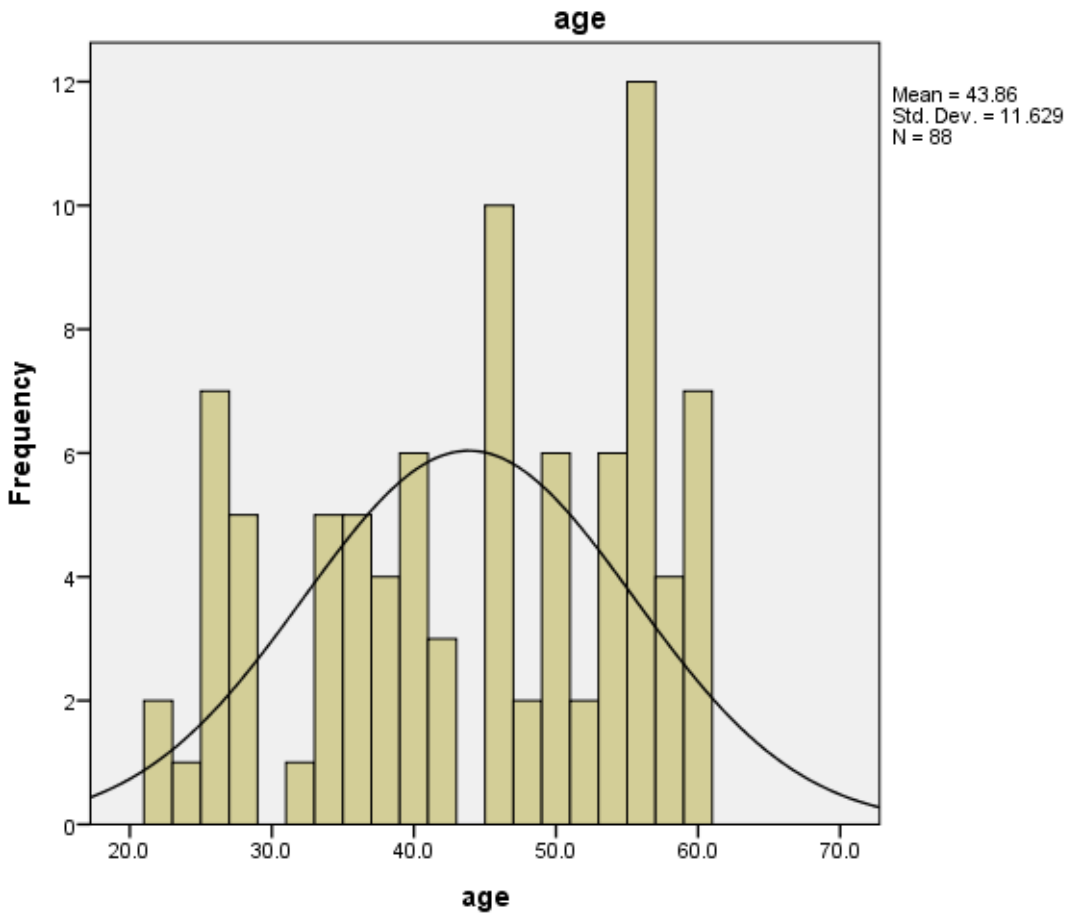
This study was conducted among 88 patients with pleural effusion to determine the role of CRP in PE.

DESCRIPTIVE STATISTICS

BASELINE CHARACTERISTICS OF THE PARTICIPANTS:

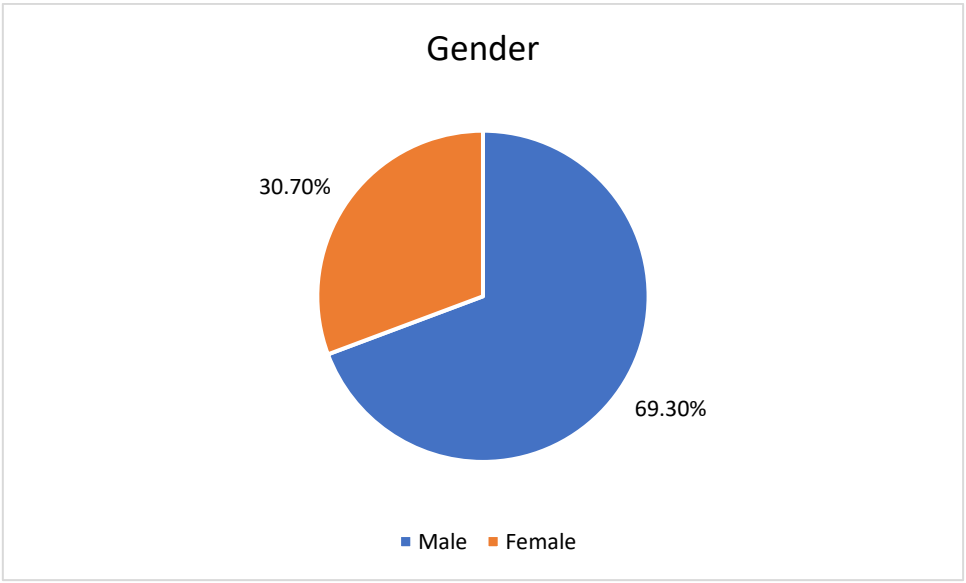
Age

The mean age of participants was 43.864±11.628 years ranging from 22 – 60 years.



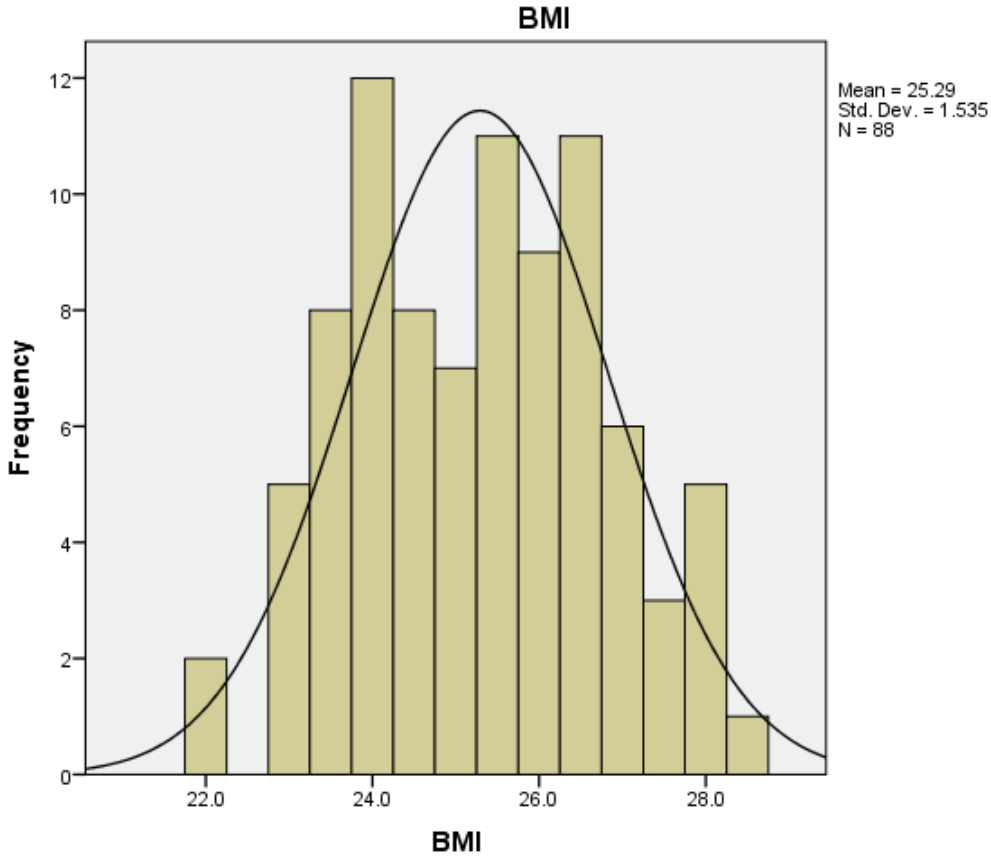
Gender

69.3% of participants were males. Male and female ratio was 2:1



BMI

The mean BMI of participants was 25.29±1.534 ranging from 22 – 28.6.



Clinical profile

Symptoms

The common presentation of participants was cough (48.9%), sputum (48.9%), hemoptysis (5.7%), fever (46.6%) and loss of weight (20.5%).

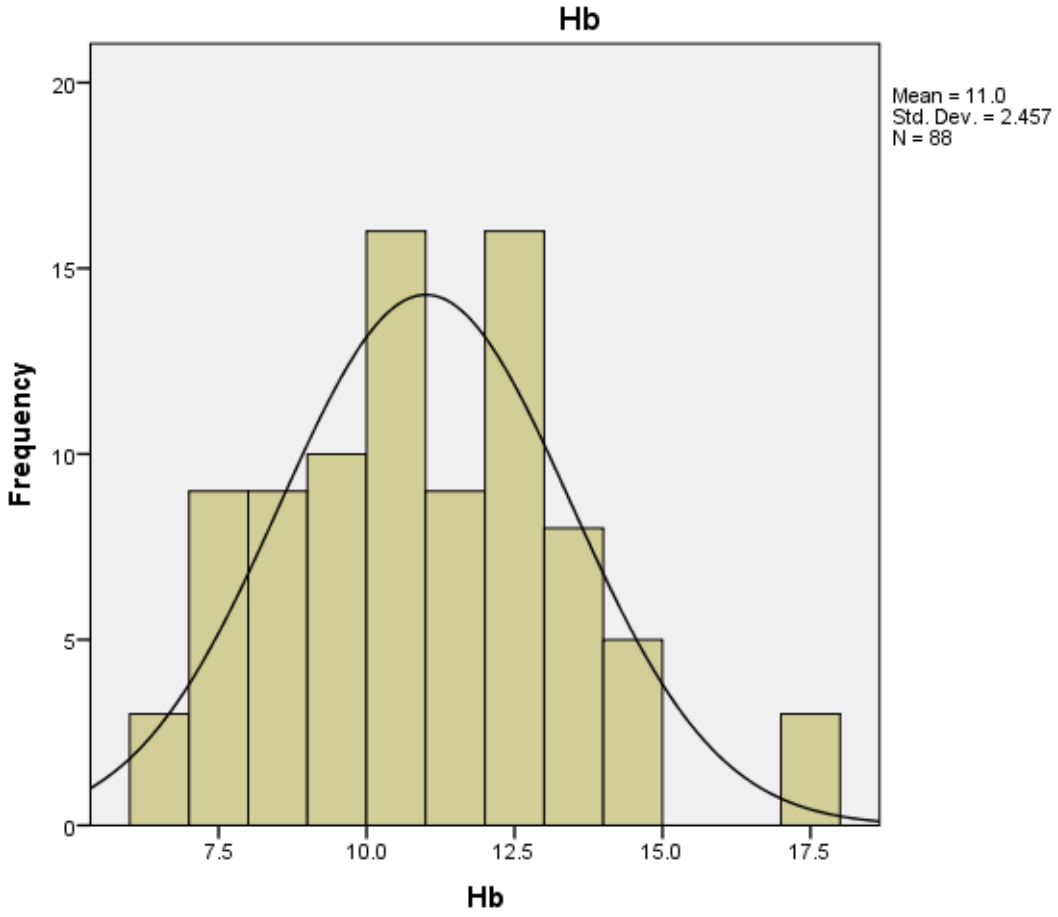
Table: Symptoms of participants			
S No	**Symptoms**	**Frequency**	**Proportion**
1	Cough	43	48.9%

2	Sputum	43	48.9%
3	Hemoptysis	5	5.7%
4	Fever	41	46.6%
5	Loss of weight	18	20.5%

Laboratory values

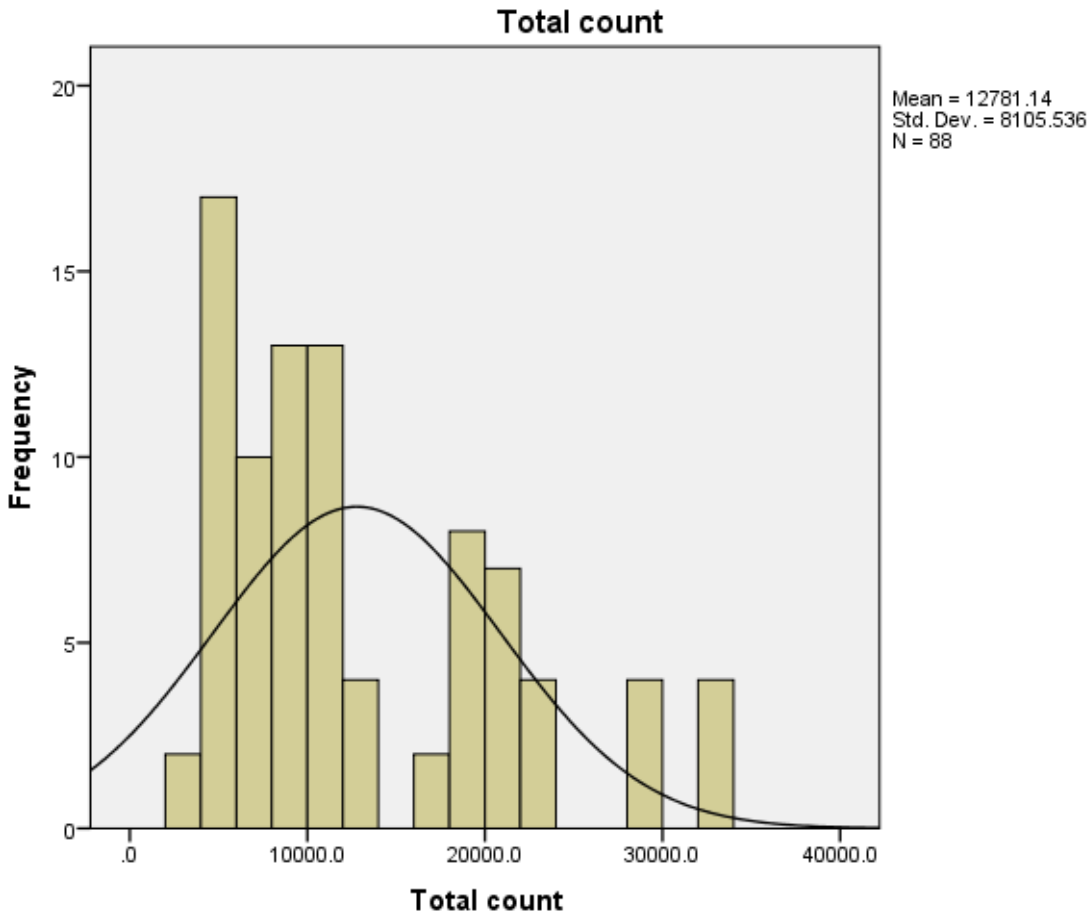
Hemoglobin

The mean hemoglobin of participants was 11±2.457 ranging from 6 – 17.3.



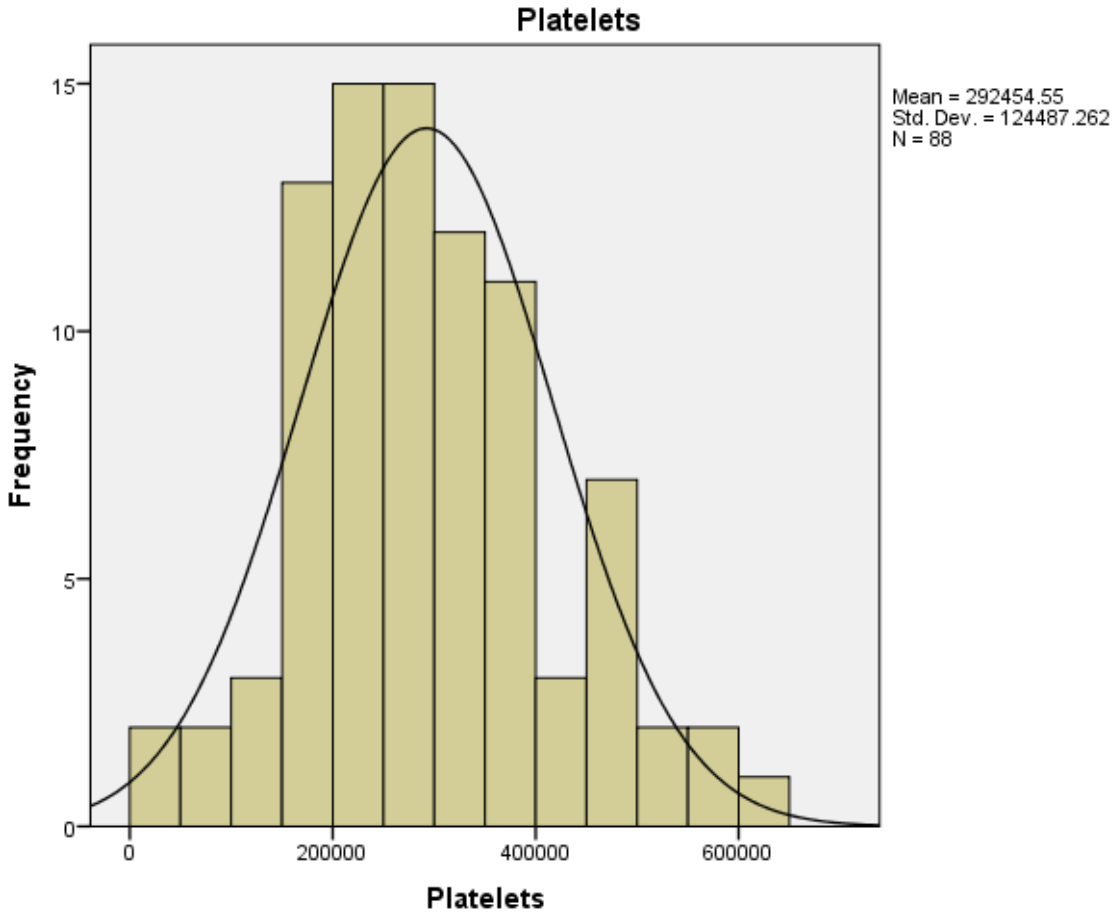
Total count

The mean total count of participants was 12781.136±8105.53 ranging from 2100 – 33000.



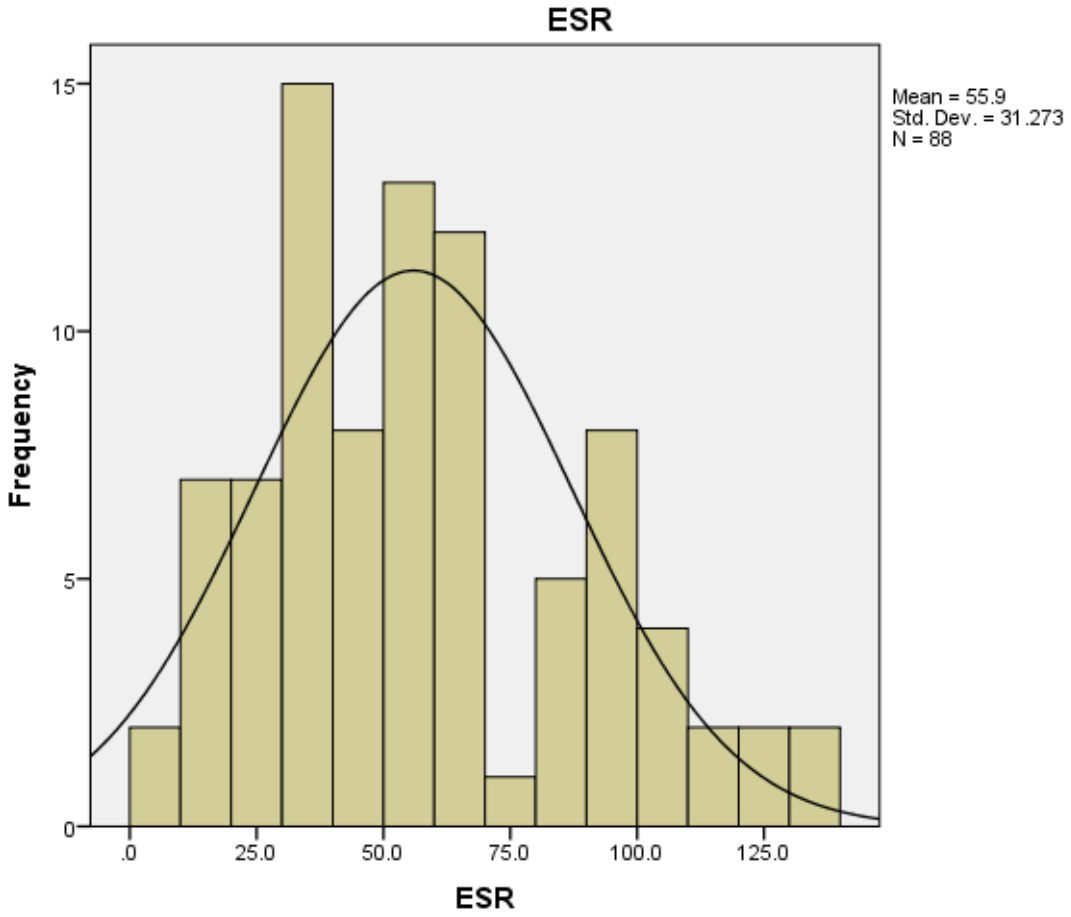
Platelet count

The mean platelet count of participants was 292454.55±124487.26 ranging from 27000 – 621000.



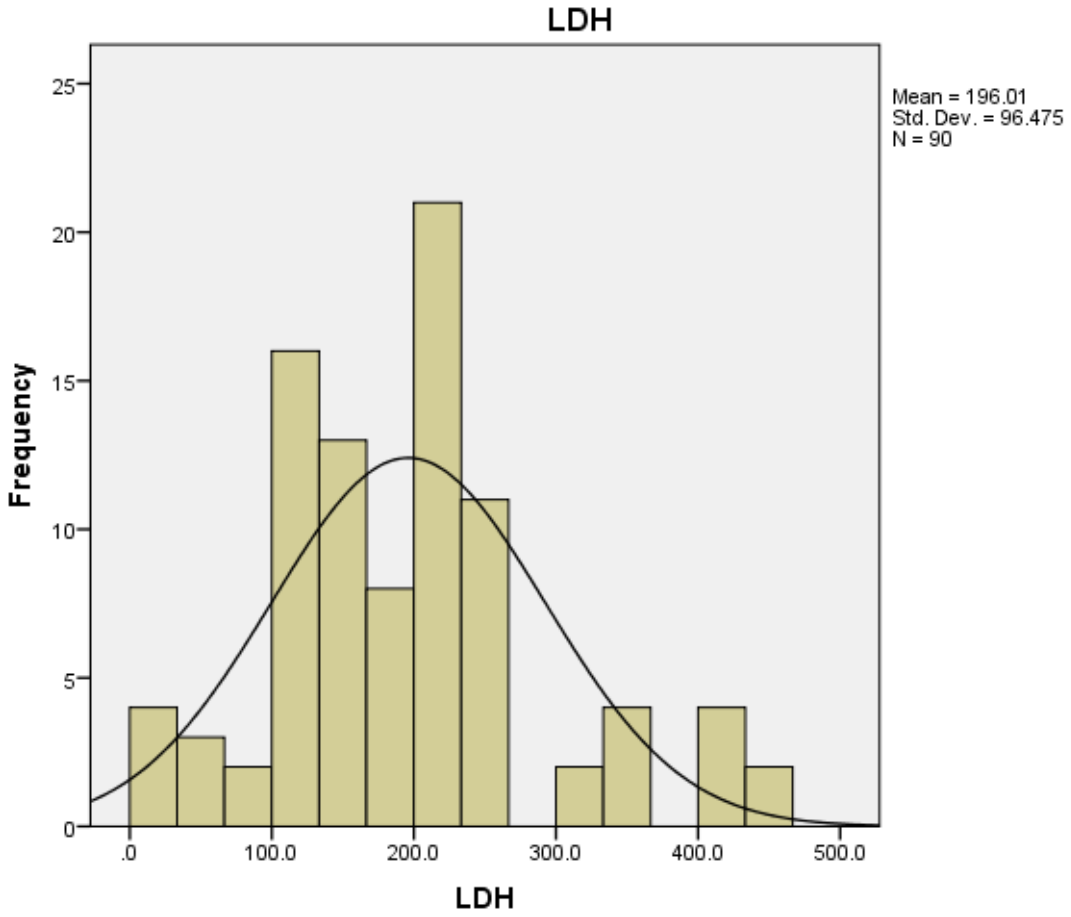
ESR

The mean ESR of participants was 55.898±31.273 ranging from 1 – 130.



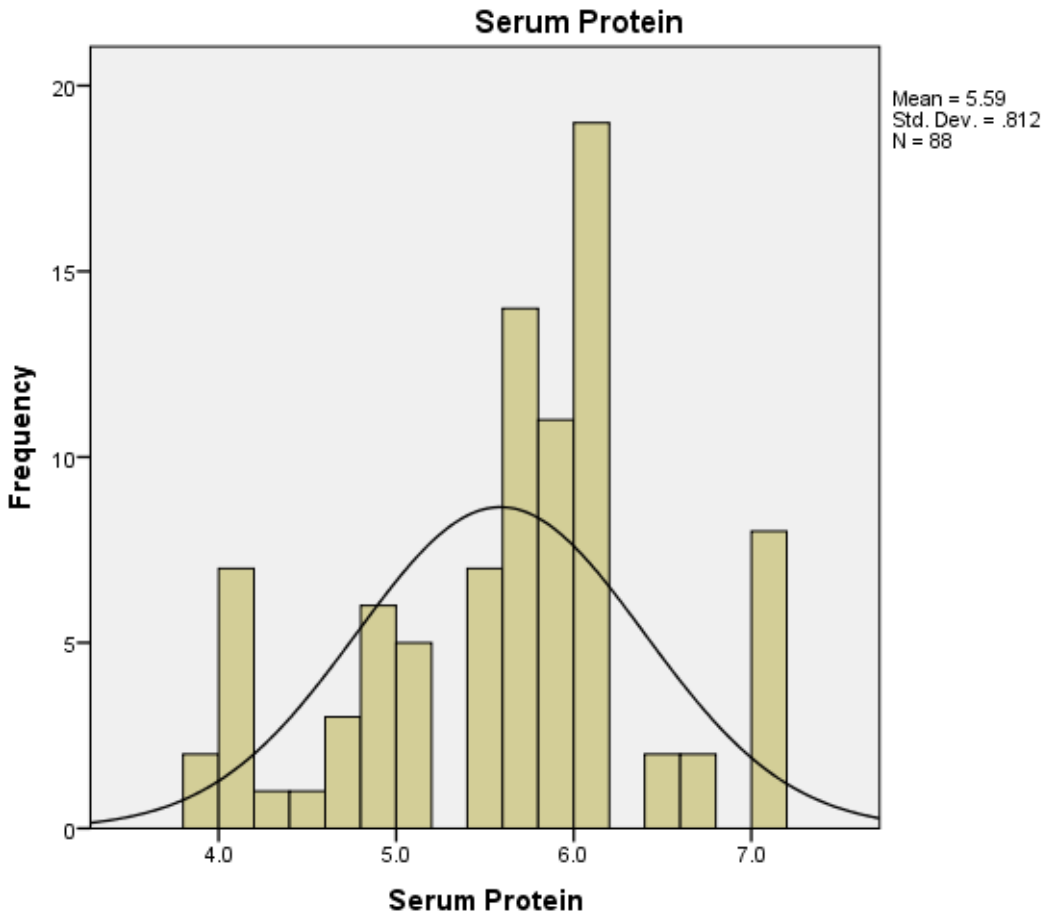
LDH

The mean LDH of participants was 196.011±96.475 ranging from 29 – 456.



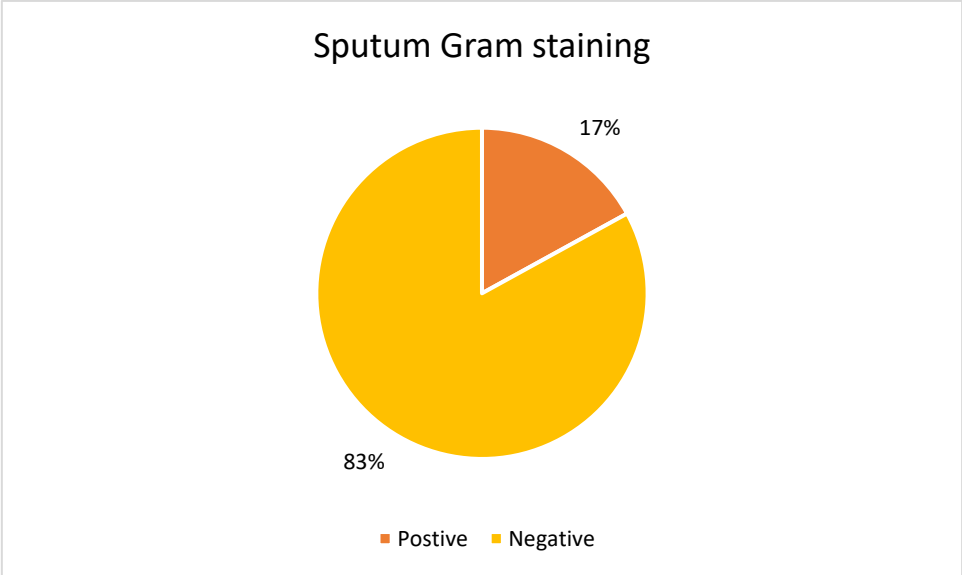
Serum protein

The mean serum protein of participants was 5.588±0.811 ranging from 3.9 – 7.1.



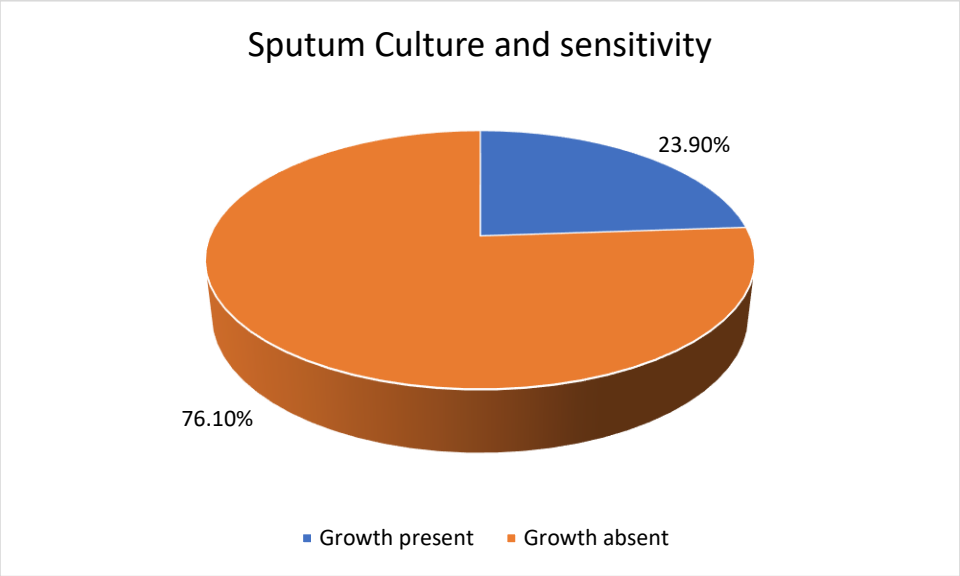
Sputum gram staining

17% of the participants were positive to sputum gram staining.



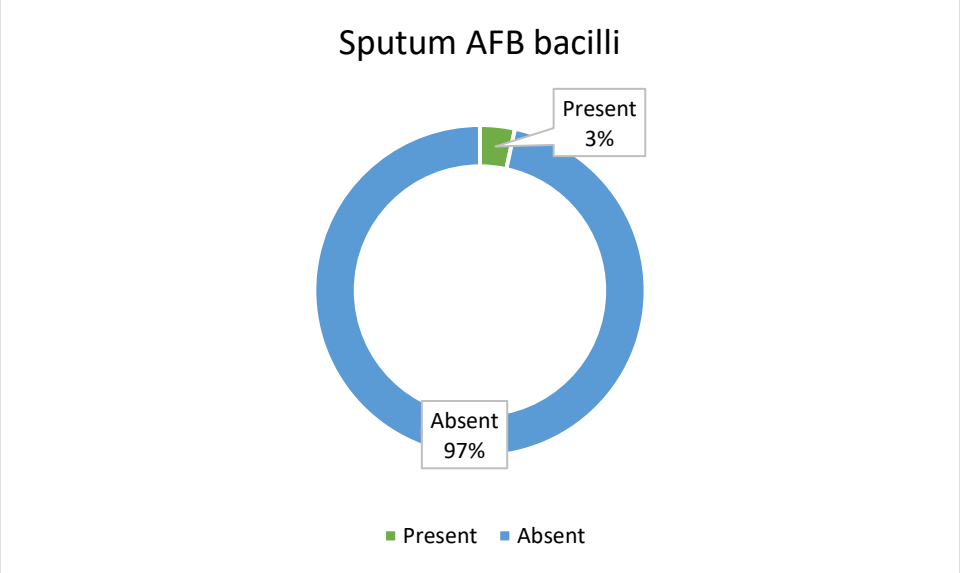
Sputum culture and sensitivity

23.9% of the participants were shown growth in their sputum culture.



Sputum Acid fast bacilli

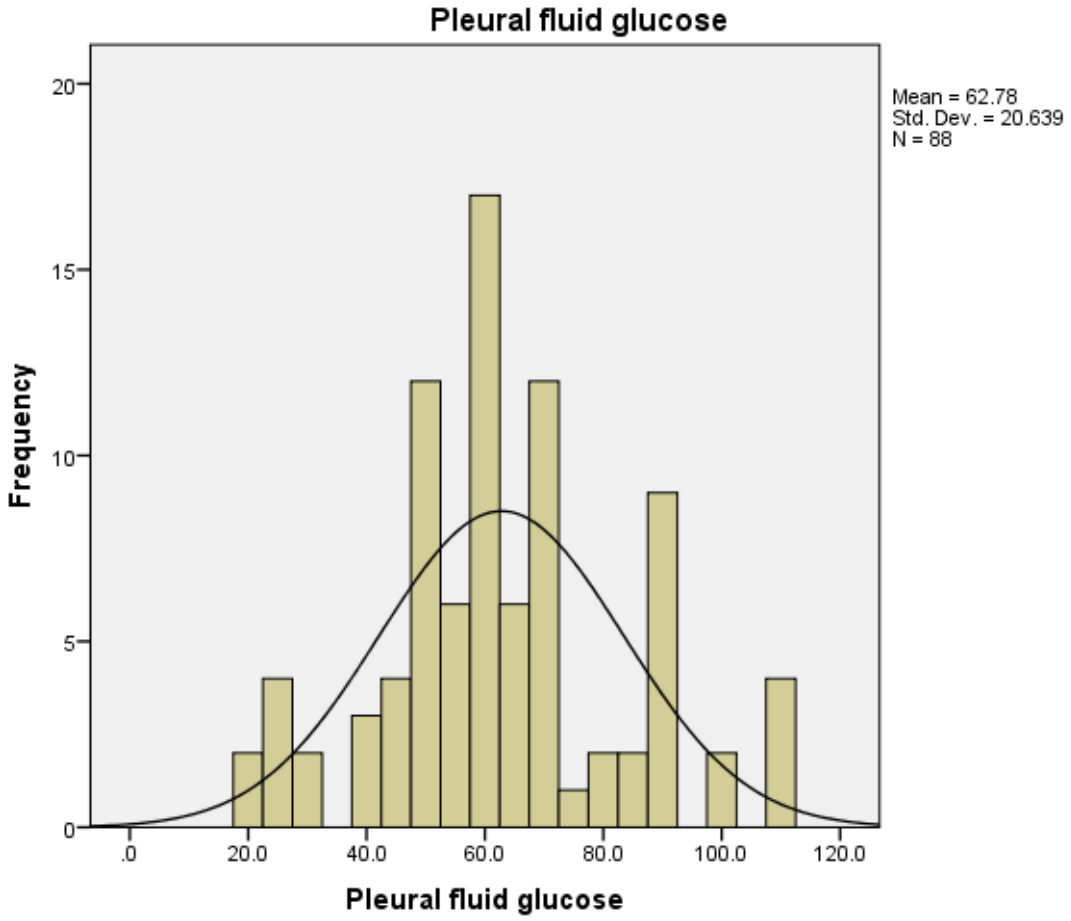
3% of the participants were shown presence of sputum AFB.



Pleural fluid analysis

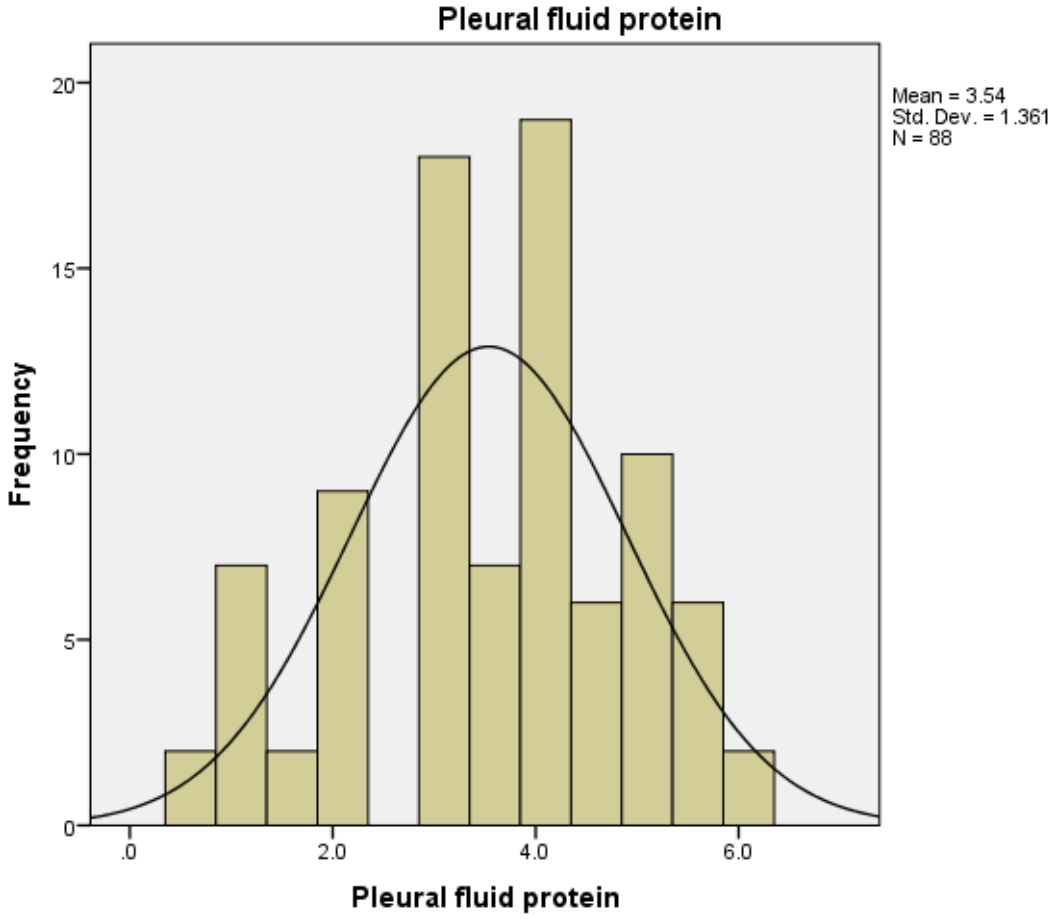
Glucose

The mean pleural fluid glucose of participants was 62.784±20.639 ranging from 20 – 110. The median value was 60 and the quartiles (25,50, 75) were 50,60,70 respectively



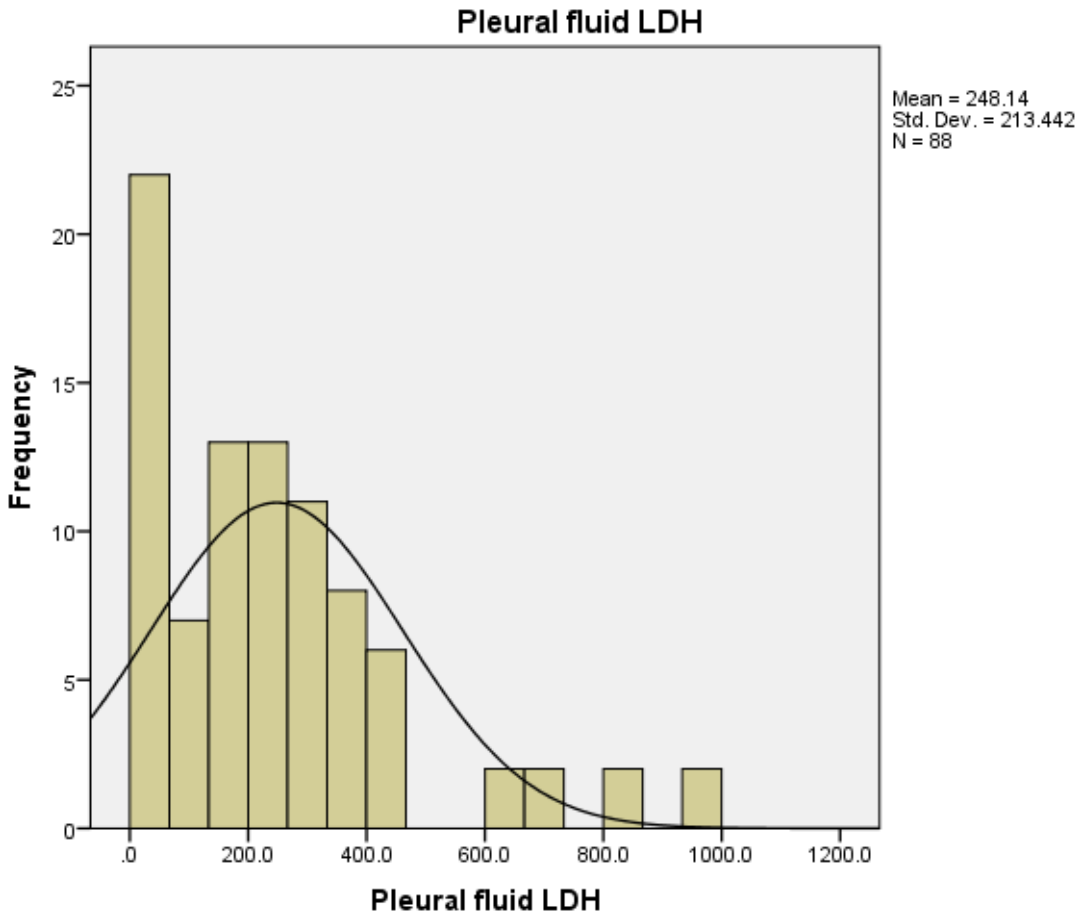
Protein

The mean pleural fluid protein of participants was 3.538±1.361 ranging from 0.6 – 6. The median value was 3.8 and the quartiles (25,50, 75) were 2.925,3.8,4.5 respectively.



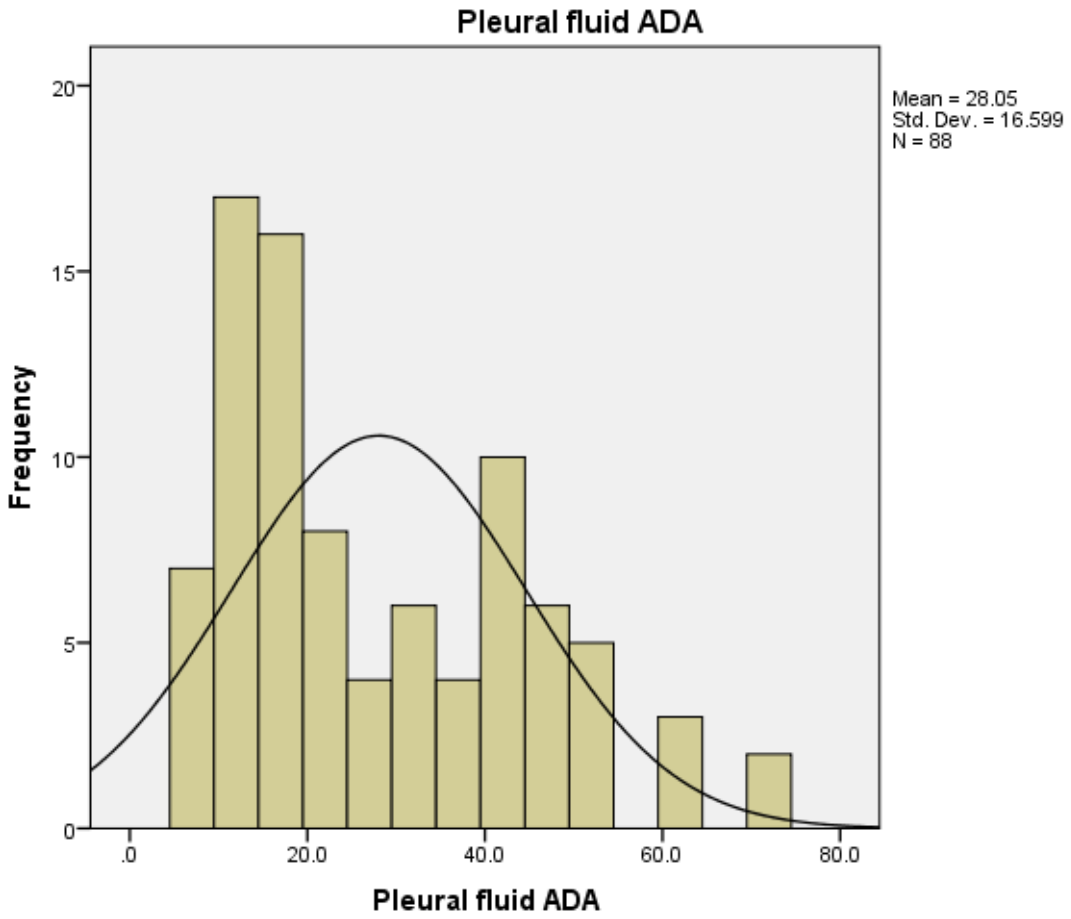
LDH

The mean pleural fluid LDH of participants was 248.136±213.441 ranging from 10 – 1000. The median value was 204.5 and the quartiles (25,50, 75) were 64.5,204.5,336.5 respectively.



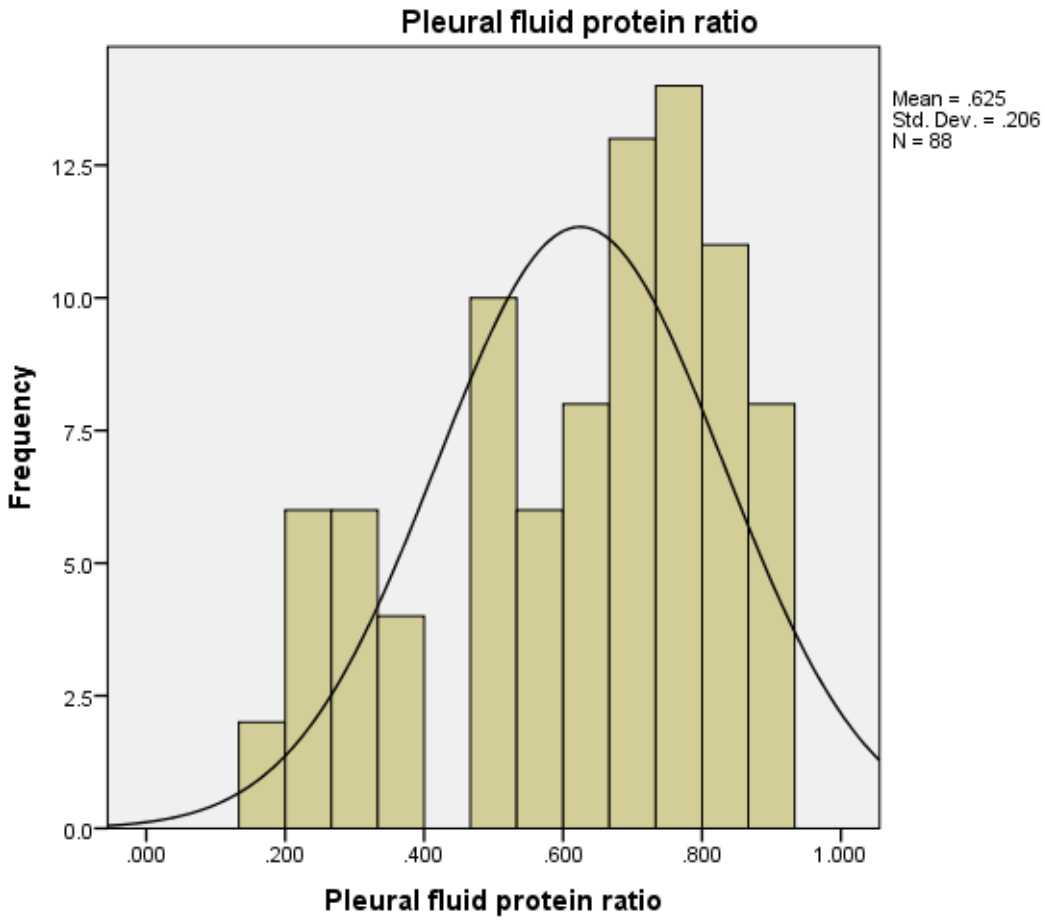
Adenosine deaminase

The mean pleural fluid Adenosine deaminase of participants was 28.045±16.598 ranging from 7 – 70. The median value was 20 and the quartiles (25,50, 75) were 14,20,41 respectively.



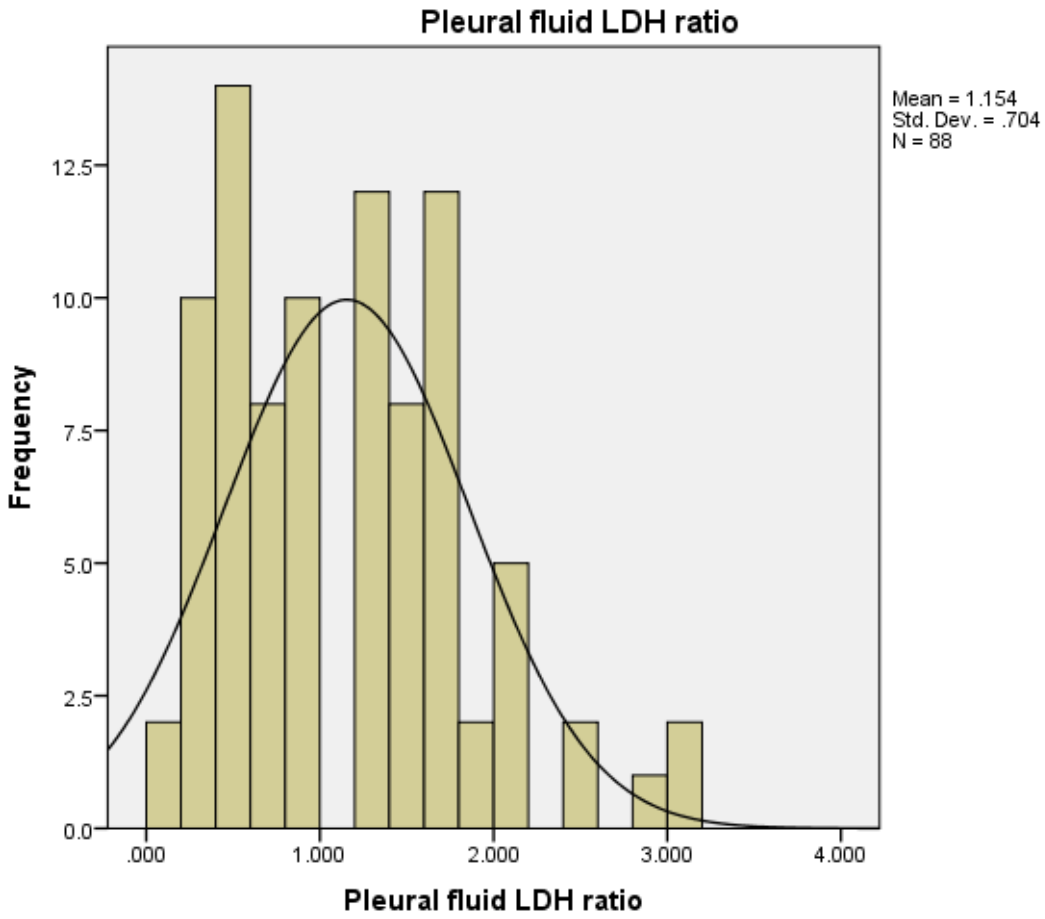
Pleural fluid protein ratio

The mean pleural fluid protein ratio of participants was 0.624±0.202 ranging from 0.15 – 0.9. The median value was 0.689 and the quartiles (25,50, 75) were 0.51,0.68, 0.79 respectively.



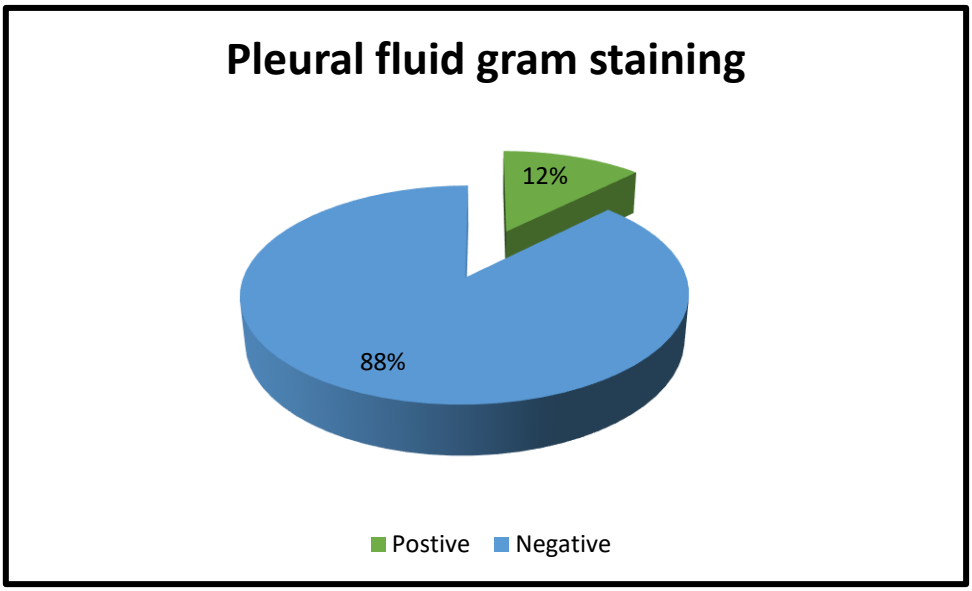
Pleural fluid LDH ratio

The mean pleural fluid LDH ratio of participants was 1.154±0.704ranging from 0.195 – 3.192. The median value was 1.10 and the quartiles (25,50, 75) were 0.49,1.101, 1.641 respectively.



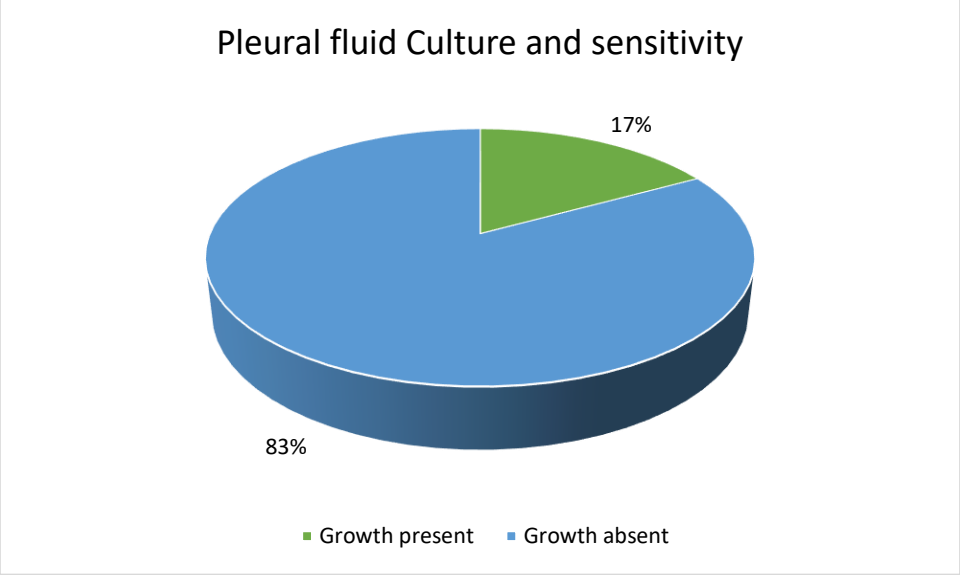
Pleural fluid gram staining

12% of pleural fluid analysis shown gram stain positive.



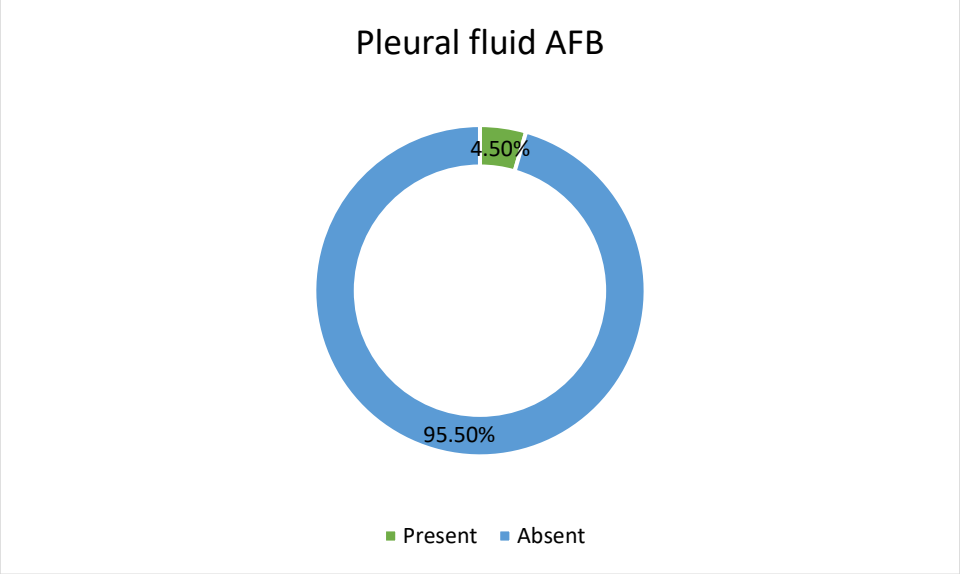
Pleural fluid culture and sensitivity

17% of pleural fluid analysis shown growth in their culture and sensitivity testing



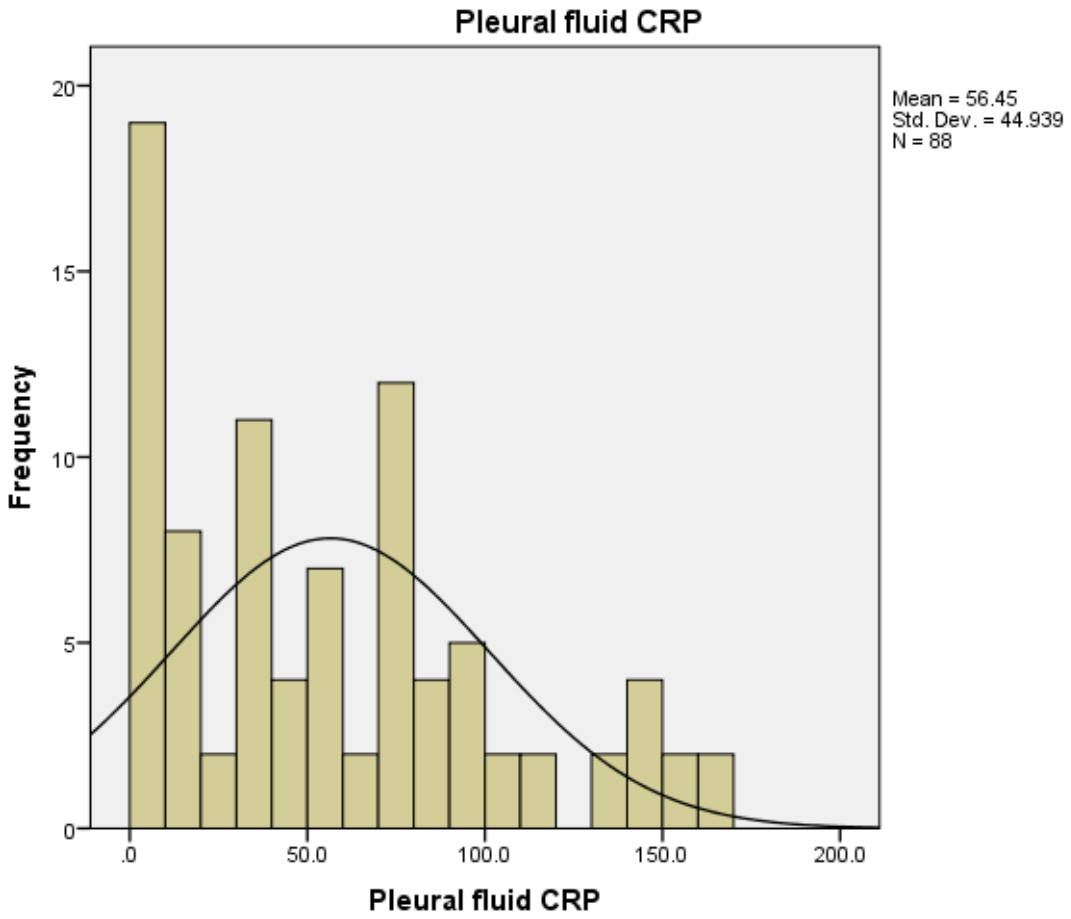
Pleural fluid Acid fast bacilli

4.5% of pleural fluid analysis shown AFB.



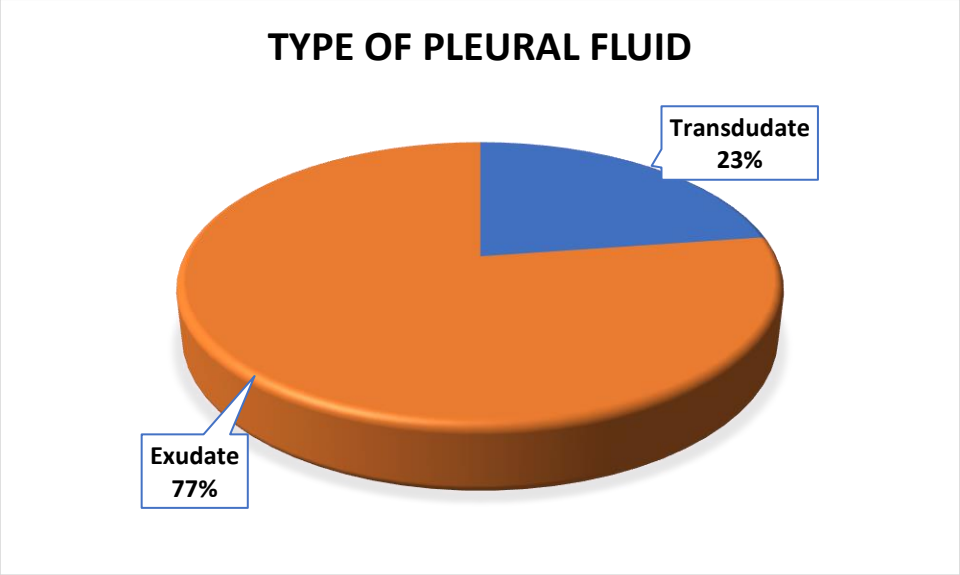
CRP

The mean pleural fluid CRP of participants was 56.453±44.938 ranging from 4 – 160.7. The median value was 44.938 and the quartiles (25,50, 75) were 16.6,46.25, 85.9 respectively.



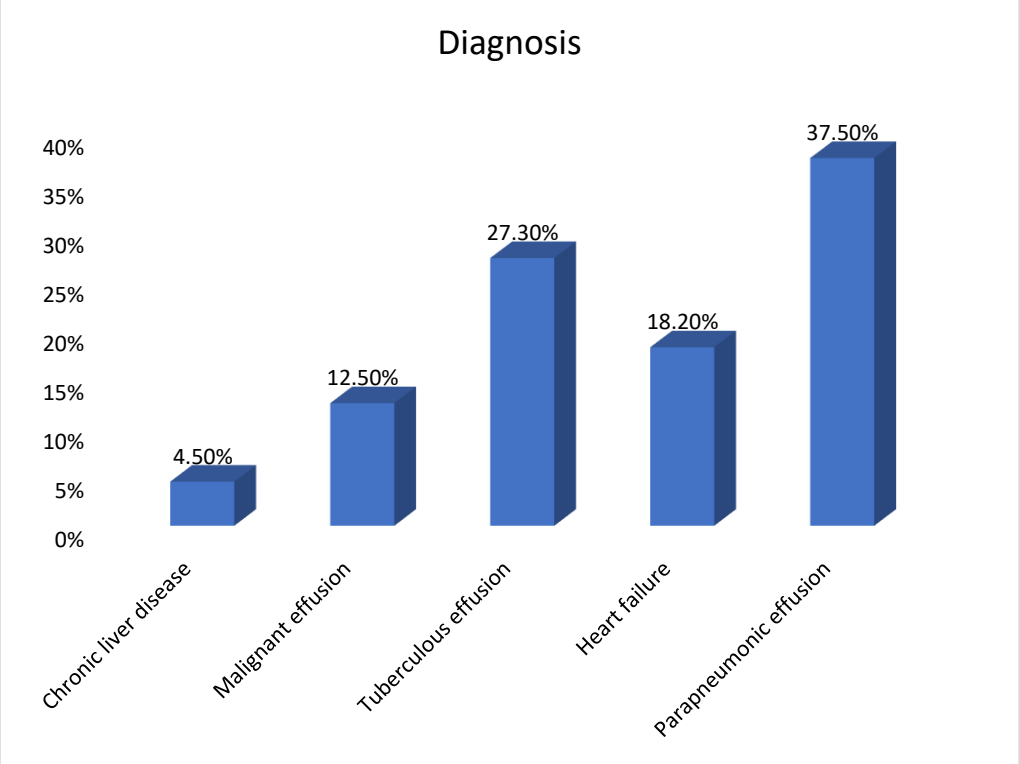
Type of Pleural effusion

23% of the participants had transudate and 77% of the exudative effusion.



Diagnosis

The etiological diagnosis of pleural fluid analysis was Malignant effusion (12.5%), tuberculous effusion (27.3%), Parapneumonic effusion (37.5%), Chronic liver disease (4.5%) and heart failure (18.2%).

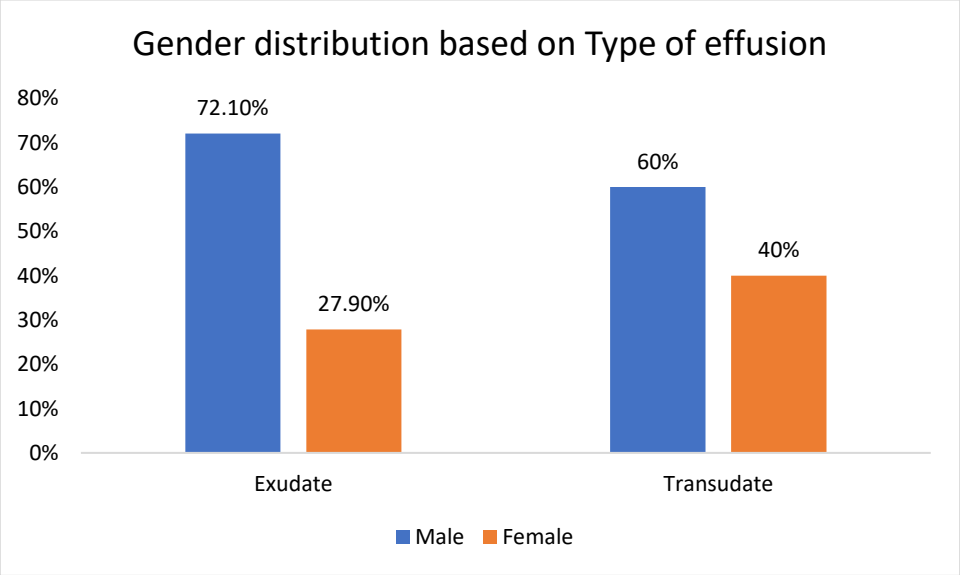


INFERENTIAL STATISTICS

TYPE OF EFFUSION

Gender and type of effusion

Males had higher proportion of exudate effusion and female had higher propotion of transudate effusion.



Symptoms and Type of effusion

In transudate effusion, the patients were presented with cough and sputum. Hemoptysis, fever and loss of weight were the commonest presentations in exudative pleural effusion.

Table: Symptoms and type of effusion				
S No	**Symptoms**	**Transudate**	**Exudate**	**p value**

1	Cough	6 (14%)	37 (86%)	0.055
2	Sputum	6 (14%)	37 (86%)	0.055
3	Hemoptysis	0	5 (100%)	0.212
4	Fever	0	41 (100%)	0.001
5	Loss of weight	0	18 (100%)	0.010

Pleural fluid analysis and type of pleural effusion

the mean values of CRP. ADA, protein, LDH, Protien ratio, LDH ratio were significantly higher among exudative effusions and Gllucose was higher in transudative effusions.

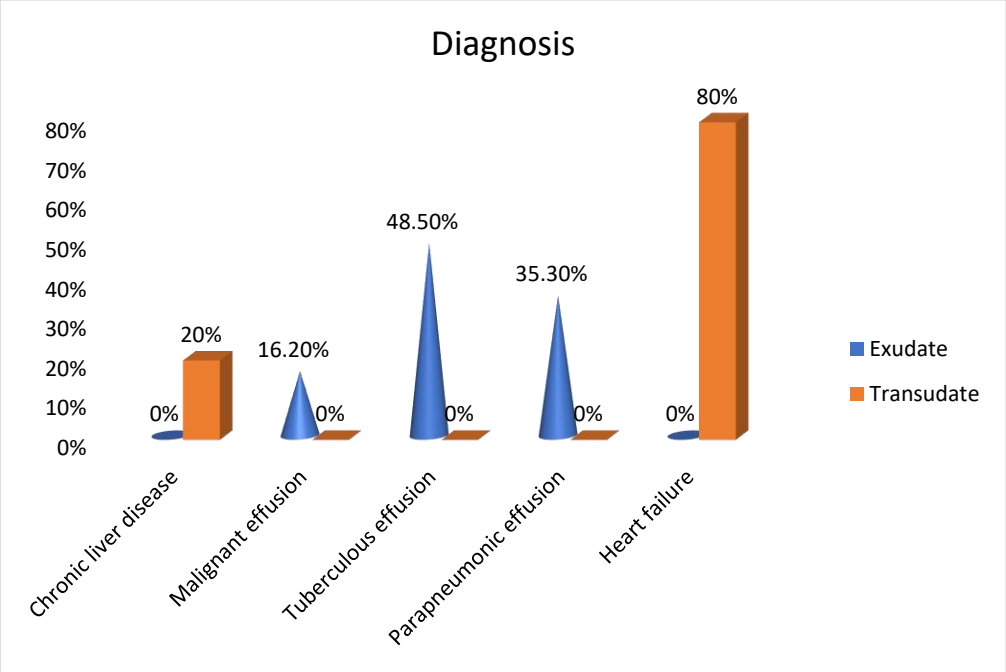
Table: Pleural fluid analysis and type of effusion

S No	Variable	Transudate	Exudate	p value
1	CRP	7.285±2.26	70.915±41.072	0.001
2	ADA	15.850±3.313	31.632±17.232	0.001
3	Glucose	84.550±25.153	56.382±13.81	0.001
4	Protein	1.655±0.652	4.091±0.957	0.001

5	LDH	34.2±15.6	311.059±203.486	0.001
6	Protein ratio	0.305±0.093	0.718±0.116	0.001
7	LDH ratio	0.416±0.104	1.37±0.656	0.001

Etiological diagnosis and Type of effusion

Malignant effusion, Tuberculous effusion and parapneumonic effusion were exudative effusions , heart failure and Chronic liver disease exhibits transudative effusions.



C- REACTIVE PROTEIN PARAMETERS

Age and CRP

Age group was not significantly associated with pleural fluid CRP.

Table: Pleural fluid CRP and age group				
S No	**Variable**	**≤ 30 years**	**More than 30 years**	**p value**
1	CRP	66.633±48.31	54.362±44.276	0.338

Gender and CRP

Gender was significantly associated with pleural fluid CRP. The male participants had higher mean CRP values than females.

Table: Pleural fluid CRP and age group				
S No	**Variable**	**Male**	**Female**	**p value**
1	CRP	66.175±47.88	34.489±27.25	0.002

Symptoms and CRP

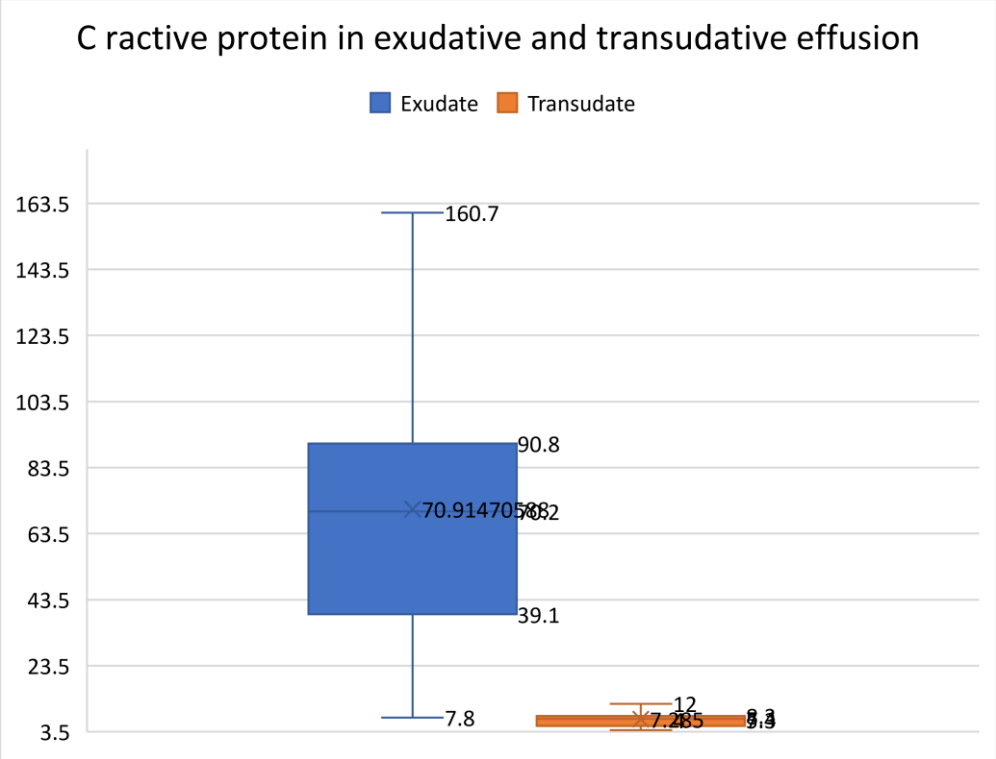
The mean values of CRP were higher with cough, sputum and fever symptoms and statistically significant.

Table: Pleural fluid CRP and symptoms				
S No	**Variable**	**Present**	**Absent**	**p value**
1	Cough	74.584±48.65	39.129±33.249	0.001
2	Sputum	75.335±47.943	38.411±33.431	0.001
3	Hemoptysis	49.48±42.57	56.873±45.288	0.723
4	Fever	89.076±41.898	27.996±22.73	0.001
5	Loss of weight	32.994±15.933	62.486±47.992	0.012

Type of effusion and CRP

The mean values of CRP were higher in exudative effusion (70.915±41.072) than transudative (7.285±2.26) effusion and the value was significant.

Table: Pleural fluid CRP and type of effusion				
S No	**Age**	**Transudate**	**Exudate**	**p value**
1	CRP	7.285±2.26	70.915±41.072	0.001



CRP and etiological diagnosis

The mean values of CRP were higher in parapneumonic effusion (101.7) than tuberculous (50.1) and malignant effusion (23.96) and the value was significant.

Table: Pleural fluid CRP and symptoms

S No	Variable	Mean	SD	p value
1	Tuberculous effusion	50.1	14.63	0.001
2	Malignant effusion	23.96	8.04	0.001
3	Parapneumonic effusion	101.70	36.024	0.001
4	Heart failure	7.681	2.21	0.001

5	Chronic liver disease	5.7	1.96	0.001

Diagnostic accuracy of CRP

Cross tabs

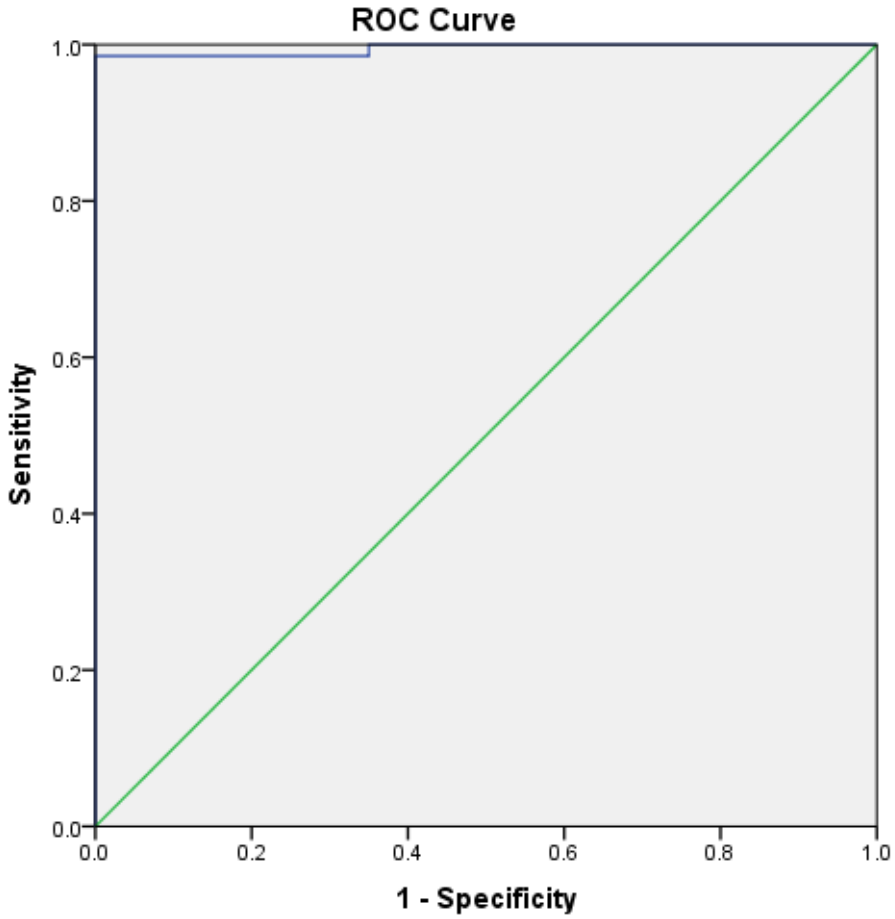
Table: Cross tabs of CRP vs Etiology			
S No	Etiology	< 43.4	43.4 and above
1	Tuberculous effusion	12	12
2	Malignant effusion	11	0
3	Parapneumonic effusion	1	32
4	Heart failure	16	0
5	Chronic liver disease	16	0

The CRP value of 43.4 was kept as the cutoff value and the diagnostic accuracy was measured for exudative aetiologies. The sensitivity was higher in differentiating tuberculous effusion from malignant effusion with CRP values.

The diagnostic accuracy of CRP accounts for 50% and 37% in differentiating tuberculosis with malignant and malignant with parapneumonic effusion.

Table: Diagnostic value of CRP			
S No	Parameters	TB vs Malignant	Malignant vs parapneumonic effusion
1	Sensitivity	72.73%	47.73%
2	Specificity	27.27%	27.27%
3	Positive predictive value	50%	39.62%
4	Negative predictive value	50%	34.29%
5	Diagnostic accuracy	50%	37.5%

ROC curves



Area under the curve

The Area under the curve was 0.995 (more than 0.5) which implies there is a role of CRP in differentiating exudative to transudate effusion which was significant statistically. The CRP values were higher in exudate than in transudate effusion.

Area Under the Curve			
Test Result Variable(s): Pleural fluid CRP			
Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval

			Lower Bound	Upper Bound
.995	.006	.000	.984	1.000

7. DISCUSSION

This study was conducted among 88 patients with pleural effusion to determine the role of pleural fluid CRP in PE.

Pleural fluid CRP

Our study found that The mean pleural fluid CRP of participants was 56.453±44.938 ranging from 4 – 160.7. The median value was 44.938 and the quartiles (25,50, 75) were 16.6,46.25, 85.9 respectively.

Type of Pleural effusion

Our study found that 23% of the participants had transudate and 77% of the exudative effusion. Rismantab et al(45) in a research stated that According to Light's criteria, 61 patients (36.1%) and 108 patients (63.9%) had exudative pleural effusion and transudative pleural effusion, respectively.

Pleural CRP in pleural effusion

Our study found that The mean values of CRP were higher in exudative effusion (70.915±41.072) than transudative (7.285±2.26) effusion and the value was significant.

Participants within exudative and transudative categories had CRP levels in their pleural fluid that were, respectively, 13.3±37.1 and 3.5±4.3mg/dl (p=0.008) by Rismantab et al(45) research.

Our study found that The mean values of CRP were higher in parapneumonic effusion (101.7) than tuberculous (50.1) and malignant effusion (23.96) and the value was significant.

Mohammed et al(51) in a study found that In TBPE and MPE, respectively, the mean values of p-CRP were 36.51 3.91 and 26.39 7.57 mg/dl, with a strongly significant difference (P=0.001).

Our study found that The CRP value of 43.4 was kept as the cutoff value and the diagnostic accuracy was measured for exudative aetiologies. The sensitivity (72.73%) was higher in differentiating tuberculous effusion from malignant effusion with CRP values. The diagnostic accuracy of CRP accounts for 50% and 37% in differentiating tuberculosis with malignant and malignant with parapneumonic effusion. The Area under the curve was 0.995 (more than 0.5) which implies there is a role of CRP in differentiating exudative to transudate effusion which was significant statistically. The CRP values were higher in exudate than in transudate effusion.

Li D et al(43) found that the diagnostic performance of pleural CRP for PPE (parapneumonic effusion): sensitivity (0.80), specificity (0.82), PLR (4.51), NLR (0.25), DOR (18.26), and AUC (0.88).

Angeles RR et al(44) meta-analysis found an ideal cut-off of 21.9 mg/dL, with either a sensitivity of 0.91 (0.73 to 0.98) or a specificity of 0.82 (results above the cut-off are classed as TPE) (0.7 to 0.9).

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the 3.31 mg/dl cut-off point of CRP level for pleural effusion were 96.3%, 72.1%, 86%, and 91.7%, respectively by Rismantab et al(45) et al research.

Basso et al(46) study at Italy described that the sensitivity of CRP was 92.5% and specificity was 71.9%.

The optimal cut-off value of ≥30 mg/dL for pleural fluid CRP used to have a sensitivity of 72% with 93% specificity, while the cut-off value of 0.45 for the ratio of pleural fluid to serum CRP had a sensitivity of 60% and 89% specificity by Chierakal N et al(47) research

Sensitivity, specificity, and area under the receiver-operating characteristic curve (AUC) for the diagnosis of CPPE and empyema with a cutoff value for pleural CRP of 8.7 mg/dl were 0.80, 0.97, and 0.94, respectively by Chen S C et al(42) study.

Makwana et al(50) study stated that CRP levels in pleural fluid can be used as an extra tool in the exudative effusion differential diagnosis

Mohammed et al(51) in a study found that Sensitivity and specificity reached 89.47 and 80.00% for p-CRP and 15.79 and 100.00%, correspondingly, for s-CRP when cutoff values of 31.6 and 43.3 mg/l were used.

Across studies it was found that the diagnostic accuracy was higher for pleural CRP for the prediction of exudative from transudative and also parapneumonic/tuberculous effusions.

Therefore, null hypothesis was rejected and it was found there was role for CRP in pleural effusion.

8. SUMMARY

This study was conducted among 88 patients with pleural effusion to determine the role of pleural fluid CRP in PE.

- **Pleural fluid CRP**
    - The mean pleural fluid CRP of participants was 56.453±44.938 ranging from 4 – 160.7. The median value was 44.938 and the quartiles (25,50, 75) were 16.6,46.25, 85.9 respectively.

- **Type of Pleural effusion**
    - 23% of the participants had transudate and 77% of the exudative effusion.

- **Diagnosis**
        - The etiological diagnosis of pleural fluid analysis was Malignant effusion (12.5%), tuberculous effusion (27.3%), Parapneumonic effusion (37.5%), Chronic liver disease (4.5%) and heart failure (18.2%).

- **Pleural CRP in pleural effusion**

- The mean values of CRP were higher in exudative effusion (70.915±41.072) than transudative (7.285±2.26) effusion and the value was significant.

- The mean values of CRP were higher in parapneumonic effusion (101.7) than tuberculous (50.1) and malignant effusion (23.96) and the value was significant.

- The CRP value of 43.4 was kept as the cutoff value and the diagnostic accuracy was measured for exudative aetiologies. The sensitivity (72.73%) was higher in differentiating tuberculous effusion from malignant effusion with CRP values. The diagnostic accuracy of CRP accounts for 50% and 37% in differentiating tuberculosis with malignant and malignant with parapneumonic effusion.

- The Area under the curve was 0.995 (more than 0.5) which implies there is a role of CRP in differentiating exudative to transudate effusion which was significant statistically. The CRP values were higher in exudate than in transudate effusion.

9. CONCLUSION

This study was conducted among 88 patients with pleural effusion to determine the role of pleural fluid CRP in PE. The mean values of CRP were higher in exudative effusion (70.915±41.072) than transudative (7.285±2.26) effusion and the value was significant.

CRP levels in pleural fluid can be used as an extra tool in the exudative effusion differential diagnosis. It notably distinguishes tuberculous and malignant effusions from parapneumonic effusions and empyema. In our investigation, the ability of pleural fluid CRP to discriminate between tuberculous and malignant effusions was crucial. Our work clearly shows that pleural fluid CRP is an extremely quick and economical method to distinguish parapneumonic effusion and empyema from other exudative effusions

10.LIMITATIONS

- The sample size was smaller, and the larger sample size was considered to generalise the results.

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ANNEXURES

ANNEXURE 1:PROFORMA

PROFORMA

NAME: AGE: SEX:

ADDRESS: OCCUPATION:

SYMPTOMS:

Cough	Fever
Expectoration	Loss of weight/loss of appetite
Dyspnoea	Symptoms of volume overload
Chest pain	Symptoms of organ dysfunction

PAST HISTORY:

Diabetes Mellitus	Chronic kidney disease	Tuberculosis
Systemic Hypertension	Liver disease	Malignancy
Coronary artery disease/CCF	Drug intake	Collagen Vascular disease

PERSONAL HISTORY:

Alcoholic- yes/no
Smoker- yes/no Overcrowded living conditions- yes/no

TREATMENT HISTORY:

Medication

GENERAL EXAMINATION:

BMI-

HEAD TO TOE EXAMINATION

Pallor	Icterus	Cyanosis
Clubbing	Lymphadenopathy	Pedal edema

VITALS:

BP	PR	SPO2	RR	TEMP

SYSTEMIC EXAMINATION:

CVS:

RS :

P/A:

CNS:

INVESTIGATIONS:

Hemogram			**RFT**		
TC		Cells/mm3	Glucose(F)		
DC			Glucose(PP)		
ESR		Mm/hr	Urea		
Hb		g/dl	Creatinine		

PCV		%	Na+		
Platelets		Lakhs/mm3	K+		
RBCs		Million/mm3			
Liver function tests			**Others**		
Total bilirubin		mg/dl	Serum LDH		
Direct fraction		mg/dl	HIV		
SGOT		IU/L	Blood C/S		
SGPT		IU/L	RF/ANA/TFT		
ALP		IU/L	Sputum AFB		
Protein		g/dl	Sputum C/S		
Albumin		g/dl	Mantoux		

PLEURAL FLUID ANALYSIS	
Sugar	AFB
Total protein and ratio	C/S
LDH and LDH ratio	Gram stain
Cytology	ADA
Cell count	CRP

ANNEXURE 2: MASTER CHART

Sno	age	gender	cough	sputum	hemoptysis	fever	LoW	TC	GM	CS	AFB	LDH	protein	plglucose	plprotien	plLDH	GM	AFB	CS	cytology	LDH	proteinratio	LDHratio	Ada	plCRP	nature	diagnosis	
1	25	M	P	P	A	P	P	13000	A	A	P	110	5	40	4	310	A	A	A	L	P	0.8	2.82	60	59.8	1	1	12
2	23	F	A	A	A	A	P	9000	A	A	A	172	4.6	50	3.1	298	A	A	A	N	P	0.7	1.73	54	60.1	1	1	12
3	56	M	A	P	A	P	A	11020	A	A	A	230	5.6	40	4.1	290	A	A	A	L	P	0.732	1.26	43	40.8	1	1	21
4	37	F	A	A	A	P	A	11000	A	A	A	231	5.5	50	4.1	167	A	P	A	L	P	0.745	0.72	47	39.9	1	1	21
5	56	M	P	P	A	A	A	10100	A	A	A	134	5.8	64	3.6	204	A	A	A	P	P	0.621	1.52	70	70.9	1	1	22
6	60	F	P	P	A	A	A	9200	A	A	P	153	6.1	70	4.5	205	A	P	A	P	P	0.738	1.34	54	70.2	1	1	22
7	50	F	A	A	A	A	A	6200	A	A	A	231	5.4	60	3	45	A	A	A	P	A	0.556	0.2	42	51.7	1	1	22
8	52	F	A	A	A	A	A	5300	A	A	A	221	4.9	59	2.9	150	A	A	A	N	P	0.592	0.68	48	39.1	1	1	21
9	37	M	A	A	A	P	P	4300	A	A	A	189	5.8	27	4.6	278	A	A	A	L	P	0.793	1.47	41	40.1	1	1	21
10	56	M	A	A	A	A	P	9800	A	A	A	189	4.9	50	3.9	78	A	A	A	L	A	0.796	0.41	52	31.2	1	1	21
11	54	M	A	A	A	A	A	10500	A	A	A	187	5.5	60	3.8	156	A	A	A	L	P	0.691	0.83	48	56.9	1	1	22
12	54	M	A	A	A	A	A	11000	A	A	A	234	5.1	70	3.9	120	A	A	A	L	P	0.765	0.51	63	31.4	1	1	21
13	59	M	A	A	A	A	P	10800	A	A	A	138	4.5	76	3.5	245	A	A	A	L	P	0.778	1.78	44	67.8	1	1	22
14	46	F	A	A	A	P	A	7200	A	A	A	110	5.4	60	4	232	A	A	A	L	P	0.741	2.11	41	70.3	1	1	22
15	56	M	A	P	A	P	A	11020	A	A	A	230	5.6	40	4.1	290	A	A	A	L	P	0.732	1.26	43	40.8	1	1	21
16	37	F	A	A	A	P	A	11000	A	A	A	231	5.5	50	4.1	167	A	P	A	L	P	0.745	0.72	47	39.9	1	1	21
17	56	M	P	P	A	A	A	10100	A	A	A	134	5.8	64	3.6	204	A	A	A	P	P	0.621	1.52	70	70.9	1	1	22
18	60	F	P	P	A	A	A	9200	A	A	P	153	6.1	70	4.5	205	A	P	A	P	P	0.738	1.34	54	70.2	1	1	22
19	50	F	A	A	A	A	A	6200	A	A	A	231	5.4	60	3	45	A	A	A	P	A	0.556	0.2	42	51.7	1	1	22
20	52	F	A	A	A	A	A	5300	A	A	A	221	4.9	59	2.9	150	A	A	A	N	P	0.592	0.68	48	39.1	1	1	21
21	37	M	A	A	A	P	P	4300	A	A	A	189	5.8	27	4.6	278	A	A	A	L	P	0.793	1.47	41	40.1	1	1	21
22	56	M	A	A	A	A	P	9800	A	A	A	189	4.9	50	3.9	78	A	A	A	L	A	0.796	0.41	52	31.2	1	1	21
23	54	M	A	A	A	A	A	10500	A	A	A	187	5.5	60	3.8	156	A	A	A	L	P	0.691	0.83	48	56.9	1	1	22
24	54	M	A	A	A	A	A	11000	A	A	A	234	5.1	70	3.9	120	A	A	A	L	P	0.765	0.51	63	31.4	1	1	21
25	28	M	P	A	P	P	P	8000	A	A	A	250	6	50	3.2	360	A	A	A	M	P	0.533	1.44	20	16.2	1	2	11
26	60	F	A	A	A	A	P	13500	A	A	A	200	6	50	3.2	320	A	A	A	M	P	0.533	1.6	18	18.9	1	2	21
27	47	F	P	P	P	A	P	10000	A	A	A	210	5.1	86	3	290	A	A	A	M	P	0.588	1.38	8	19.5	1	2	21
28	58	F	A	A	A	A	P	9900	A	A	A	156	4	47	3.6	129	A	A	A	M	P	0.9	0.83	7	37.6	1	2	21
29	26	M	A	A	A	A	P	9600	A	A	A	120	3.9	54	2	256	A	A	A	M	P	0.513	2.13	20	21.9	1	2	11

30	35	F	A	A	A	A	P	5500	A	A	A	200	4.2	89	3	342	A	A	A	M	P	0.714	1.71	10	17.8	1	2	21
31	45	M	P	A	A	A	P	6500	A	A	A	120	5.8	59	3	113	A	A	A	M	A	0.517	0.94	17	33.1	1	2	21
32	60	F	P	P	A	P	P	4600	A	A	A	174	5.6	50	4	156	A	A	A	M	P	0.714	0.9	18	19.6	1	2	21
33	47	F	P	P	P	A	P	10000	A	A	A	210	5.1	86	3	290	A	A	A	M	P	0.588	1.38	8	19.5	1	2	21
34	58	F	A	A	A	A	P	9900	A	A	A	156	4	47	3.6	129	A	A	A	M	P	0.9	0.83	7	37.6	1	2	21
35	26	M	A	A	A	A	P	9600	A	A	A	120	3.9	54	2	256	A	A	A	M	P	0.513	2.13	20	21.9	1	2	11
36	32	M	P	P	A	P	A	20000	P	P	A	160	5.7	60	3	250	P	A	P	P	P	0.526	1.56	23	90.7	1	3	22
37	34	M	P	P	P	P	A	23600	P	P	A	400	7	59	5.3	1000	P	A	P	P	P	0.757	2.5	9	96.1	1	3	22
38	58	M	P	P	A	P	A	28300	P	P	A	456	5.7	59	5	239	A	A	A	P	P	0.877	0.52	20	150.9	1	3	22

39	39	M	P	P	A	P	A	32300	P	P	A	342	6.1	70	5	609	A	A	A	P	P	0.82	1.78	12	110.7	1	3	2	2
40	50	M	P	P	A	P	A	19100	A	A	A	432	4.9	67	3	807	P	A	P	P	P	0.612	1.87	14	7.8	1	3	2	1
41	45	M	A	A	A	P	A	20400	A	A	A	342	5.6	53	4	432	P	A	P	N	P	0.714	1.26	15	85.9	1	3	2	2
42	54	M	P	P	A	P	A	2100	A	A	A	243	6.1	30	4.2	399	A	A	A	P	P	0.689	1.64	28	70.9	1	3	2	2
43	35	M	A	A	A	P	A	19200	A	A	A	213	5.7	45	5	680	A	A	A	P	P	0.877	3.19	38	102.6	1	3	2	2
44	60	M	P	P	A	P	A	21200	A	P	A	159	5.7	23	3	239	A	A	P	P	P	0.526	1.5	32	89.7	1	3	2	2
45	26	M	P	P	A	P	A	22300	P	P	A	200	6.4	60	4.5	342	P	A	P	N	P	0.703	1.71	40	70.3	1	3	1	2
46	33	M	P	P	A	A	A	16700	A	A	A	264	7	59	5.7	456	A	A	A	N	P	0.814	1.73	32	55.8	1	3	2	2
47	22	M	P	P	A	P	A	13900	P	P	A	254	5.8	67	5	342	A	A	A	N	P	0.862	1.35	15	79.7	1	3	1	2
48	56	M	P	P	A	P	A	28000	P	P	A	321	7.1	70	6	432	A	A	A	P	P	0.845	1.35	13	149.7	1	3	2	2
49	45	M	P	P	A	P	A	19800	P	P	A	231	7	68	5.8	200	A	A	A	P	P	0.829	0.87	13	143.8	1	3	2	2
50	35	M	A	A	A	P	A	20200	A	A	A	150	6	50	5.4	320	A	A	P	P	P	0.9	2.13	39	131.8	1	3	2	2
51	25	F	P	P	A	P	A	33000	A	P	A	231	6.1	51	4	198	A	A	A	P	P	0.656	0.86	28	90.8	1	3	1	2
52	28	M	P	P	A	P	A	18700	A	P	A	253	6.6	57	4.2	200	P	A	P	P	P	0.636	0.79	32	160.7	1	3	1	2
53	34	M	P	P	P	P	A	23600	P	P	A	400	7	59	5.3	1000	P	A	P	P	P	0.757	2.5	9	96.1	1	3	2	2
54	58	M	P	P	A	P	A	28300	P	P	A	456	5.7	59	5	239	A	A	A	P	P	0.877	0.52	20	150.9	1	3	2	2
55	39	M	P	P	A	P	A	32300	P	P	A	342	6.1	70	5	609	A	A	A	P	P	0.82	1.78	12	110.7	1	3	2	2
56	50	M	P	P	A	P	A	19100	A	A	A	432	4.9	67	3	807	P	A	P	P	P	0.612	1.87	14	78.9	1	3	2	2
57	45	M	A	A	A	P	A	20400	A	A	A	342	5.6	53	4	432	P	A	P	N	P	0.714	1.26	15	85.9	1	3	2	2
58	54	M	P	P	A	P	A	2100	A	A	A	243	6.1	30	4.2	399	A	A	A	P	P	0.689	1.64	28	70.9	1	3	2	2
59	35	M	A	A	A	P	A	19200	A	A	A	213	5.7	45	5	680	A	A	A	P	P	0.877	3.19	38	102.6	1	3	2	2
60	60	M	P	P	A	P	A	21200	A	P	A	159	5.7	23	3	239	A	A	P	P	P	0.526	1.5	32	89.7	1	3	2	2
61	26	M	P	P	A	P	A	22300	P	P	A	200	6.4	60	4.5	342	P	A	P	N	P	0.703	1.71	40	70.3	1	3	1	2
62	33	M	P	P	A	A	A	16700	A	A	A	264	7	59	5.7	456	A	A	A	N	P	0.814	1.73	32	55.8	1	3	2	2
63	22	M	P	P	A	P	A	13900	P	P	A	254	5.8	67	5	342	A	A	A	N	P	0.862	1.35	15	79.7	1	3	1	2
64	56	M	P	P	A	P	A	28000	P	P	A	321	7.1	70	6	432	A	A	A	P	P	0.845	1.35	13	149.7	1	3	2	2
65	45	M	P	P	A	P	A	19800	P	P	A	231	7	68	5.8	200	A	A	A	P	P	0.829	0.87	13	143.8	1	3	2	2
66	35	M	A	A	A	P	A	20200	A	A	A	150	6	50	5.4	320	A	A	P	P	P	0.9	2.13	39	131.8	1	3	2	2
67	25	F	P	P	A	P	A	33000	A	P	A	231	6.1	51	4	198	A	A	A	P	P	0.656	0.86	28	90.8	1	3	1	2
68	28	M	P	P	A	P	A	18700	A	P	A	253	6.6	57	4.2	200	P	A	P	P	P	0.636	0.79	32	160.7	1	3	1	2
69	33	F	A	A	A	A	A	4000	A	A	A	47	6	90	2	20	A	A	A	N	A	0.333	0.43	17	5	2	4	2	1

70	45	M	P	P	A	A	A	4800	A	A	A	78	4.6	110	1.2	25	A	A	A	N	A	0.261	0.32	13	9.1	2	4	2	1
71	56	M	A	A	A	A	A	5200	A	A	A	110	6	80	2.1	45	A	A	A	N	A	0.35	0.41	19	12	2	4	2	1
72	45	M	A	A	A	A	A	6600	A	A	A	120	5.6	90	1.2	45	A	A	A	N	A	0.214	0.38	18	6.2	2	4	2	1
73	27	F	A	A	A	A	A	4100	A	A	A	120	5.8	89	2	40	A	A	A	N	A	0.345	0.33	12	8.3	2	4	1	1
74	40	F	P	P	A	A	A	4100	A	A	A	111	5.9	98	3	35	A	A	A	N	A	0.508	0.32	14	4.6	2	4	2	1
75	55	M	P	P	A	A	A	6000	A	A	A	30	6	20	1.5	20	A	A	A	N	A	0.25	0.67	17	7.1	2	4	2	1
76	39	M	A	A	A	A	A	5400	A	A	A	48	6	89	2	23	A	A	A	N	A	0.333	0.48	14	7.6	2	4	2	1
77	42	F	A	A	A	A	A	8400	A	A	A	124	4.1	91	1.3	60	A	A	A	N	A	0.317	0.48	8	8.1	2	4	2	1
78	45	M	P	P	A	A	A	4800	A	A	A	78	4.6	110	1.2	25	A	A	A	N	A	0.261	0.32	13	9.1	2	4	2	1
79	56	M	A	A	A	A	A	5200	A	A	A	110	6	80	2.1	45	A	A	A	N	A	0.35	0.41	19	12	2	4	2	1
80	45	M	A	A	A	A	A	6600	A	A	A	120	5.6	90	1.2	45	A	A	A	N	A	0.214	0.38	18	6.2	2	4	2	1
81	27	F	A	A	A	A	A	4100	A	A	A	120	5.8	89	2	40	A	A	A	N	A	0.345	0.33	12	8.3	2	4	1	1
82	40	F	P	P	A	A	A	4100	A	A	A	111	5.9	98	3	35	A	A	A	N	A	0.508	0.32	14	4.6	2	4	2	1
83	55	M	P	P	A	A	A	6000	A	A	A	30	6	20	1.5	20	A	A	A	N	A	0.25	0.67	17	7.1	2	4	2	1
84	39	M	A	A	A	A	A	5400	A	A	A	48	6	89	2	23	A	A	A	N	A	0.333	0.48	14	7.6	2	4	2	1
85	49	M	A	A	A	A	A	8000	A	A	A	29	4	110	0.6	10	A	A	A	N	A	0.15	0.35	19	7.4	2	5	2	1
86	42	F	A	A	A	A	A	6200	A	A	A	127	4.1	69	1.3	59	A	A	A	N	A	0.317	0.47	20	4	2	5	2	1
87	49	M	A	A	A	A	A	8000	A	A	A	29	4	110	0.6	10	A	A	A	N	A	0.15	0.35	19	7.4	2	5	2	1
88	42	F	A	A	A	A	A	6200	A	A	A	127	4.1	69	1.3	59	A	A	A	N	A	0.317	0.47	20	4	2	5	2	1

ANNEXURE 3: PATIENT CONSENT FORM

Study detail**:" A DESCRIPTIVE STUDY ON ROLE OF PLEURAL FLUID C-REACTIVE PROTEIN IN PLEURAL EFFUSIONS"**

Study centre :GOVT. KILPAUK MEDICAL COLLEGE/
GOVT. ROYAPETTAH HOSPITAL, CHENNAI
Patient Name :
Patient Age :
OP number :

Patient may check in✓( ) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well-being or any unexpected or unusual symptoms. ☐

I hereby consent to participate in this study. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests. ☐

Signature/thumb impression:

Patient Name and Address: Place: Date:

Signature of investigator :

Study investigator's Name : Place: Date :

நோயாளி ஒப்புதல் படிவம்

ஆய்வுவிவரம்: **"A DESCRIPTIVE STUDY ON ROLE OF PLEURAL FLUID C-REACTIVE PROTEIN IN PLEURAL EFFUSIONS"**

ஆய்வுமையம்: அரசு கீழ்ப்பாக்கம் மருத்துவக்கல்லூரி,

சென்னை

நோயாளி பெயர்:
நோயாளி வயது:
புறநோயாளி எண்:
நோயாளி இந்தப்பெட்டிகள் உள்ளே டிக்செய்யலாம்

மேலே உள்ள ஆய்வின் நடைமுறையின் நோக்கத்தை நான் புரிந்துகொண்டேன் என உறுதிப்படுத்துகிறேன். கேள்வி கேட்பதற்கு எனக்கு வாய்ப்பு உள்ளது, எனது முழுதிருப்திக்கு எனது கேள்விகளும் சந்தேகங்களும் பதிலளிக்கப்பட்டன.
-இந்த ஆய்வில் நான் பங்கேற்பது தன்னார்வத்திலானது மற்றும் எனது சட்டபூர்வ உரிமைகள் பாதிக்கப்படாமல் எந்த நேரத்திலும் எந்தக்காரணமும் கூறாமல் விலகிக்கொள்வதற்கு நான் சுதந்திரமாக உள்ளேன் என்பதை நான் புரிந்துகொண்டேன்.
-சிகிச்சையக ஆய்வை வழங்கும் நிறுவனம், ஆய்வை வழங்கும் நிறுவனத்தின் சார்பாக பணிபுரியும்மற்றவர்கள், நெறிமுறைக்குழு மற்றும் ஒழுங்கு முறைஅமைப்புகள், தற்போதைய ஆய்வு மற்றும் அவற்றில் இருக்கக்கூடிய எந்த ஒரு ஆராய்ச்சியிலும் எனது உடல்நலப்பதிவேடுகளைப் பார்ப்பதற்கு எனது அனுமதி தேவையில்லை என்று நான் புரிந்துகொண்டேன். அதுதொடர்பாக நடத்தப்படும், நான் ஆய்விலிருந்து விலகினாலும் கூட இந்த அணுகலை ஒப்புக்கொள்கிறேன். எனினும், சட்டத்தின்கீழ் தேவைப்பட்டால் ஒழிய, மூன்றாம் தரப்பினருக்கு வெளியிடப்படும் அல்லது பிரசுரிக்கப்படும் எந்தத் தகவல்களில் எனது அடையாளம் வெளிப்படுத்தப்படாது

என்பதைநான் புரிந்துகொண்டேன். இந்த ஆய்விலிருந்து எழும் தரவுகள் அல்லது முடிவுகளின் பயன்பாட்டை கட்டுப்படுத்தாமல் இருக்க நான் ஒப்புக்கொள்கிறேன்

.-மேலே உள்ள ஆய்வில் பங்கேற்க நான் ஒப்புக்கொள்கிறேன், ☐

ஆய்வின்போது அளிக்கப்பட்ட அறிவுரைகளுக்கு இணங்கவேண்டும், ஆய்வுக்குழுவுடன் விசுவாசத்துடன் ஒத்துழைக்கவும், எனது உடல்நலத்தில் அல்லது நல்வாழ்வில் ஏதேனும் சீர்கேடு ஏற்பட்டால் அல்லது எதிர்பாராத அல்லது வழக்கத்திற்கு மாறான அறிகுறிகள். ☐

-இந்த ஆய்வில் பங்கேற்பதற்கு நான் ஒப்புதல் அளிக்கிறேன். ☐

-இரத்தவியல், உயிர்வேதியியல், ரேடியோலாஜிக்கல் பரிசோதனைகள் உட்பட முழுமையான மருத்துவ பரிசோதனை மற்றும் பகுப்பாய்வு பரிசோதனைகளை மேற்கொள்ள நான் அனுமதி கொடுக்கிறேன். ☐

கையொப்பம் /கட்டை விரல்ரேகை:
நோயாளியின் பெயர் மற்றும்முகவரி:
ஆய்வாளரின் தேதி கையொப்பம்:

ஆய்வு ஆய்வாளரின் பெயர், இடம்,தேதி