DISSERTATION TITLED

"ROLE OF PLEURAL FLUID C-REACTIVE PROTEIN IN ETIOLOGICAL DIAGNOSIS OF PLEURAL EFFUSION"

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CERTIFICATE

This is to certify that the dissertation entitled "**ROLE OF PLEURAL FLUID C-REACTIVE PROTEIN IN ETIOLOGICAL DIAGNOSIS OF PLEURAL EFFUSION** " is a bonafide work done by **DR.VICKRAM VIGNESH.R**, Post Graduate Student, Institute of Internal Medicine, Madras Medical College, Chennai-3, in partial fulfillment of the University Rules and Regulations for the award of MD Branch – I Internal Medicine, under our guidance and supervision, during the academic year 2010 - 2013.

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I solemnly declare that the dissertation entitled "**ROLE OF PLEURAL FLUID C-REACTIVE PROTEIN IN ETIOLOGICAL DIAGNOSIS OF PLEURAL EFFUSION**" is done by me at Madras Medical College, Chennai-3 during May 2012 to November 2012 under the guidance and supervision of Prof**.** R. PENCHALAIAH, M.D., to be submitted to The Tamilnadu Dr M.G.R Medical University towards the partial fulfillment of requirements for the award of M.D DEGREE IN GENERAL MEDICINE BRANCH-I.

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CONTENTS

LIST OF ABBREVATIONS:

CRP	-	C-REACTIVE PROTEIN
LDH	-	LACTATE DEHYDROGENASE
ADA	-	ADENOSINE DEHYDROGENASE
IL	-	INTERLEUKIN
PMN	-	POLYMORPHONUCLEAR CELLS
AFB	-	ACID FAST BACILLI
TB	-	TUBERCULOSIS
SLE	-	SYSTEMIC LUPUS ERYTHEMATOSUS
SD	-	STANDARD DEVIATION

INTRODUCTION

INTRODUCTION

Pleural effusion is one of the common problems in internal medicine where diagnosis is easily made in most of the cases. The landmark article by Light et al. is the most significant eventin the diagnosis of pleural effusion. He classified the pleural effusion into transudate and exudate and simplified the diagnostic approach to our modern day diagnosis of pleural effusion. In Indian subcontinent infectious causes of pleural effusion particularly tuberculosis and parapneumonic effusion are still the leading causes of pleural effusion. Though the incidence of empyema has come down due to initiation of early antibiotic therapy worldwide but in India considerable number of empyema and loculated pleural effusion is encountered in tertiary care setup. Tuberculosis is the most common cause of effusion in most of the case series conducted in India and often diagnosed and treated empirically. After the advent of ADA, the diagnosis of tuberculosis has become simple and the need for the pleural biopsy is greatly reduced. Malignant effusion is often suggested by the hemorrhagic nature of effusion, it is common in both primary as well as secondary lung malignancy. It produces massive effusion and the diagnostic yield of the pleural fluid is low and the diagnosis is easily made without advent of biopsy if the pleural fluid aspiration is positive for malignant cells. The rare causes of pleural effusion such as rheumatoid effusion,

mesothelioma associated effusion, pulmonary embolism associated effusion are rarely encountered in our day to day practice. High index of suspicion is necessary to diagnosis these rare causes. There is an array of newer investigations for diagnosis of effusion in pipeline but none has gained wider acceptance among the clinicians. Trials have proven these newer investigations are no better than the Light's criteria. Polymerase chain reaction and lysozyme for the diagnosis of tuberculous effusion is presently being taken up for study in many centers. Tuberculous antigen and antibody is advocated for easier diagnosis and various studies have supported their usefulness but needs further validation. C-Reactive Protein(CRP) is an early acute phase reactant that is elevated in blood and pleural fluid in various inflammatory conditions. CRP measurement will be a simple,quick and cost effective for the diagnosis of pleural effusion and give a clue to the further workup. Though the measurement of CRP has not been advocated by any international guidelines, various studies done outside Indian subcontinent has showed positive correlation between level of CRP and the type of exudate. This study is undertaken to assess the ROLE OF CRP IN THE DIAGNOSIS OF ETIOLOGY OF PLEURAL EFFUSION.

AIMS AND OBJECTIVES

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AIM:

To find the role of pleural fluid CRP in etiological diagnosis of pleural effusion

OBJECTIVES:

- To find the diagnostic value of pleural fluid CRP in differentiating exudative from transudative effusion.

- To find out the significance of pleural fluid CRP in categorizing the cause of exudative pleural effusion into tuberculous effusion, parapneumonic effusion, malignant effusion and other.

- To find the place of CRP in diagnostic algorithm of pleural effusion.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

ANATOMY OF THE PLEURA:

The pleura consist of two membranes: the visceral pleura cover the lung surface and the parietal pleura lies outside the visceral pleura. Between these two membranes there is a potential space named pleural space, which is filled with a thin sheet of fluid, called pleural fluid. The main function of the pleural fluid is to eliminate friction forces allowing extensive movement of the lung to the chest wall during respiratory Movements.

FUNCTIONAL ANATOMY OF PLEURA[1]:

Pleura consists of five layers: a) the mesothelium, b)a layer of submesothelialconnective tissue, c) a thin layer of elastic tissue d)a second layer of connective tissue containing blood and lymph vessels and nerves., and e)a fibroelastic layer adherent to the underlying tissue. The visceral pleura lack innervation, and its blood supply is more complex than the parietal pleura.

BLOOD SUPPLY OF PLEURA:

Systemic capillaries supply the parietal pleura and acts as principal blood supply to parietal pleura.

PARIETAL PLEURA	BLOOD SUPPLY
COSTAL PLEURA	INTERCOASTAL ARTERY
MEDIASTINAL PLEURA	PERICARDIOPHRENIC ARTERY
DIAPHRAGMATIC PLEURA	SUPERIOR PHRENIC AND MUSCULOPHRENIC ARTERY

The venous drainage of the parietal pleura is primarily by the intercostal veins. Visceral pleura of human beings are thick, and nourished by bronchial vessels.

LYMPHATICS OF PLEURA:

The lymphatic plexus in the costal pleura are mainly confined to the intercostal spaces and are absent or minimal over the ribs. The lymphatic channels of the pleura covering the costal surface drain ventrally towards nodes along the internal thoracic vessels and dorsally towards lymph nodes of internal intercostal nodes near the heads of the ribs. The lymphatic vessels of the mediastinal pleura pass to the tracheobronchial and mediastinal nodes, where as lymphatics of the diaphragmatic pleura pass to the parasternal, middle phrenic, and posterior mediastinal nodes.

The visceral pleura[3] is abundantly endowed with lymphatic vessels[3]. These lymphatics form a plexus of intercommunicating vessels

that run over the surface of the lung toward the hilum and also penetrate the lung to join the bronchial lymph vessels by passing through the interlobular septa.

INNERVATION OF THE PLEURA:

Sensory nerve endings are present in the costal and diaphragmatic parietal pleura. The intercostal nerves supply the pleura covering the costal surface and the outer part of the pleura covering the diaphragm. When either of these areas is stimulated, pain is perceived in the adjacent chest wall. The central part of the diaphragm is innervated by phrenic nerve, and stimulation of diaphragmatic pleura causes the pain to be perceived in the ipsilateral shoulder. The visceral pleura is pain insensitive due to absence of nerve supply. Therefore, parietal pleura is the source of catchy pain and it is due to any disease process that cause inflammatory process in the pleura like tuberculous pleurisy.

PLEURAL FLUID:

In physiological state, pleural fluid is present in between the two pleura is very minimal. The mean amount of fluid in the right pleural space in normal individuals is 8.4 $\pm$4.3 mL. Normally, the quantity of fluid in the spaces of each lung is quite similar. Expressed per kg of body mass, the total pleural volume in normal, non-smoking humans space is 0.26 $\pm$ 0.1mL per kg.

PLEURAL FLUID PRESSURE AND DYNAMICS:

Movement of fluid within pleural membranes is based on the balance of hydrostatic and oncotic pressure[4]between the microvasculature and the pleural space. Fluid exchange across the pleural membranes is described by Starling's law[7]:

FLUID MOVEMENT = L X S $\{(P_{cap}-P_{pl})\} - \sigma\ (\pi_{cap}-\pi_{pl})$ where p and π are the hydrostatic and osmotic pressures, respectively, within the capillaries (cap) and pleural (pl); L is the hydraulic conductivity of the membrane; S is the surface area; and σ is the osmotic co-efficient for proteins. At the parietal pleura, there is fluid filtration from systemic capillaries into the adjacent interstitium and from the latter across the mesothelium to pleural space. The actual pleural pressure in humans is approximately –5cm H_2O at functional residual capacity and –30 cm H_2O at the total lung capacity. According to this model of pressure gradients, net transmembrane starling pressure moves fluid from pleural space to visceral pleura and then into pulmonary capillaries.

Recently, there have been conflicting data concerning the entry and exit of pleural fluid normally. Pressure gradients are not the only explanation of fluid turnover. The pleural space is analogous to any interstitial space, this pressure difference constitutes a gradient for fluid movement into, but not out of, the pleural cavity. The normal protein

concentration in the pleural fluid is low, which implies sieving of the proteins across a high-pressure gradient such as from the high-pressure systemic vessels[5]. Lymphatic drainage via the lymphatic stomas of the parietal pleura, solute-coupled liquid absorption on both parietal and visceral, contributes additionally to the exit of fluid from the pleural cavity.

MECHANISM OF PLEURAL EFFUSION:

❖ **INCREASED PLEURAL FLUID FORMATION**:

INCREASED INTERTITIAL FLUID IN THE LUNG:

- LEFT VENTRICULAR FAILURE
- PNEUMONIA
- PULMONARY EMBOLUS

INCREASED INTRAVASCULAR PRESSURE IN PLEURA:

- RIGHT OR LEFT VENTRICULAR FAILURE
- SUPERIOR VENA CAVAL SYNDROME

INCREASED PERMEABILITY OF THE CAPILLARIES IN PLEURA:

- PLEURAL INFLAMMATION
- INCREASED LEVEL OF VASCULAR ENDOTHELIAL FACTOR

INCREASED LEVEL OF PLEURAL FLUID PROTEIN:

DECREASED PLEURAL PRESSURE:

- LUNG ATELECTASIS OR INCREASED ELASTIC RECOIL OF THE LUNG

INCREASED FLUID IN PERITONEAL CAVITY

- ASCITES OR PERITONEAL DIALYSIS

DISTRUPTION OF THORACIC DUCT

DISRUPTION OF BLOOD VESSELS IN THE THORAX

❖ **DECREASED PLEURAL FLUID ABSORPTION:**

- OBSTRUCTION OF THE LYMPHATICS DRAINING THE PARIETAL PLEURA
- ELEVATION OF SYSTEMIC VASCULAR PRESSURE
- DISRUPTION OF THE AQUAPORIN SYSTEM IN THE PLEURA

CAUSES OF PLEURAL EFFUSION:

TRANSUDATIVE CAUSES OF PLEURAL EFFUSIONS ARE

1. CONGESTIVE HEART FAILURE
2. HEPATIC HYDROTHORAX
3. NEPHROTIC SYNDROME
4. PERITONEAL DIALYSIS

5. FONTAN OPERATION
6. URINOTHORAX
7. SUPERIOR VENACAVAL SYNDROME
8. ATELECTASIS
9. MISPLACED CENTRAL LINE
10. PERICARDIAL DISEASE
11. PULMONARY EMBOLI
12. SARCOIDOSIS
13. AMYLOIDOSIS
14. CEREBROSPINAL FLUID LEAK INTO THE PLEURA

EXUDATIVE CAUSES OF PLEURAL EFFUSION:

1. MALIGNANCY:

   (Mesothelioma, lymphoma of body cavity, metastasis to lung and pleura, lymphoma associated with pyothorax)

2. INFECTION:

   (TB, bacterial pneumonia, invasive fungal disease, viral infections, parasitic disease)

3. PULMONARY EMBOLIZATION

4. ABDOMINAL CAUSES

   (Oesophageal perforation, acute and chronic pancreatitis, abdominal abscesses, diaphragmatic hernia, post abdominal surgery, varicealsclerotherapy, post hepatic transplant)

5. COLLAGEN VASCULAR DISORDERS

   (Rheumatoid pleuritis, Systemic lupus erythematosus, Wegeners granulomatosus, Churg-Strauss syndrome)

6. POST CORONARY ARTERY BYPASS GRAFT OPERATION

7. EXPOSURE TO ASBESTOS.

8. SARCOID LUNG

9. UREMIC PLEURITIS AND EFFUSION

10. MEIGS SYNDROME

11. YELLOW NAIL SYNDROME

12. DRUG CAUSING PLEURAL EFFUSION.

a. Nitrofurantoin

b. Clozapine

c. Methotrexate

d. Interleukin

e. Dandrolene

f. Methysergide

g. Bromocriptine

h. Procarbazine

i. Amiodarone

j. Dasatinib

13. TRAPPED LUNG SYNDROME.

14. RADIATION EXPOSURE

15. AFTER CARDIAC SURGERY

16. HEMOTHORAX

17. IATROGENIC INJURY

18. OVARIAN HYPERSTIMULATION SYNDROME

19. DISEASES OF PERICARDIUM

20. CHYLOTHORAX

SYMPTOMS OF PLEURAL EFFUSION:

The symptoms of pleural effusion are per se due to effusion rather than due to underlying etiology.

PLEURITIC CHEST PAIN
DULL ACHING CHEST PAIN
DRY NON PRODUCTIVE COUGH
DYSPNEA

Some of the patients with pleural effusion do not have catchy pain instead have dull aching chest pain that may suggest underlying pleural malignancy. Very rarely pleuritic pain resulting from pleural inflammation radiates to abdomen due to the intercostal nerves that

supply the parietal pleura. Pain may also radiate to the tip of the shoulder when the diaphragm is involved. The reason behind the dry cough production by pleural effusion is probably due to the compression of the pleural fluid resulting in contact of the opposing bronchial walls resulting in cough. Pleural effusion reduces the lung volume and result in breathlessness.

PHYSICAL EXAMINATION:

The physical examination findings of pleural effusion is deviation of trachea to opposite side, shifting of apical impulse, intercostal fullness, diminished expansion of chest on the affected side, stony dull on percussion and diminished breathsounds and decreased vocal resonance. The presence of tenderness in the intercostal area indicates empyema and occasionally there will be pus pointing and it is called as empyema necessitans.

CLASSIFICATION OF PLEURAL FLUID INTO TRANSUDATE AND EXUDATE:

It is imperative to classify the pleural effusion into exudate and transudate. In the past before the Lights classification[6] was used pleural fluid protein was alone used to classify the pleural effusion. About 10% of pleural effusion was misclassified by this method and led to the introduction of Light's criteria. Light's criteria proved 99% of accuracy

in separating exudate and transudate led to the Light's criteria as the standard rule.

LIGHT'S CRITERIA:

1) Pleural fluid protein divided by serum protein greater than 0.5
2) Pleural fluid LDH divided by serum LDH greater than 0.6
3) Pleural fluid LDH more than 2/3rd of the upper limit of normal serum LDH.

For the effusion to be classified as exudate atleast one of the criteria should be met. Transudate should not meet any of the criteria. There are numerous tests in voyage for classification of the pleural effusion like pleural fluid cholesterol, pleural fluid-serum albumin ratio, soluble leukocyte selectin, cytokines, uric acid, and pleural fluid to serum cholinesterase.

IMAGING OF PLEURAL EFFUSION:

Diseases of the pleural space[8] can be made out with ease by a various radiographic methods using frontal, lateral, oblique and decubitus skiagrams. Pleural effusions accumulate in the most dependent part of the pleural cavity, because lung which is relatively less dense than the surrounding pleural fluid, floats in the effusion. Because of the downward pull due to gravity the initial accumulation of fluid occurs in a subpulmonic location, ie between the inferior surface of the lower lobes

and diaphragm.75 % of fluid occupies the subpulmonic space without moving into other pleural recess.As it accumulates pleural liquid spills over into the costophrenic sulcus posteriorly, anteriorly and then laterally.The amount of effusion can be calculated based on standard posterior-anterior and lateral view of standard chestX ray. Minimum of 75 mL is needed to obliterate the posterior costophrenic sulcus, and a minimum of 175 mL is necessary obscure the lateral costophrenic sulcus on the upright chest X- ray. 500 mL is necessaryto obliterate the diaphragmatic contour on an erect chest X ray; if pleural effusion reaches the level of the fourth rib, close to 1000 mL are present in the pleural space.

Chest ultrasound can detect as little as 5-50 ml of pleural fluid. Ultrasound is useful in small and loculated effusions. Ultrasound also detects tumors associated with pleura and very useful in in diagnosing effusions in recumbent patients like patients on mechanical ventilation. When septations are present ultrasound detects better than CT scan. Parietal pleural thickening, visceral pleural thickening diaphragmatic thickening diaphragmatic nodules has good sensitivity and specificity for diagnosis of malignant effusions.

CT thorax detects very small effusions. In the presence of inflammation CT can clearly identify thickening of the visceral and parietal pleura and their enhancement after the contrast injection. CT also

helps to visualize the lung parenchyma. A pleural effusion appears on CT as a dependent sickle-shaped opacity with a lower CT number than that of any adjacent pleural thickening or mass. Loculated pleural effusions have lenticular configuration with smooth margins and they displace the adjacent parenchyma.

CAUSE OF BILATERAL EFFUSION:(Rabin et al)

1. CONGESTIVE HEART FAILURE
2. VIRAL INFECTIONS CAUSING SEROSITIS, eg. DENGUE
3. RHEUMATOLOGICAL DISEASES
   eg. SLE AND RHEUMATOID ARTHRITIS
4. MALIGNANCY
5. CONTARINI'S SYNDROME.
6. PULMONARY EMBOLISM
7. NEPHRITIS
8. AMYLOIDOSIS
9. CIRRHOSIS
10. EOSINOPHILIC PNEUMONIA
11. CONSTRICTIVE PERICARDITIS.

RIGHT SIDED PLEURAL EFFUSION:

1. CONGESTIVE HEART FAILURE
2. HEPATIC HYDROTHORAX

3. SUBDIAPHRAGMATIC ABSCESS

4. LIVER ABSCESS RUPTURE

LEFT SIDED EFFUSION:

1. PANCREATITIS.

2. DRESSLERS SYNDROME.

3. LEFT SUBDIAPHRAGMATIC ABSCESS.

4. ESOPHAGEAL RUPTURE.

MASSIVE EFFUSION[9]:

Massive effusion is defined as effusion occupying upto second intercostal space. The other definition is the effusion occupying the entire hemithorax is called massive.

CAUSES:

1. MALIGNANCY.

2. PARAPNEUMONIC EFFUSION.

3. TUBERCULOSIS

4. TRANSUDATIVE EFFUSION.

THORACENTESIS:

Thoracocentesis is a principal diagnostic procedure in a patient with pleural effusion. Analysis of the pleural fluid will help us to categorize as either transudate or exudate. Thoracocentesis, as a

therapeutic procedure, may help to decrease respiratory distress in patients with massive effusions. There is insufficient data on the safety of this procedure in patients who are using anticoagulants or decreased platelet count. It should be performed with great caution in patients who are on ventilators because of increased risk of tension pneumothorax.

COMPLICATIONS OF THORACENTESIS:

1. Pneumothorax
2. Kidney or Lung puncture
3. Hemothorax

APPROACH TO DIAGNOSIS OF PLEURAL EFFUSION:

GROSS APPEARANCE, ODOR, AND CHARACTER OF PLEURAL FLUID:

The transudate effusion on gross appearance is mostly clear fluid and straw coloured. Exudate tends to be more amber like and appears cloudy, if the total count in the fluid is high. A fresh drawn exudate clots on prolonged standing, while an older one has less fibrin content and, remains in a fluid state. Bloody effusionis due to damage to a vessel during thoracocentesis and by pleural or lung biopsy. If the fluid is uniformly red, or brown colour, it indicates presence of malignancy in most cases, although tuberculosis, leukemia, infarction and rheumatoid pleuritis may also cause haemorrhagic effusion.chyle, appears like milk,

though chronic effusions of any cause can mimic chyle and it is called pseudochyle. It is due to presence of globules of fat formed from dying cells. Purulent fluid in cases of frank empyema is easily recognized. Ammonia odor indicates urinothorax. Putrid odor indicates anaerobic empyema.

COLOR	**SUGGESTED DIAGNOSIS**
STRAW	TRANSUDATE, PAUCICELLULAR EXUDATE
RED	HEMOTHORAX,MALIGNANCY,OTHERS
WHITE (MILKY)	CHYLOTHORAX OR, PSEUDOCHYLE
YELLOWISH GREEN	RHEUMATOID ARTHRITIS
BILE	CHOLOTHORAX-BILIOPLEURAL FISTULA
BROWN	OLD HAEMORRHAGIC EFFUSION, RUPTURE OF AMOEBIC LIVER ABSCESS.
BLACK	ASPERGILLUS NIGER SPORES

CHARACTER OF PLEURAL EFFUSION:

ANCHOVY SAUCE	RUPTURE OF AMOEBIC LIVER ABSCESS
FOOD PARTICLES	RUPTURE OF OESOPHAGUS
VISCOUS	PLEURAL EFFUSION IN MESOTHELIOMA
SATIN LIKE SHEEN	CHOLESTEROL EFFUSION
DEBRIS	RHEUMATOID EFFUSION
PUS	EMPYEMA

DISEASES	**COMMENT**
TUBERCULOSIS	COMMONEST CAUSE.LYMPHOCYTE - 90-95%
LYMPHOMA	ALL CELLS WHICH HAS NUCLEI ARE LYMPHOCYTES
RHEUMATOID PLEURISY	SOMETIMES ASSOCIATED WITH UNEXPANDED LUNG
CHYLOTHORAX	COMMONEST CAUSE-LYMPHOMA.
SARCOIDOSIS	LYMPHOCYTES >90%
POST CORONARY ARTERY BYPASS GRAFT	OCCURS AFTER 2 months FOLLOWING SURGERY
YELLOW NAIL SYNDROME	CHARACTERISTICALLY A DISCORDANT EXUDATE.

PLEURAL FLUID pH:

The pleural fluid pH is considered low if pH value is less than 7.30 with a blood pH in normal range. Most transudate has pH ranging from 7.45 to 7.55. pH of most exudate effusion will be in the range of 7.30-7.45. In parapneumonic effusion and esophageal rupture the acidic pH is due to rapid rate of glucose usage and accumulation of end products of metabolism.

In malignancy and rheumatoid pleural effusion abnormally thickened pleura prevents diffusion of glucose into the pleural space and back diffusion of carbon dioxide resulting in decreased pH.

PLEURAL FLUID GLUCOSE:

In normal state glucose concentration in the blood and pleural space is equal due to free diffusion of glucose[26]. Pleural fluid glucose<60 mg/dLis present in almost always due to one of the four disorders, namely TB effusion, parapneumonic effusion, pleural tumors, or rheumatoid disease.Rarely pleural effusion with glucose <60mg/dL is found include paragonimiasis infection, hemothorax, Churg-Strauss syndrome and, lupus pleuritis. The lower the pleural fluid glucose, the more likely that one is dealing with a complicated parapneumonic effusion. In rheumatoid pleurisy glucose is less than 30 mg/dL in 75% of patients. Low glucose in empyema and parapneumonic effusion is

associated with bad prognosis and indication for intercostal drainage tube insertion.

PLEURAL FLUID PROTEIN AND LDH:

The total protein may be helpful in diagnosing pleural effusion. Tubercular effusion almost always has protein concentration more than 4 g/dL, while parapneumonic, malignant effusion have a wide range of total protein level.when total protein level[10] is more than 7g/dLWaldenstromsmacroglobulinemia and multiple myeloma should be considered. Several features about the pleural fluid LDH may also help in the diagnostic evaluation of a pleural effusion. With a discordant exudate (an exudate by protein but not LDH criterion), the differential should include malignancy, resolving parapneumonic effusion, sarcoidosis, chylothorax, yellow nail syndrome, and a hypothyroidism. When an exudate is discordant by LDH only, malignancy, parapneumonic effusion and pneumocystis carinii pneumonia should be considered. Considering the upper end of the serum LDH of 200 IU/l, pleural fluid LDH concentration of >1000 IU/L is found in one of the following disorders complicated parapneumonic effusion or emphyema, rheumatoid pleurisy, or pleural paragonimiasis. AnLDH of > 1000 IU/L in pleural fluid is rarely observed with malignancy and with a tuberculous pleural effusion.

PLEURAL FLUID CYTOLOGY[19]:

Increased neutrophil[15] count in the pleural fluid isdue to interleukin 8, which is the major chemotaxin for neutrophils. The causes of increased polymorphs are parapneumonic effusions, tuberculosis in early stages.

The causes of increased lymphocyte count in the pleural fluid are tuberculosis and malignancy,

PLEURAL FLUID EOSINOPHILIA[20]:

Eosinophilia in pleural fluid is defined as a eosinophil count in pleural fluidmore than 9% of the total cells. Interleukin-5 is the vital chemotactic factor attracting eosinophils from bone marrow into the pleural cavity. Pneumothorax is one of the common causes of pleural fluid esinophilia. Other causes include hemothorax, benign asbestos pleural effusion, pulmonary embolism, postthoracentesis, parasitic disease, fungal disease, drug induce, lymphoma, carcinoma, Churg-Strauss syndrome.

MESOTHELIAL CELLS:

Pleural cavity is lined by mesothelial cells[2]. They are present in small amount in normal pleural fluid. Size of mesothelial cells is usually 12 to 30 micrometer in diameter. Mesothelial cells are uncommon in tuberculous pleural effusion. But patients with AIDS may have increased amount of mesothelial cells when they develop tuberculous pleural

effusion. The absence of mesothelial cells is common with complicated parapneumonic effusion.

PLEURAL FLUID AMYLASE:

The finding of an amylase rich pleural effusion, defined as a increased amylase in pleural fluidmore than upper limit of normal for serum amylase or a pleural fluid-serum amylase ratio more than 1 signifies that the exudative effusion is either due to pancreatic disease, malignancy, esophageal rupture. Pleural fluid amylase may be normal initially in acute pancreatitis but increases as the disease progresses. In chronic pancreatitis amylase is always elevated and may reach very high level, often >100,000 IU/L. Serum amylase may be elevated due to diffusion from the pleural space back into the blood or may be normal. Approximately 10-14% of patients with a malignant pleural effusion, present with an increased pleural fluid amylase concentration. Isoenzyme analysis of these amylase rich effusion demonstrate that most of the amylase is of salivary type. The most common malignancy causing a salivary amylase rich pleural effusion is adenocarcinoma of lung with adenocarcinoma of ovary being the next frequent cause. Hematological malignancies are also associated with salivary type amylase in pleural fluid.

PLEURAL FLUID ADA:

Adenosine deaminase, an enzyme important in the degradation of purine and required for lymphocyte differentiation and is involved in maturation of monocyte-macrophage lineage. ADA level is higher in tubercular effusions than other exudativepleural effusion. In general, a cutoff level between 40 and 45 U/L is used with levels above indicating tuberculous pleural effusion. The sensitivity and specificity of pleural fluid ADA level in the diagnosis of tuberculous pleural effusion is more than 90%. The level of ADA in patients with and without AIDS is comparable and renal transplant patients who develop a tuberculous pleural effusion have an elevated pleural fluid ADA level. Other important causes of increased ADA level are empyema and effusion in rheumatoid arthritis. Rare causes of higher pleural fluid ADA levels are minor percent of other neoplasms, patients with Q fever and with brucellosis. The isoenzymes of ADA are ADA1 and ADA2. ADA1 is ubiquitous and is produced by lymphocytes, neutrophils, monocytes, and macrophages. In contrast, ADA2 exists only in monocytes and macrophages. The increase in activity of ADA is mainly due to ADA2. In routine practice, ADA isoenzymes measurementis not needed to ascertainthe diagnosis of tuberculous effusion. However, in certain instances they can be quite useful.

INTERFERON –GAMMA:

Interferon –gamma is produced by the CD4 + T lymphocytes that migrate into pleural cavity in tuberculosis. Interferon-gamma appears to be a useful defence mechanism. Interferon-gamma enhances polymyristate acetate-induced hydrogen peroxide production in macrophages, facilitating elimination of intracellular parasites. This lymphokine also inhibits mycobacterial growth in human monocytes. Interferon gamma >140pg/ml is significant for tubercular pleural effusion.

LIPID ANALYSIS:

Analysis of pleural fluid triglyceride is vital to the diagnosis of a suspected chylothorax. Pleural fluid level of triglyceride more than 110mg/dL strongly supports the diagnosis. In about 15% of patients with triglyceride concentration < 110 mg/dL and 3% have values less than 50mg/dL.If there is strong suspicion of chylothorax in these patients lipoprotein electrophoresis of the pleural fluid should be done. The cholesterol level in a chylothorax is generally less than 200mg/dL. Fat globules may be noted on sudanIII staining which stains chylomicrons orange.

N- TERMINAL PRO-BNP:

Measurement of N-terminal pro-brain natriuretic peptide[10,11]in serum or blood should be considered in cases of effusion in the setting of congestive heart failure if the cause of effusion is in doubt. When the ventricles are subjected to increased pressure or volume, BNP is released. The biologically active BNP and the larger N-terminal-pro-brain natriuretic peptide are released into circulation. The threshold for the diagnosis of heart failure recommended is 1500pg/mL of pro-BNP.

TUMOR MARKERS IN PLEURAL FLUID:

No single pleural fluid tumor marker is accurate enough for routine use in the diagnostic evaluation of pleural effusion. CEA, CA-125,CA-15-3 and cytokeratin 19 fragments, but clinical usefulness is limited. Mesothelin is a newer tumor marker for malignant mesothelioma that is present increased in both effusion and serum. Soluble mesothelin-related peptides are believed to be either cleaved peptide fragments of mesothelin, or abnormal variants of mesothelin that are unable to bind to membranes and are found in the serum. Mesothelin has got a sensitivity range of 48-84% and specificity range 70-100% for diagnosis of mesothelioma. Adenocarcinoma of lung, lymphoma, ca ovary, metastatic pancreatic carcinoma also have positive results.

PLEURAL BIOPSY:

Pleural biopsy typically follows CT scan in undiagnosed pleural effusion. There are two common types of biopsy used. One is closed pleural biopsy and cutting needle biopsy done with the help of CT scan called as guided biopsy. When tuberculosis is suspected closed pleural biopsy using ultrasound guidance is preferred. When pleural-based mass is visible CT guided biopsy is needed. Thoracoscopic pleural biopsy is increasingly used to diagnose malignancy when an obvious mass is not visible on CT, when percutaneous biopsy is negative or when patchy disease is suspected. Open pleural biopsy is rarely used nowadays.

CLOSED PLEURAL BIOPSY:

Abrams needle or Cope needle is used to for performing closed pleural biopsy. It is operator dependent. It is most useful to diagnose diseases such as tuberculous pleural disease and rheumatoid pleuritis. It is also useful tool in undiagnosed case of lymphocytic effusion. Pneumothorax is an established complication of this procedure.

CT guided cutting needle biopsy:

It is used to get biopsy of pleural based mass and pleural biopsy in cytology negative malignant effusion. Incidence of pneumothorax is lesser when compared to closed pleural biopsy.

ELECTRON MICROSCOPIC EXAMINATION:

The diagnosis of mesothelioma and metastatic carcinoma to the pleural is made in most instances by cytology and immunohistochemical assessment, but electron microscopy still plays a decisive role in cases with unusual morphology or anomalous histochemical reactions. The ultrastructural features of mesothelioma are so characteristic as to be almost diagnostic. These characteristics include characteristic microvilli; the absence of microvillus core rootlets, glycocalyceal bodies, and secretory granules; the presence of intracellular desmosomes, junctional complexes, and intracytoplasmiclumina, and characteristic microvilli. The appearance of the microvilli is the most important diagnostic feature.

HYALURONIC ACID:

Pleural fluid from patients with mesothelioma is abnormally viscid. The increased viscosity in such fluids is due to the presence of increased hyaluronic acid. The measurement of hyaluronic acid is yet to be validated.

LECTIN BINDING:

Lectins are a class of glycoproteins of non-immune origin that bind specifically bind to carbohydrate groups found ubiquitously in various biologics products. Kawai et al investigated lectin biding in 23 pleural mesotheliomas, 6 effusions with reactive mesothelial cells, and 28 well

differentiated pulmonary adenocarcinomas and found significant.At - present time, such studies should be considered experimental.

LYSOZYME:

Lysozyme is a low molecular weight protein with bacteriolytic property. The level of lysozyme in the pleural fluid tends to be elevated in the patients with tuberculous pleural effusion,when compared to other exudates. Lysozyme levels in tuberculous pleural effusions are greater than those in malignant pleural effusions. The role of lyzozymes in diagnosing pleural effusion needs further study to confirm its role. Recent studies have suggested positive role of this enzyme in evaluation of effusion

DISCRIMINATION BETWEEN EXUDATIVE AND TRANSUDATIVE PLEURAL EFFUSION: EVALUATING DIAGNOSTIC TESTS IN THE PLEURAL SPACE:

The etiologies of many effusions[12] remain uncertain after routine pleural fluid analysis. For such patients, classification of pleural fluid into transudate and exudate allows the clinicians to simplify their differential diagnosis and pursue the more likely diagnosis with further testing. It should be emphasized, however, that classification of an effusion as an exudate or transudate for any individual patient by existing techniques

represents an inexact, probabilistic statement of what conditions are more likely than others as potential etiologies of an effusion.

Exudative effusion is defined by the presence of high concentrations of relatively large molecular weight compound. Pleural fluid protein and LDH arethe two large molecular weight compound. Light's rule is the most commonly used strategy and include three criteria (1) A pleural fluid LDH of more than 67% of the upper limit of normal for the laboratory's serum value, (2) a pleural fluid-to-serum LDH ratio >0.6 (3) a pleural fluid-to-serum protein ration >0.5. These criteria are used in an "or" rule wherein a positive result for any one criterion defines exudate. Many clinical studies found that Light's rule has a sensitivity of 95% to 97%, a specificity of 65% to 80% and an overall diagnosis accuracy of 88% to 93% for identifying exudates. Because of its high sensitivity, Light's rule performs well as a screening test for identifying nearly all exudate. Despite the high sensitivity, the identification of a transudative effusion by Light's criteria does not exclude the possibility of a malignant etiology considering that 5% of malignant pleural effusion present with transudates by Light's rule. Due to its only moderate specificity, however, Light's rule misclassifies as exudates in 15 to 30% of transudative effusion. This misclassification exposes some patients with true transudates to potential risks of unnecessary diagnostic studies

if clinicians over rely on the results of Light's rule with out considering a patients entire clinical picture.

Another limitation of Light's rule[13]relates to its two criteria that are mathematically coupled and consequently, do not function well when combined diagnostic rule due to multicollinearity effects. Both the criteria "pleural fluid LDH" and "pleural fluid-to-serum LDH ratio" contain the same biochemical feature, that is, LDH concentrations.

Heffner and coworkers proposed an "Abbreviated Light's rule" that removes the LDH ratio criterion and thereby simplifies Light's rule that yet maintains a high overall diagnostic accuracy equivalent to the three-criteria rule. The high diagnostic accuracy of the Abbreviated Light's rule as compared with the full three-criteria was recently confirmed.

The importance of accurate classification[14] of pleural effusions and the moderate specificity of Light's rule have stimulated many investigators to evaluate other pleural fluid tests and diagnostic rules and compare their performance with Light's rule. Examined tests include pleural fluid –to-serum albumin ratio, pleural fluid cholesterol, pleural fluid-to-serum cholesterol ratio, pleural fluid-to-serum bilirubin ratio, pleural fluid-to-serum cholinesterase ratios, cell free DNA and a host of other tests that include aspartate transaminase, interleukin-1 beta, uric acid, C-reactive protein, alanine transaminase, alkaline phosphatase,

creatinine kinase, ferritin, interleukin-8, tumor necrosis factor-alpha and gamma-glutamyltransferase to name a few. The cutoff points established for the most commonly proposed tests table

TEST	REPORTED CUTOFF POINTS
Pleural fluid protein	>3
Pleural fluid cholesterol	54mg/dL
Pleural fluid to serum cholesterol ratio	>0.3
Albumin gradient	<1.2
Pleural fluid to serum bilirubin ratio	>0.6

EXUDATIVE PLEURAL EFFUSION:

TUBERCULOUS PLEURAL EFFUSION:

Pleural effusion is the second most common[22] form of extrapulmonary tuberculosis after lymphatic involvement. The tubercular pleural effusions are thought to result from a delayed hypersensitivity reaction to mycobacteria and mycobacterial antigens in the pleural space. The organism and /or their antigens probably enter the pleural space due to leakage of a sub-pleural focus. They can manifest as primary disease or reactivated tuberculosis. Isolated pleural effusion usually reflects recent primary infection, and collection of fluid in the pleural space represents a hypersensitivity reaction resulting in increased capillary permeability and

subsequent derangement in lymphatic clearance of proteins and fluid from pleural cavity because of occlusion of pleural stoma. But in reactivated disease often lesions in lung are present.

MALIGNANT PLEURAL EFFUSION[18]:

A malignant pleural effusion is diagnosed by detecting exfoliated malignant cells in pleural fluid or demonstrating these cells in pleural tissue obtained by percutaneous pleural biopsy, thoracoscopy, or thoracotomy.In number of patients even though the pleural effusion is caused by malignancy, neoplastic cells cannot be demonstrated in pleural fluid or pleural tissue and, in fact probably are not present in these tissue. These are called as paramalignanteffusions[23]. Lymphatic obstruction appears to be most common mechanism for the development of a paramalignant effusion, for the accumulation of large volumes of fluid. Other local effects of the tumorcausing a paramalignant effusion are bronchial obstruction resulting in pneumonia or atelectasis.lymphatics are situated beneath the parietal pleura over the intercostal spaces. An important feature of the parietal pleura is lymphatic stoma, 2- to 12-micrometer openings between parietal pleural mesothelial cells. Involvement of lymphatics play a major role in development of effusion. The common tumor[31] producing effusion is lung, breast, lymphoma, ovary, stomach, unknown primary.

The treatment modalities available for malignant effusions are

1) Observation

2) Therapeuticthoracentesis

3) Chest catheter drainage only

4) Chest catheter drainage with chemical pleurodesis

5) Thoracoscopy with talc insufflation

6) Long term indwelling pleural catheter

7) Pleural abrasion

8) Chemotherapy

9) Radiotherapy

PARAPNEUMONIC EFFUSION:

A parapneumonic effusion is any pleural effusion associated with bacterial pneumonia or lung abscess[25].Parapneumonic effusions are usually small, but if depth of the effusion is greater than 10mm on the decubitus chest radiograph, a diagnostic thoracentesis should be done. Pleural effusions secondary to pneumonia arise from an inflammatory process contiguous to the visceral pleura[27].The effusion derives from the fluid entering the lung interstices, transversing the visceral pleura, and accumulates in the pleural space when the rate of accrual exceeds the capacity of the parietal pleural lymphaticsto remove the fluid. The fluid is classically as an exudate satisfying the Light's criteria. Parapneumonic

effusion occurs in 50% of streptococcus pneumonia but the organism can be demonstrated in fewer than 5% of patients. In contrast, culture of the pleural fluid is positive in 20% of adults and 80% of children with pleural effusion secondary to staphylococcus aureus infection. Pleural effusion also develop in 40 to 50% of gram negative aerobic pneumonias, and majority of these are culture positive pseudomonas species and Escherichia coli account for more than two thirds of all infections of pleural space caused by aerobic gram-negative organisms. Pleural effusions occur in 30-50% of patients with pneumonia due to legionella species. Complicated parapneumonic effusion requires tube thoracostomy. The indications for tube thoracostomy are pleural fluid loculations, effusion filling more than half of the hemithorax, air-fluid level, pus in the pleural space, positive stain for microorganisms, positive pleural fluid culture, pleural fluid pH<7.2, pleural fluid glucose <60mg/dl. Empyema is defined by the presence of pus in the pleural space. Direct extension of a pulmonary parenchymal infection into the pleural space causes empyema. Anaerobic infections cause foul smelling empyema. Tuberculosis can also cause empyema.

RHEUMATOID ARTHRITIS AND SYSTEMIC LUPUS ERYTHEMATOSUS:

Pleural disease is the most common intrathoracic manifestation of rheumatoid arthritis[16]. It usually affects middle-aged men and is characterized by a low pleural fluid glucose level. Thickening of visceral and parietal pleura is prominent in rheumatoid pleural effusion. The most consistent finding is the replacement of the normal mesothelial cell covering by a pseudo-stratified layer of epithelial cells with focal multinucleated giant cells, regular papillae containing branched capillaries, and occasional cholesterol clefts. Most patients are asymptomatic, but breathlessness may result from pulmonary compression in large effusions. Rheumatoid effusions are associated with nodules in 50% of patients and many patients have severe disease.

In SLE[17], pleural effusions appear up to 40% of patients. Even more,many patients may present with pleuritic chest pain without effusion. The pleural effusions are small in volume and bilateral in 50% of patients.

PULMONARY EMBOLISM:

The diagnosis most commonly overlooked in the differential diagnosis of a patient with an undiagnosed pleural effusion[21] is pulmonary embolism. At least 30% of patients with pulmonary embolism

have an associated pleural effusion. The pleural effusion may be unilateral or bilateral. The effusion is almost always exudate. The pleural red blood cell counts exceeds 100,000/l in fewer than 20% and is below 10,000/l in at-least 30%.

RARE CAUSES OF PLEURAL EFFUSION:

PARASITIC CAUSE OF PLEURAL EFFUSION:

PARASITIC CAUSES:
AMEBIASIS
HYDATID DISEASE
PARAGONIMIASIS
PNEUMOCYSTIS CARINI

AMEBIAIS:

Pleural effusion occurs by two mechanisms

1) Sympathetic effusion[37] due to irritation of diaphragm.
2) Rupture of liver abscess

About 20 to 30% of patients have exudative sympathetic effusion. And the effusion is usually mild to moderate in quantity. Pain referring to shoulder gives a clue to the underlying liver process.

FUNGAL INFECTIONS:

ASPERGILLOSIS
BLASTOMYCOSIS
COCCIDIOIDOMYCOSIS
CRYPTOCOCCOSIS
HISTOPLASMOSIS
CANDIDIASIS

ASPERGILLOSIS:

It occurs in two clinical scenarios. 1.Patient treated by artificial pneumothorax and 2. post operative patients after lobectomy and pneumonectomy[32].The diagnosis is made by demonstration of the aspergillus in the culture.

BLASTOMYCOSIS:

This presents similar to tuberculosis. It has both pulmonary infiltrate with accompanying effusion. The pleural effusion is an exudate and cytology is either neutrophils or lymphocytes. Pleural fluid biochemical parameters are significant for normal glucose and lactate dehydrogenase.

COCCIDIOIDOMYCOSIS:

It is an exudate and produced by rupture of the cavity containing coccidioidomycosis. It characteristically produces hydropneumothorax.

HISTOPLASMOSIS:

It is a very rare cause of pleural effusion and produces an exudate type of pleural effusion with lymphocyte predominance. X ray reveals characteristic subpleural nodule.

CANDIDIASIS:

Esophageal perforation should be searched in any case associated with candidial effusion. It is usually seen in post -operative settings.

ACTINOMYCOSIS:

More than half of the patients with thoracic actinomycosisis associated with pleural effusion. Multiple draining sinus tracks give a clue to the etiology. Gram staining is useful in the demonstration of the organism.it may produce gross pus in the pleural cavity with neutrophils dominance or serous fluid with lymphocyte dominance.

NOCARDIOSIS:

Nocardiasis occurs in the setting of imunocompromised patients. It has pulmonary infiltrate and effusion.

ASBESTOS RELATED PLEURAL EFFUSION[24]:

Probable pathogenesis of this relation is depostion of the asbestos in the pleural cavity stimulates the mesothelial cells to produce cytokines that acts as a chemoattractant for the neutrophils. Presence of pleural plaques and pleural calcification gives a clue to the diagnosis. About 10% of patients have bilateral pleural effusion. Effusion is usually mild to moderate and serous or serosanguineouswith high WBC count.

POST LUNG TRANSPLANT EFFUSION:

Due to the transection of lymphatics pleural effusion occurs commonly after lung transplantation.

YELLOW NAIL SYNDROME:

Characteristic feature of yellow nail syndrome is

1) Yellow nails.
2) Lymphedema.
3) Pleural effusion.

It occurs due to poorly formed lymphatics. Pleural effusion is bilateral in more than half of the patients. Pleural effusion usually recurs after draining the effusion. Nails give a vital clue to the diagnosis. Changes include color changes from yellow and thickened, often smooth and occasionally show ridges. The rate of nail growth is slow and onycholysis is present.

PLEURAL EFFUSION SECONDARY TO DISEASE OF HEART:

1) CONGESTIVE CARDIAC FAILURE
2) POST CORONARY ARTERY BYPASS SURGERY
3) DRESSLER'S SYNDROME
4) PERICARDIAL DISEASE.

POST CORONARY ARTERY BYPASS SURGERY:

Incidence of pleural effusion is high following post coronary bypass graft surgery. If performed using internal mammary artery the incidence is more than that occur with saphenous graft. Effusion can to the proportion of massive effusion and it is an exudate and lymphocyte predominant. Dyspnea is the common presentation. If the effusion occupies more than twenty five percent then needle aspiration is necessary to rule out other causes.

DRESSLER'S SYNDROME:

It is characterized by high temperature, pleuritic nature of chest pain, and pulmonary infiltrate after weeks following pericarditis or myocardial infarction. Around 4% of patients develop this syndrome following myocardial infarction. It is an exudative effusion, occurs commonly in second or third week post myocardial infarction.

PLEURAL DISEASES IN OBSTERICS AND GYNECOLOGY:

1) OVARIAN HYPERSTIMULATION SYNDROME
2) MEIG'S SYNDROME
3) ENDOMETRIOSIS

OVARIAN HYPERSTIMULATION SYNDROME:

It is probably produced by vasoactive product that is produced during the induction of ovulation artificially by HCG. In this disorder ovary enlarges, with accumulation of fluid in the peritoneal cavity and pleural space with associated hypovolemia. The effusion is often right sided and exudative. The mean protein concentration in this syndrome is 4.1 g/dL.

MEIG'S SYNDROME:

It occurs with benign ovarian neoplasms and those that occur from other cause Is called as Pseudo Meig's syndrome. it is an exudate and resolves after treating primary ovarian tumor.

ENDOMETRIOSIS:

It is usually associated with ascites and effusion is haemorrhagic in most instances. Usually treated with hormonal therapy and it is difficult to cure in more than fifty percent of patients. Treated with hysterectomy with salphingo-oophorectomy.

CHYLOTHORAX:

Chylothorax[34] is defined as accumulation of lymph in the pleural space. It contains high concentration of triglyceride in the form of chylomicron particles. If there is accumulation of cholesterol it is called as pseudochyle or chyliform effusion. The milky appearance of the pleural chyle disappears during fasting.

The causes of chylothorax:

It can be due to either benign or malignant disorders and trauma. Malignant causes include

1) Lymphoma.
2) lung cancer.
3) Mediastinal spread of any malignant process

Benign disorders:

1) Lymphangioleiomyomatosis
2) Intestinal lymphangiectasia
3) Enteropthy
4) Rarely cirrhosis of liver
5) Tuberculosis
6) Aneurysm of thoracic aorta
7) Amyloidosis

TRAUMATIC ETIOLOGY:

Surgery involving thoracic aorta, lung resection, esophageal surgery and Penetrating injuries to neck region presents with chylous effusion.

CT scan, lymphangiography and lymphoscintigraphy is used as diagnostic tool for diagnosis. It is commonly managed with pleuroperitoneal shunt if it is due to malignancy.

TRANSUDATIVE PLEURAL EFFUSIONS:

CONGESTIVE CARDIAC FAILURE:

It is the most common cause of pleural effusion. More than 80% of the pleural effusion occurs bilaterally[35]. Remaining patients have mostly right-sided effusion. Concepts of pleural fluid formation and reabsorption inpatients with heart failure have undergone significant modifications. Initially the fluid formation was proposed to be based in accordance with Starling's law. Increased pressure in the capillaries in the visceral or the parietal pleura is present. These increased pressure were thought to result in an increased entry of fluid into the pleural space from the parietal pleura and a decreased removal of fluid through the visceral pleura. The current concept of pleural effusion in CCF is based on the theory that most of the fluid that enters the pleural space in patients comes from the alveolar capillaries rather than the pleural capillaries.

When the pressure in the pulmonary capillaries is elevated increased amounts of fluid enters the interstitial spaces of lung. The increased interstitial fluid results in an increased interstitial pressure in the subpleural interstitial spaces. The fluid then moves from the pulmonary interstitial spaces across the visceral pleura into the pleural space. There appears to be relatively little resistance to fluid movements from the pulmonary interstitial spaces across the visceral pleura. Pleural fluid accumulates in patients with CCF when the rate of entry of fluid into the pleural space exceeds the capability of the lymphatics in the parietal pleura to remove the fluid.

The pleural effusion in patients with heart failure is typically a transudate satisfying the Light's criteria. In 15 to 20% of patients the pleural effusion is classified as exudate by Light's criteria. Most patients who are misclassified are receiving diuretics therapy. If the effusion is thought to be due to heart failure then serum to pleural fluid protein gradient should be done. If this gradient is more than 3.1g/dL, the pleural effusion in all chances is due to heart failure.

HEPATIC HYDROTHORAX:

Hepatic hydrothorax is a pleural effusion (usually greater than 500mL) caused by hepatic cirrhosis and portal hypertension in the absence of cardiopulmonary disease. Hepatic hydrothorax is usually

associated with ascites but can occur in its absence. Pleural fluid is almost always transudative. It occurs most commonly in the right side and rarely bilateral and left. Accumulation of fluid occurs due to the defects in the diaphragm that enable the fluid in the peritoneal cavity to move in to the pleural cavity due the negative pressure in the pleura.

CHARACTERISTIC OF HEPATIC HYDROTHORAX:

1) Right side(85%)

2) Left side(13%)

3) Bilateral(2%)

FLUID:

1) Cell count <250 PMN cells

2) Protein <2.5g/dL

3) Serum to pleural fluid albumin gradient >1.1

4) pH>7.4

5) Pleural fluid/serum bilirubin ratio<0.6

NEPHROTIC SYNDROME:

Nephrotic syndrome is a well-known cause of transudative pleural effusion. The overall incidence is about 20%. Pleural effusion in patients with nephrotic syndrome is usually bilateral. Pulmonary embolism occurs at a higher rate with the nephrotic syndrome and this etiology for the

pleural effusion should be excluded in all patients with nephrotic syndrome.

HYPOALBUMINEMIA:

Hypoalbuminemia per se is not a cause of clinically significant transudative pleural effusion. In patients with cirrhosis with hypoalbuminemia and absence of ascites, pleural effusion is rarely encountered.

URINOTHORAX:

Urinothorax[36] denotes presence of urine in the pleural space. This condition is due to ipsilateral obstructive uropathy resulting in retroperitoneal leakage of urine. The pleural fluid looks and smells like urine. The pH is usually less than 7.2 and protein level is usually less than 1.0 gm/dL. Pleural fluid glucose is usually normal or below but effusion contains markedly elevated LDH. Pleural fluid creatinine is usually greater than the serum creatinine.

PERITONEAL DIALYSIS:

Transudative pleural effusions are occasionally encountered in patients undergoing peritoneal dialysis. The pleural fluid in these patients is characterized by a glucose level intermediate between that of the

dialysate and the serum, protein level below 3gm/dL, and low LDH whichis higher than that in the ascitic fluid.

MYXEDEMA:

Pleural effusion occasionally occurs as a complication of myxedema. When pleural effusion occurs simultaneously with a pericardial effusion, the pleural fluid is usually a transudate. The isolated pleural effusion secondary to hypothyroidism is either exudate or transudate.

C-REACTIVE PROTEIN(CRP):

Acute phase reactants are defined as those proteins whose serum concentrations increase or decrease by atleast 25% during inflammatory states. They are usually produced in the liver. These may increase called positive acute phase reactants or decrease which are called negative acute phase reactant.

Increase in concentration of acute phase reactants comprises a major pathophysiologic phenomenon that accompanies inflammation and tissue injury. C-reactive protein belongs to acute phase reactant group which rises during the inflammatory process. CRP consists of five identical non-covalently linked subunits, each with a molecular weight of approximately 23kD, which are arranged symmetrically around a central pore. CRP and related proteins with this structure are termed pentraxins.

Its production is stimulated by IL-6, which is produced by macrophage system and adipocytes. CRP binds to phosphocholine on the microbes. It helps in enhancing compliment activity and phagocytosis of macrophage system. Determining the level of CRP is simple, quick, and cheap.

CRP riseupto 50,000 times in acute inflammation, particularly infection. Within 6 hours the level of CRP level start to rise. The value of CRP peaks at forty -eight hours. The half-life of CRP is constant. The severity and the rapidity with which the disease develops determine the level of CRP.

THE ROLE OF CRP IN PLEURAL EFFUSION:

Hoda Abu-Yosssef et al conducted a study of CRP protein in exudative pleural effusion and to find the diagnostic value of it on forty Patients. The study found a significant difference for mean values of high sensitive CRP between exudative and transudative effusion.

Yilmaz et al. found the discrimination[39-42] between exudate and transudate pleural effusions with sensitivity and specificity for fluid CRP was 93.7% and 76.5%, respectively.

Study conducted by Alexandrakis et al. found that CRP in pleural fluid were significantly higher in exudates than in transudate effusion
In many studies it was found CRP[43-46] level critically high in tubercular and parapneumonic effusions than in other causes of pleural effusion. The

determination of CRP is useful in the diagnostic pleural effusion with predominant lymphocytosis.

Virdahis and Amores et al. found fluid CRP level was twice as higher in tuberculous than in malignancy.

Yilmaz et al. concluded that CRP in pleural fluid and pleural fluid –serum ratio of CRP is useful in workup of various effusions such as parapneumonic, tuberculous, and malignant effusions.

Garcia E Pachon found pleural fluid CRP is higher in benign when compared to malignant effusions.

MATERIALS AND METHODS

MATERIAL AND METHODS

SETTING:

This study was conducted at the Institute of Internal Medicine, Rajiv Gandhi Government General Hospital, and Madras Medical College.

ETHICAL COMMITTEE APPROVAL:

Obtained.

STUDY DURATION:

This study was conducted over a period of six months.

STUDY POPULATION:

Patients admitted with pleural effusion in medical wards, Institute of Internal medicine.

SAMPLE SIZE:

Fifty cases admitted with pleural effusion.

TYPE OF STUDY:

Cross sectional study:

INCLUSION CRITERIA:

- Newly detected cases of pleural effusion.

EXCLUSION CRITERIA:

- Patients not willing to consent.
- Patients taking oral contraceptives.
- Patients with collagen vascular diseases on treatment.
- Patients with HIV and AIDS.

DATA COLLECTION AND METHODS:

Patients have their history taken according to questionnaire and subjected to clinical examination. All patients with clinical and x ray diagnosis of pleural effusion underwent pleural fluid analysis comprising of protein, sugar, LDH, ADA, cytology, AFB, culture. Renal function tests, complete blood count, liver function tests, serum protein and LDH, sputum gram stain and culture and sensitivity. CRP was measured in all cases of pleural effusion. Light's criteria was used to classify the patients into exudate and transudate. Transudate group were further subjected to find the cause of transudate by subjecting them to ultrasound abdomen, echocardiogram. Exudative pleural effusion was studied under four categories-parapneumoniceffusion, tuberculous effusion, malignant effusion, and others. Each of these were defined by definite criteria for the purpose of study. Parapneumonic effusion is defined by signs and symptoms of pneumonia with characteristic infiltrate radiologically with or without positive gram stain and culture of blood or pleural fluid cytology with neutrophilic predominance with negative sputum AFB and

low ADA levels with no clinical evidence of other cause and clinical improvement with antibiotic theraphy. Tuberculous effusion defined by absence of evidence for bacterial pneumonia and ADA>40 IUwith or without reactive mantoux test with or without positive sputum or pleural fluid AFB. Pleural fluid biopsy with granuloma was taken as final in the absence of above investigations. Malignant effusion was diagnosed by positive cytology of pleural fluid for malignant cells or biopsy proven or haemorrhagic effusion in known case of malignancy. All data were entered in proforma (enclosed)

STATISTICAL ANALYSIS

Descriptive statistics were used for presenting the patient characteristics. All data would be subjected to FISHER'S EXACT TEST, UNPAIRED 't' and ANOVA tests. Individual group comparisons would be made using parametric tests and non-parametric tests as appropriate. P value of <0.05 is taken as significant in this study. Statistical analysis was done with GRAPH PAD PRISM software.

OBSERVATIONS AND ANALYSIS

OBSERVATION AND ANALYSIS

TOTAL CASES:

Total number of patients taken up for study was 50. Among the fifty patients 11 belonged to transudate and 39 belonged to exudate category of pleural effusion. In percentage 22% were transudate and 78% were exudate.

TABLE 1: CASE DISTRIBUTION

CASES	NO. OF CASES	% OF CASES
TRANSUDATE	11	22%
EXUDATE	39	78%

CHART 1-CASE DISTRIBUTION

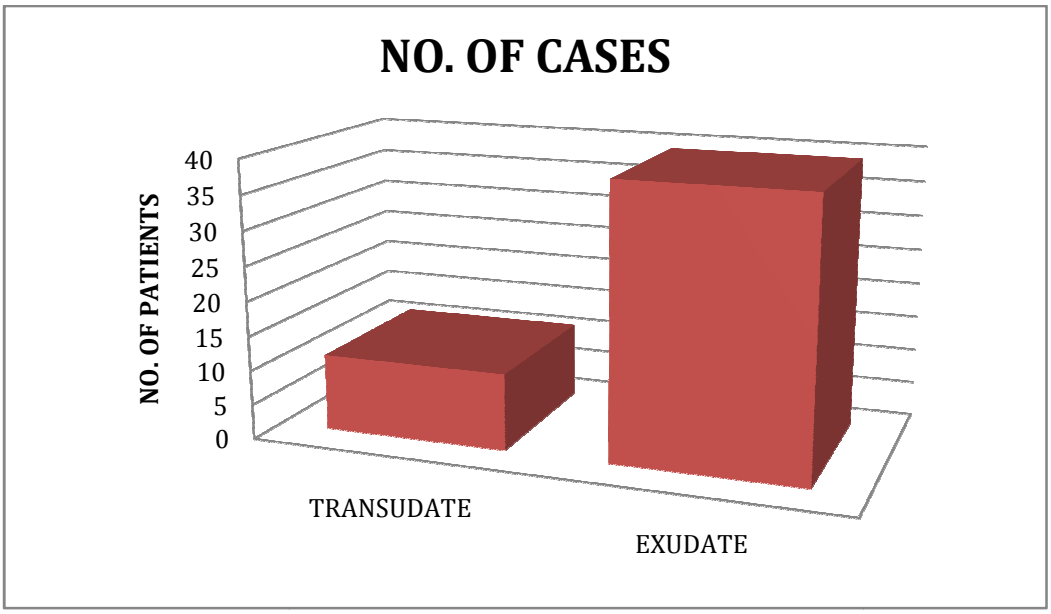
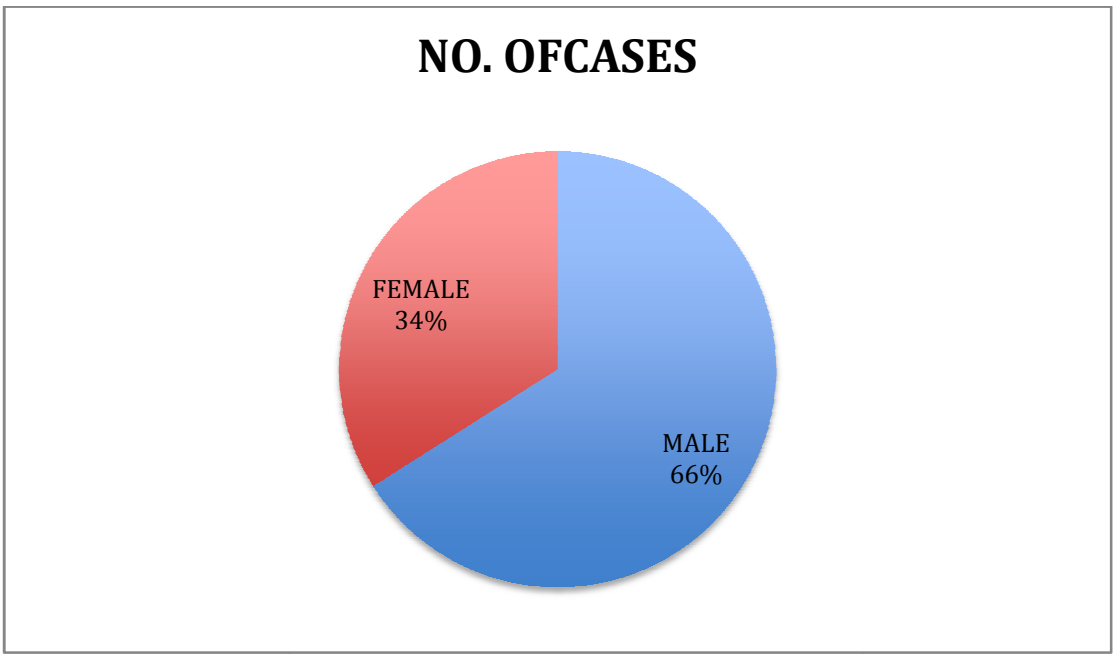


TABLE 2:SEX DISTRIBUTION:

SEX	NO. OF CASES
MALE	33
FEMALE	17

CHART -2: SEX DISTRIBUTION



SYMPTOM ANALYSIS:

The total number of patients who had cough- 48%,sputum-44%, hemoptysis -3%, fever- 23%, and loss of weight- 13%.

In parapneumnoic effusion, cough with sputum production was present in 82.3% and 5.8% had hemoptysis and 94.1% patient had fever. In tuberculosis group, only 21% had cough, and none of them had hemoptysis and fever was present in 35.7% and loss of weight was present in 35.7%.

TABLE 3:SYMPTOM ANALYSIS

	NO. OF PATIENTS	PERCENTAGE
COUGH	**24**	**48**
SPUTUM	**22**	**44**
HEMOPTYSIS	**3**	**6**
FEVER	**23**	**46**
LOSS OF WEIGHT	**13**	**26**

CHART 3: SYMPTOM ANALYSIS OF ALL PATIENTS

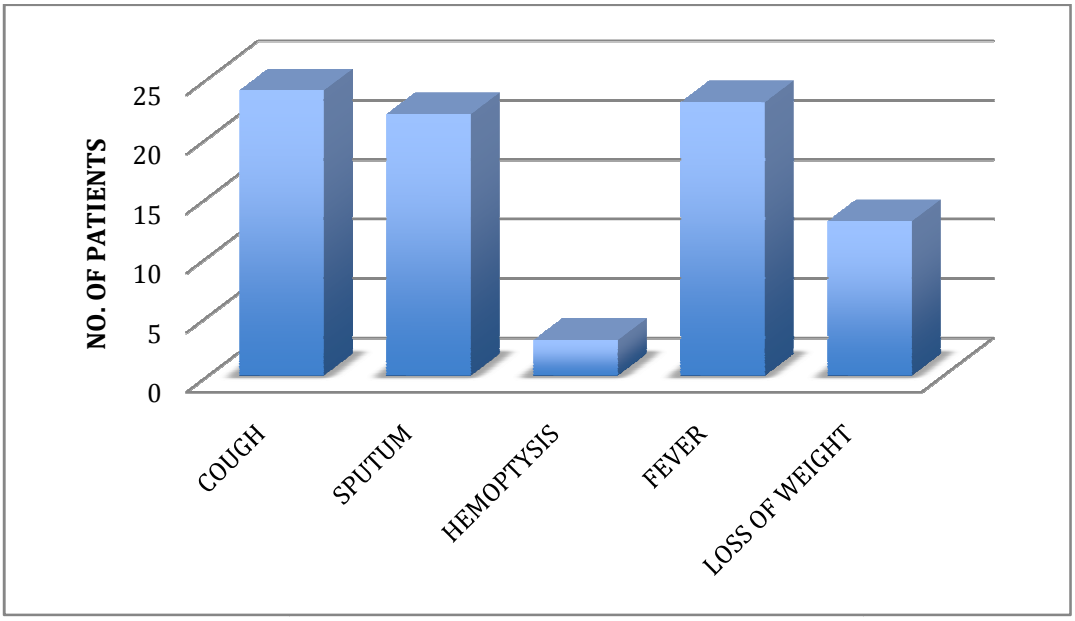


TABLE:4 PARAPNEUMONIC EFFUSION- SYMPTOM ANALYSIS:

	NO.OF CASES	PERCENTAGE
COUGH	14	82.3
SPUTUM	14	82.3
HEMOPTYSIS	1	5.8
FEVER	16	94.1
LOSS OF WEIGHT	0	0

CHART:4 PARAPNEUMONIC EFFUSION

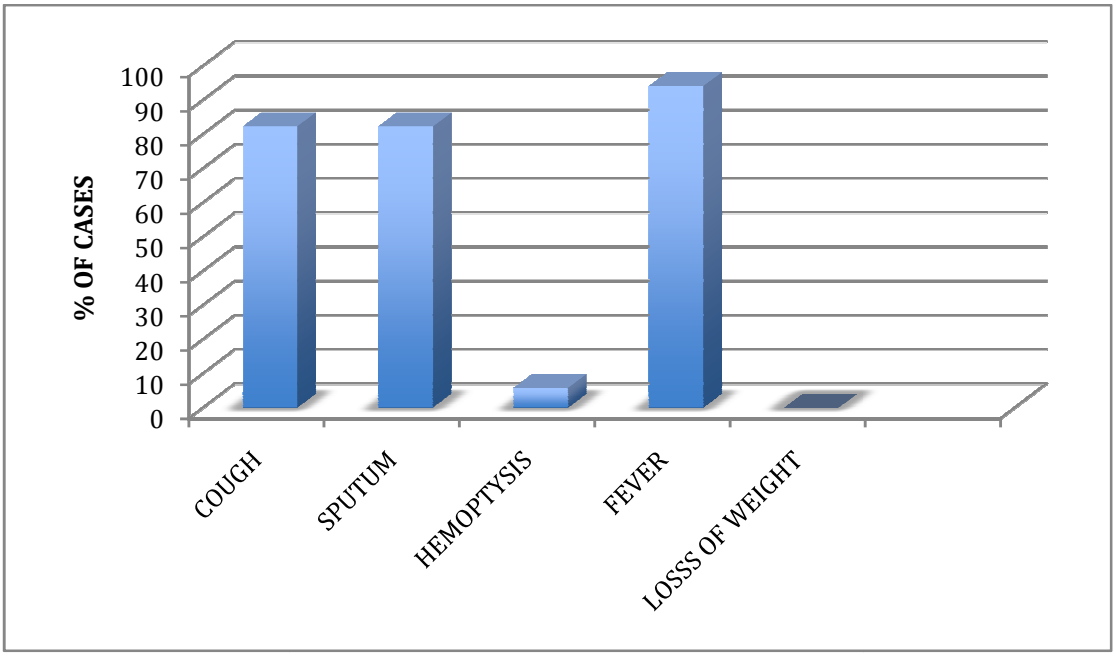


TABLE: 5 TUBERCULOUS PLEURAL EFFUSION

	NO.OF CASES	PERCENTAGE
COUGH	3	21
SPUTUM	4	28.5
HEMOPTYSIS	0	0
FEVER	5	35.7
LOSS OF WEIGHT	5	35.7

CHART:5 TUBERCULOUS PLEURAL EFFUSION

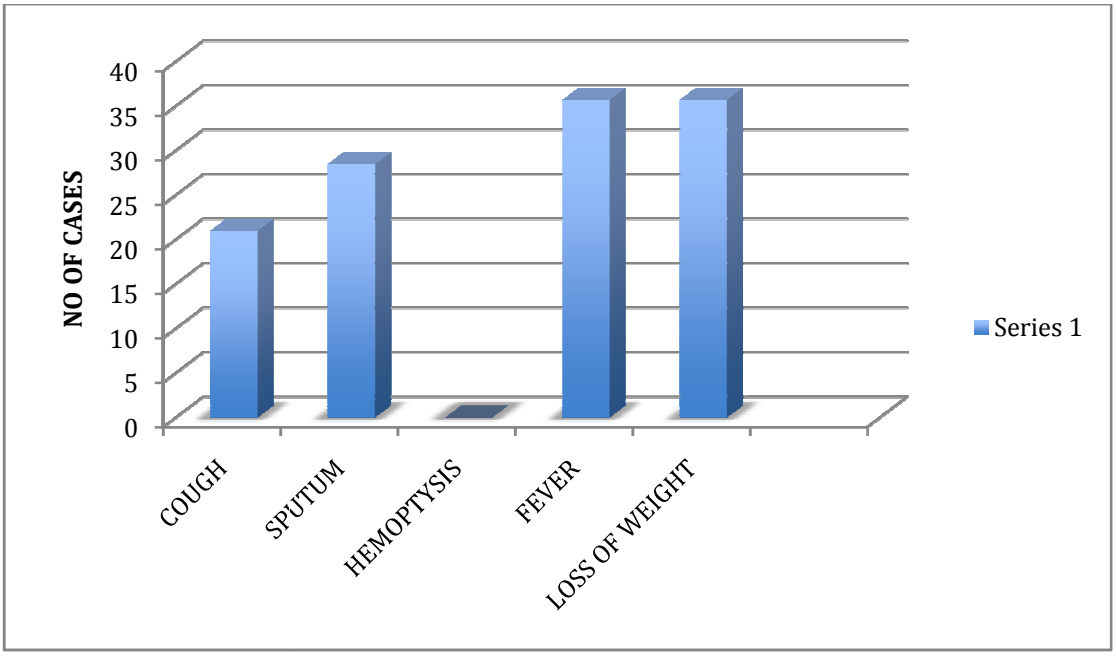


TABLE: 6 MALIGNANT PLEURAL EFFUSION SYMPTOMS

	NO.OF CASES	PERCENTAGE
COUGH	4	50
SPUTUM	2	25
HEMOPTYSIS	2	25
FEVER	2	25
LOSS OF WEIGHT	8	100

CHART:6 MALIGNANT PLEURAL EFFUSION SYMPTOMS

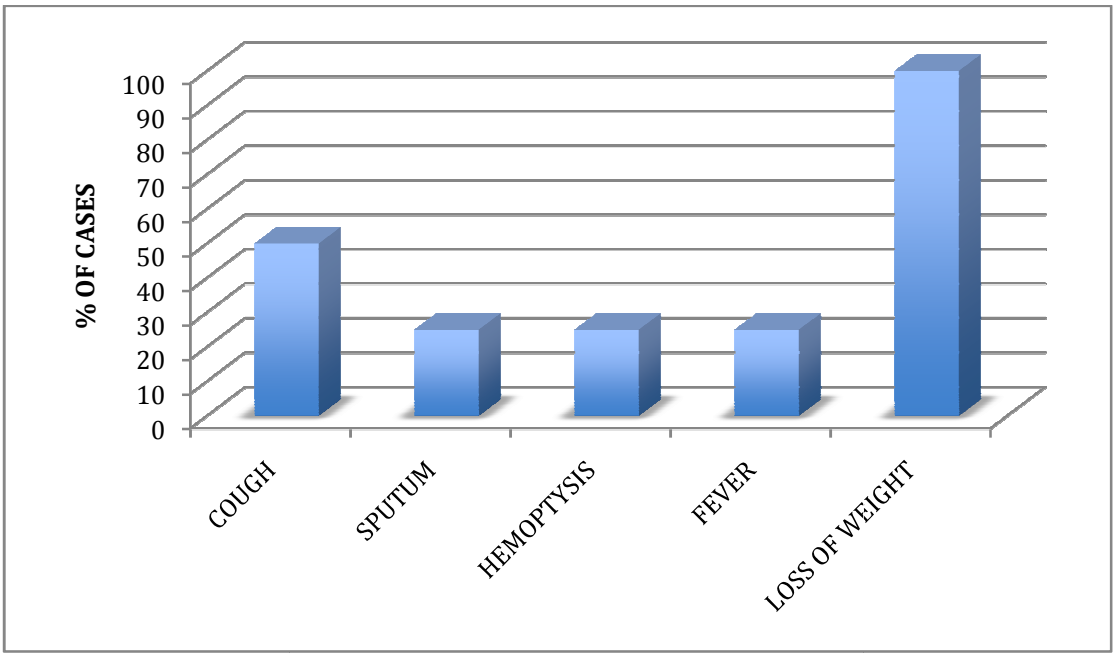


TABLE:7 CAUSES OF TRANSUDATIVE EFFUSION:

TRANSUDATE	NO.OF CASES
HEART FAILURE	9
DCLD	2

CHART: 7 CAUSES OF TRANSUDATIVE EFFUSION

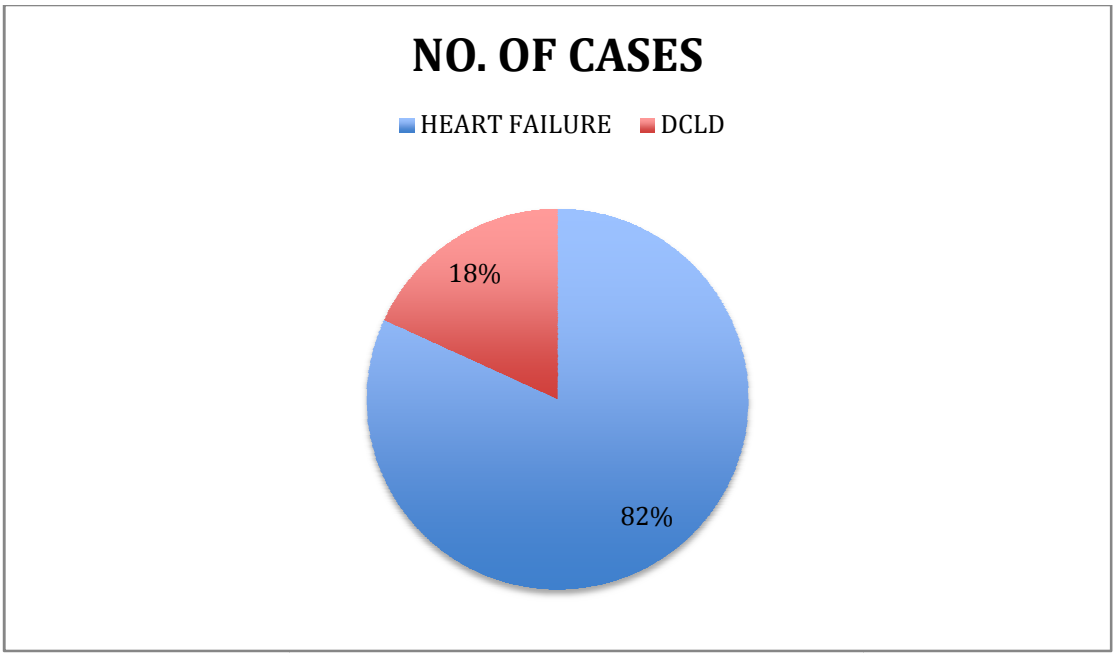
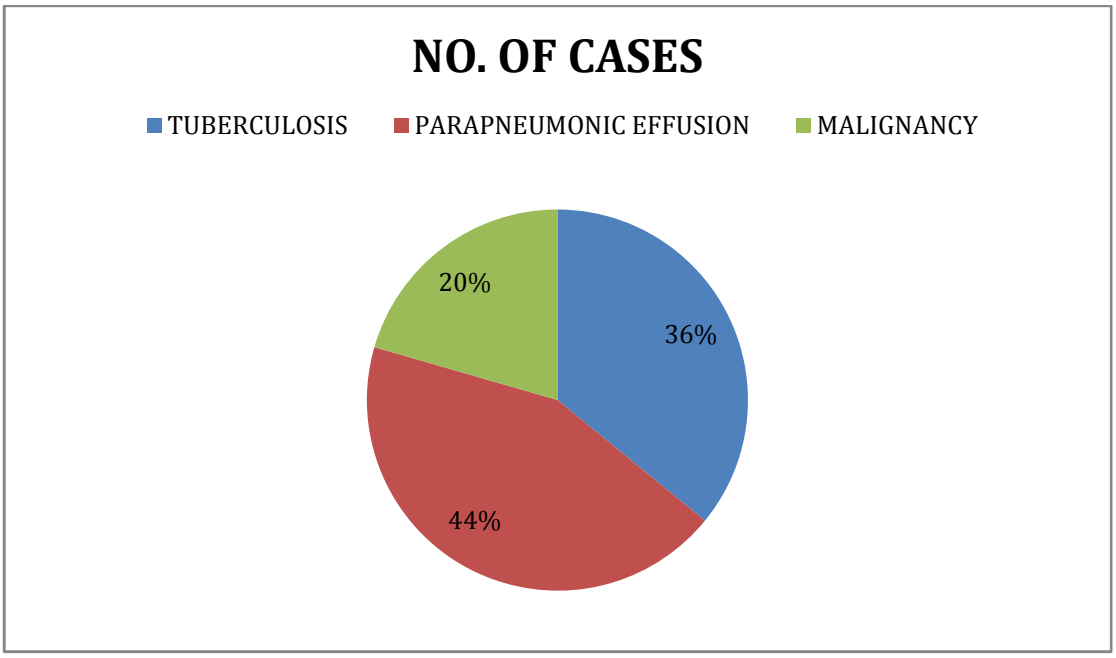


TABLE:8 CAUSES OF EXUDATIVE PLEURAL EFFUSION :

EXUDATE	NO.OF CASES
TUBERCULOSIS	14
PARAPNEUMONIC EFFUSION	17
MALIGNANCY	8

CHART :8 CAUSES OF EXUDATIVE PLEURAL EFFUSION



AGE DISTRIBUTION OF PLEURAL EFFUSION

The majority of patient belonged to 50-60 years:

TABLE: 9 AGE DISTRIBUTION

AGE IN YEARS	NO. OF CASES
20-30	**9**
30-40	**12**
40-50	**12**
50-60	**17**

TABLE: 10 AGE DISTRIBUTION

PLEURAL FLUID CHARACTER	MEAN AGE	SD OF AGE
EXUDATE	43	8.60
TRANSUDATE	43.48	11.90

TRANSUDATIVE PLEURAL EFFUSION:

CHARACTERISTICS:

The mean ESR among the transudate group were15.6 mm/hr(SD-7.52). Serum LDH were 85.81 IU/L(SD-40.06) and LDH ratio was 0.41(SD-0.10). Mean Pleural fluid protein was 1.65 (SD-0.64)and the protein ratio was 1.65. Mean Pleural fluid ADA 15.54 IU. Mean pleural fluid CRP was 7.21mg/L(SD-2.27)

TABLE:11 TRANSUDATE EFFUSION LAB FEATURES

VARIABLE	MEAN	SD
ESR (mm/hr)	**15.6**	**7.52**
SERUM LDH(IU/L)	**85.81**	**40.06**
PF PROTEIN	**1.65**	**0.64**
PROTEIN RATIO	**0.30**	**0.09**
PF LDH(IU/L)	**34.72**	**16.56**
LDH RATIO	**0.41**	**0.10**
PF ADA(IU/L)	**15.54**	**3.67**
PF CRP(mg/L)	**7.21**	**2.27**

EXUDATIVE PLEURAL EFFUSION:

TUBERCULOSIS:

TABLE:12 TUBERCULOSIS SEX DISTRIBUTION

SEX	NO.OF CASES
MALE	8
FEMALE	6

TABLE:13 TUBERCULOSIS- LAB FEATURES

VARIABLE	MEAN	SD
AGE	47.5	12.23
ESR mm/hr	39.28	25.17
SERUM LDH(IU/L)	180.64	45.55
PF LDH(IU/L)	198.42	83.10
LDH RATIO	1.24	0.73
PF PROTEIN (g/dL)	3.78	0.51
PROTEIN RATIO	0.71	0.07
PF ADA(IU/L)	50.5	8.89
PF CRP(mg/L)	52.15	14.83

TUBERCULOUS PLEURAL EFFUSION ANALYSIS:

The ESR of this group is 39.28mm/hr.(SD-25.17) Mean serum LDH and LDH ratio was 198.42IU/L(SD-83.10) and 1.24IU/L(SD-0.73) respectively. The pleural fluid protein and protein ratio was 3.78(SD-0.51) and 0.71(SD-0.07). Pleural fluid CRP ADA was 50.5IU/L(SD-8.89).

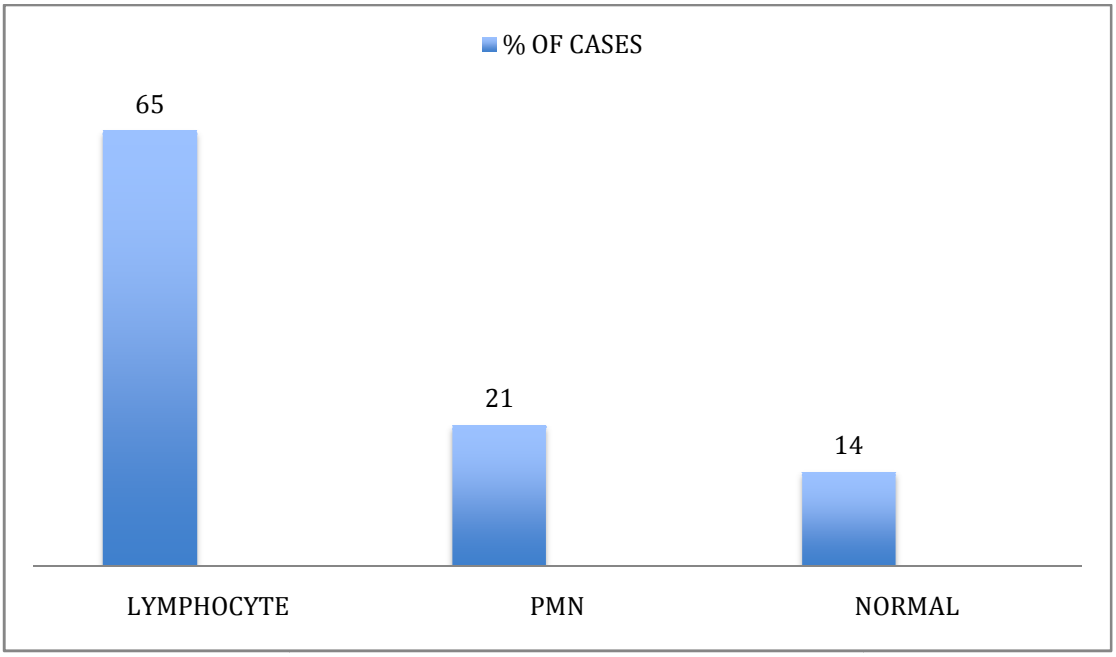
PLEURAL FLUID CYTOLOGY:

The cytology of pleural fluid in tubercular group were mostly lymphoctyte predominant, and three were surprisingly having predominant polymorphs.

TABLE:14 TUBERCULOSIS PLEURAL FLUID CYTOLOGY -

CYTOLOGY	NO. OF CASES	% OF CASES
LYMPHOCYTE	**9**	**65**
PMN	**3**	**21**
NORMAL	**2**	**14**

CHART:9 TUBERCULOSIS- PLEURAL FLUID CYTOLOGY



PARAPNEUMONIC EFFUSION:

Parapneumonic effusions were predominantly present in male in this study. With sixteen out of seventeen patients are male. And ESR was elevated and mean ESR was 34.17(SD-8.71). The serum LDH was elevated and mean serum LDH 273.58 IUand pleural fluid LDH was highly elevated and mean value was 420.29 IUand LDH ratio was satisfying the criteria of exudate and mean value was 1.565. The pleural fluid ADA was not significantly elevated as expected and mean was 23.70 IU.

TABLE:15 PARAPNEUMONIC EFFUSION

	MEAN	SD
AGE	**39.82**	**12.28**

SEX	MALE	FEMALE
NO. OF CASES	**16**	**1**

VARIABLE	MEAN	SD
ESR (mm/hr)	**34.17**	**8.71**
SERUM LDH(IU/L)	**273.58**	**94.14**
PF LDH(IU/L)	**420.29**	**231.05**
LDH RATIO	**1.565**	**0.65**
PF PROTEIN(g/dL)	**4.59**	**0.97**
PROTEIN RATIO	**0.743**	**0.12**
PF ADA (IU)	**23.70**	**10.57**
PF CRP(mg/L)	**103.47**	**32.23**

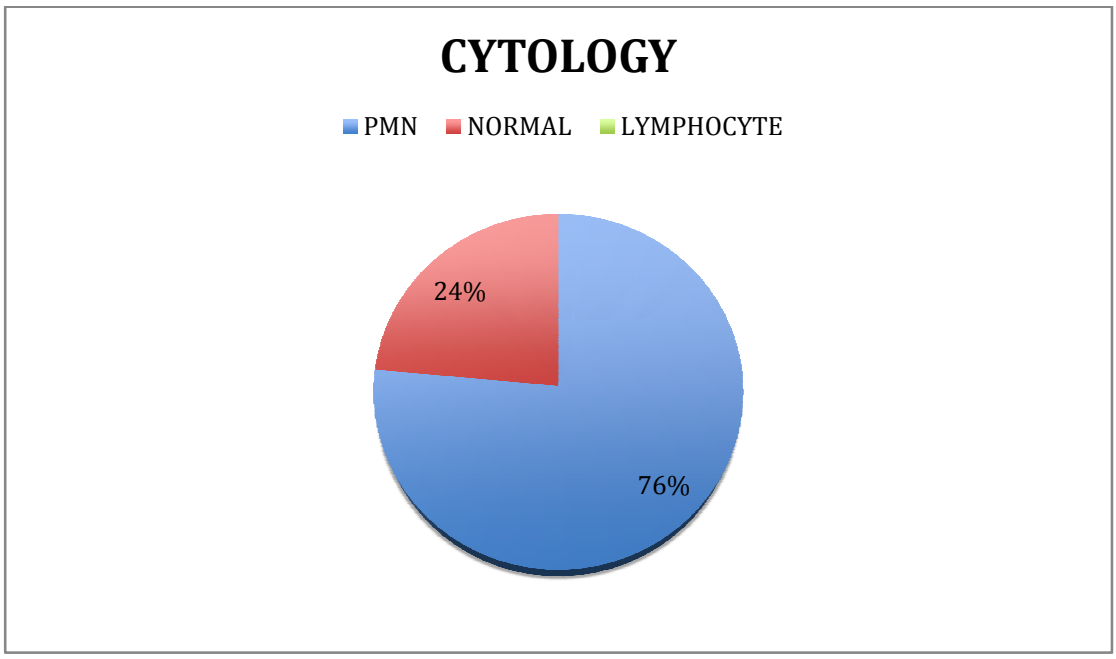
PLEURAL FLUID CYTOLOGY:

The cytology of pleural fluid is predominantly polymorphonuclearcells.

TABLE:16 PARAPNEUMONIC EFFUSION CYTOLOGY

CYTOLOGY	NO. OF CASES	% OF CASES
PMN	13	76.5
NORMAL	4	23.5

CHART: 10 PLEURAL FLUID CYTOLOGY OF PARAPNEUMONIC EFFUSION



MALIGNANT EFFUSION:

The mean ESR of malignant effusion is 15.5mm/hr(SD-6.11). The serum LDH is 178.75IU(SD-45.35). The total protein and protein ratio is 3.125g/dl (SD-0.575) and 0.62(SD-0.13). The mean pleural fluid ADA is 14.75IU(SD-5.47).

TABLE:17 MALIGNANT EFFUSION

AGE	MEAN	SD
	44.87	14

SEX	MALE	FEMALE
NO. OF CASES	3	5

VARIABLE	MEAN	SD
ESR(mm/hr)	15.5	6.11
SERUM LDH (IU)	178.75	45.35
PF LDH(IU)	245.75	99.42
LDH RATIO	1.366	0.45
PF PROTEIN(g/dL)	3.125	0.575
PROTEIN RATIO	0.62	00.13
PF ADA (IU)	14.75	5.47
PF CRP(mg/L)	23.075	7.83

TABLE: 18 P VALUE FOR TRANSUDATIVE AND EXUDATIVE EFFUSION:

VARIABLE	P VALUE	SIGNIFICANCE
AGE	0.8	NS
SEX	0.4	NS
ESR	<0.0001	S
SERUM LDH	<0.0001	S
PF LDH	<0.0001	S
LDH RATIO	<0.0001	S
PF PROTEIN	<0.0001	S
PROTEIN RATIO	<0.0001	S
ADA	<0.0001	S
CRP	<0.0001	S

CHART:11 PLEURAL FLUID PROTEIN:

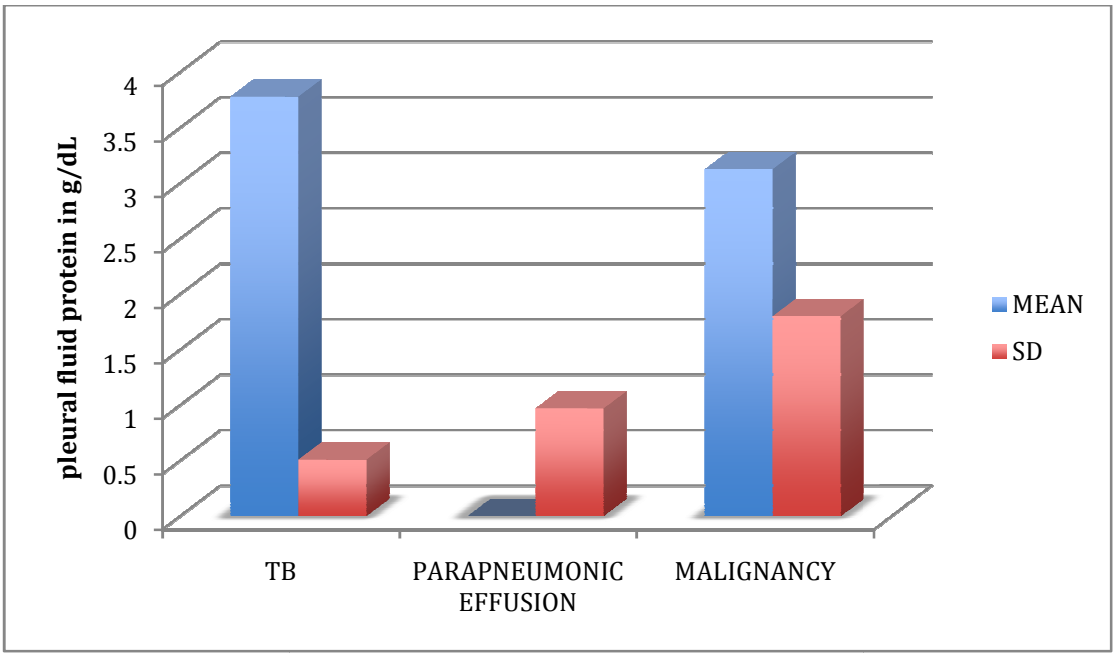


CHART:12 PROTEIN RATIO:

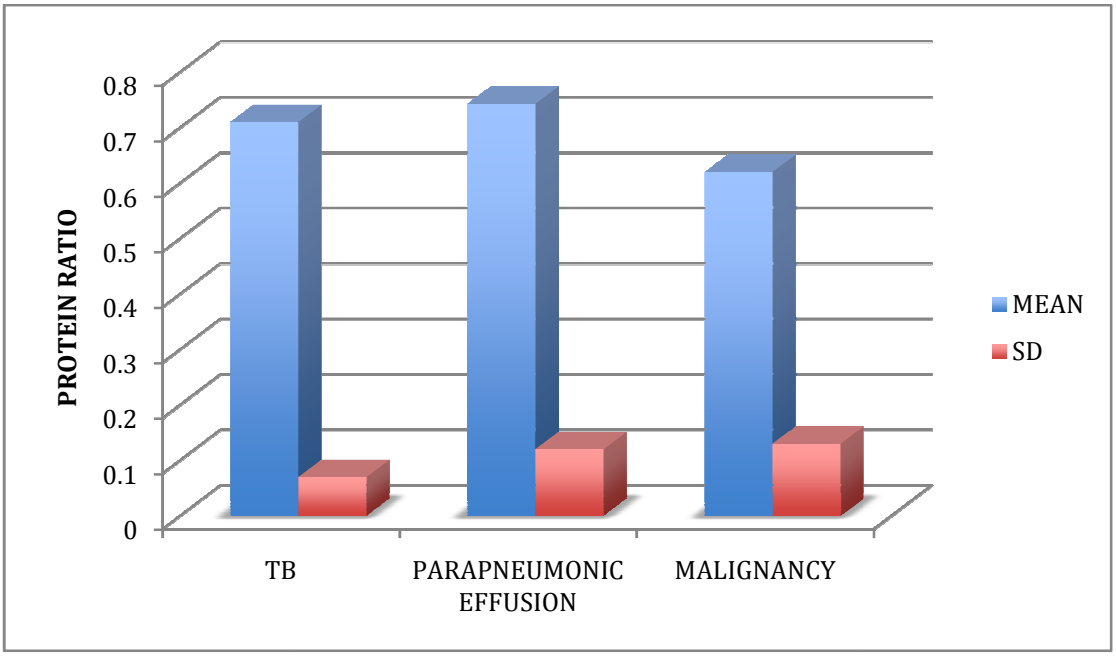


CHART:13 PLEURAL FLUID LDH

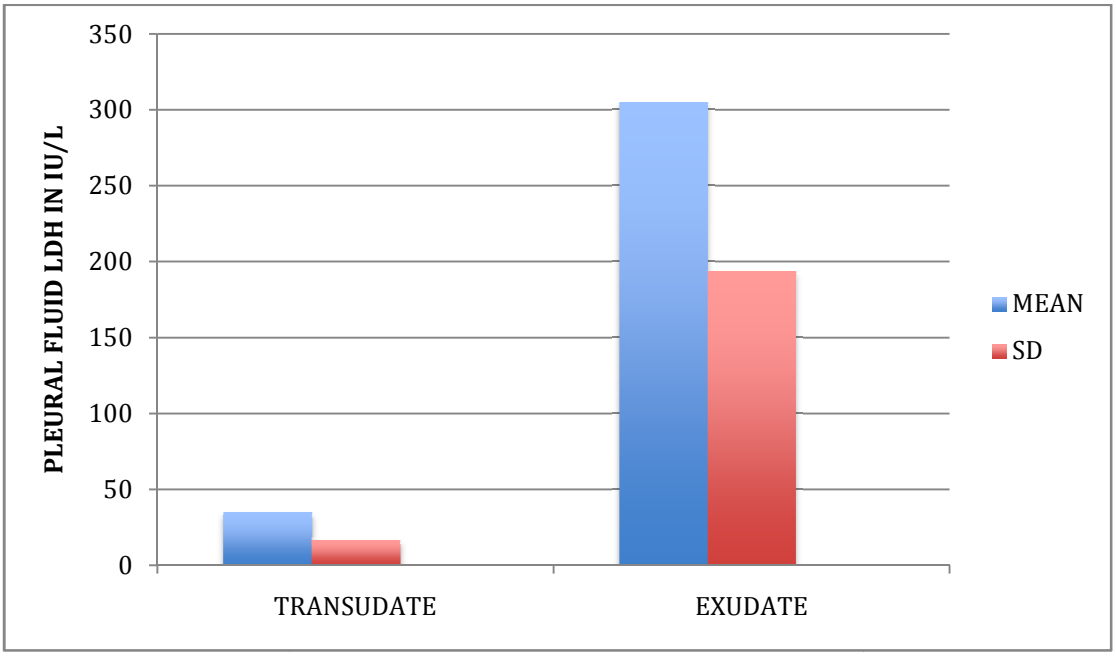


CHART:14 PLEURAL FLUID LDH IN EXUDATIVE PLEURAL EFFUSION

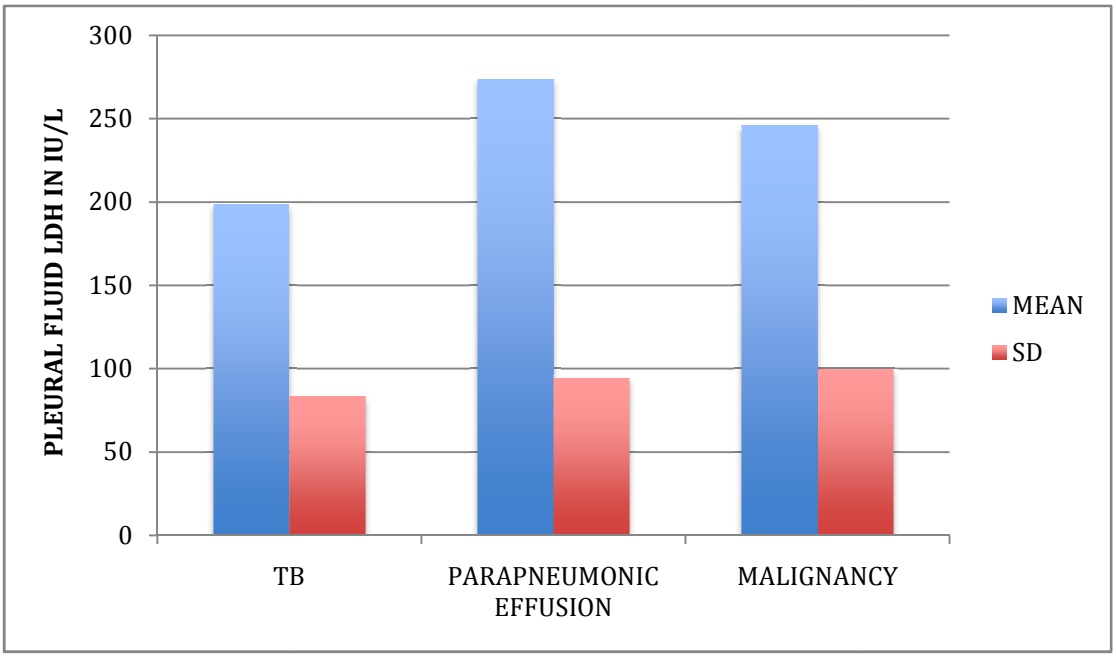


CHART:15 LDH RATIO

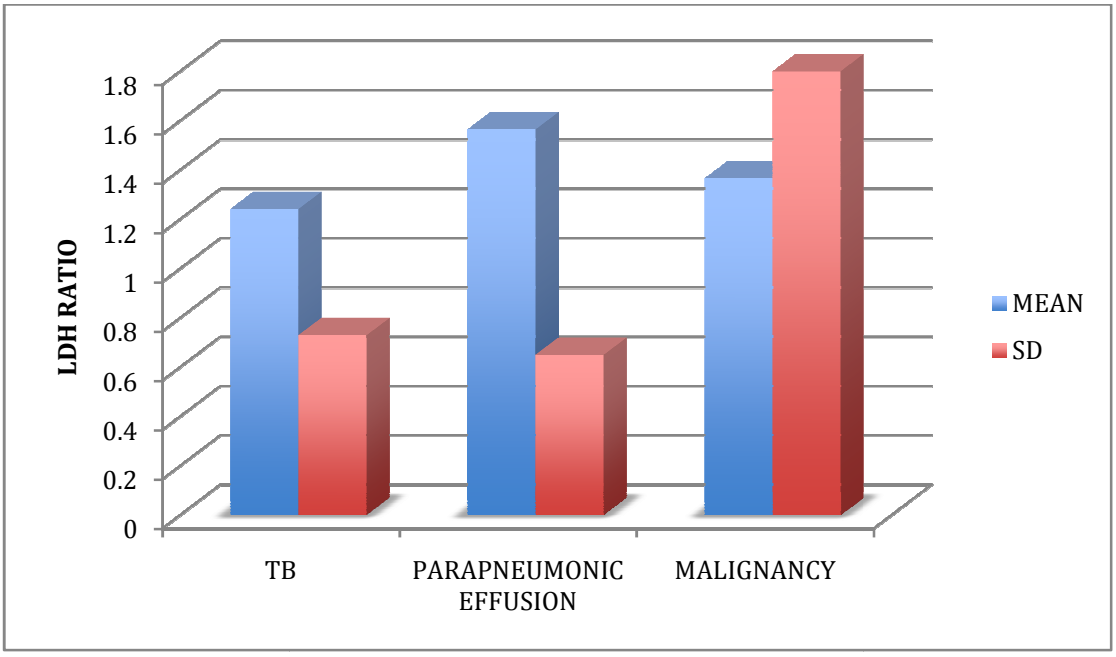


CHART:16 CRP IN PLEURAL EFFUSION

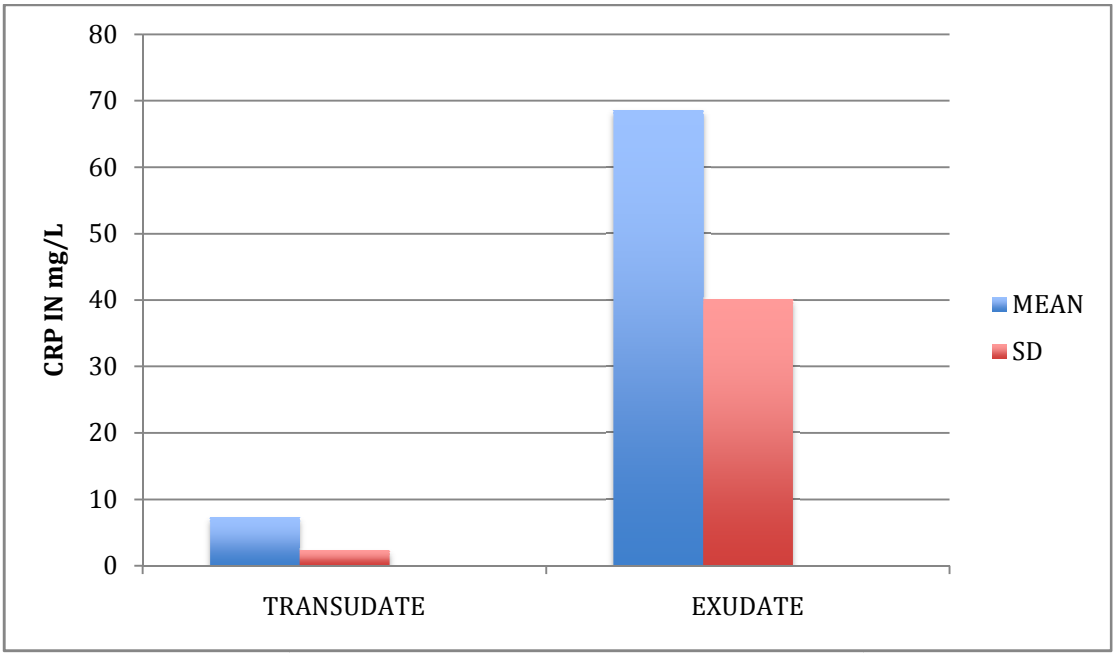


CHART:17 CRP IN EXUDATIVE EFFUSION

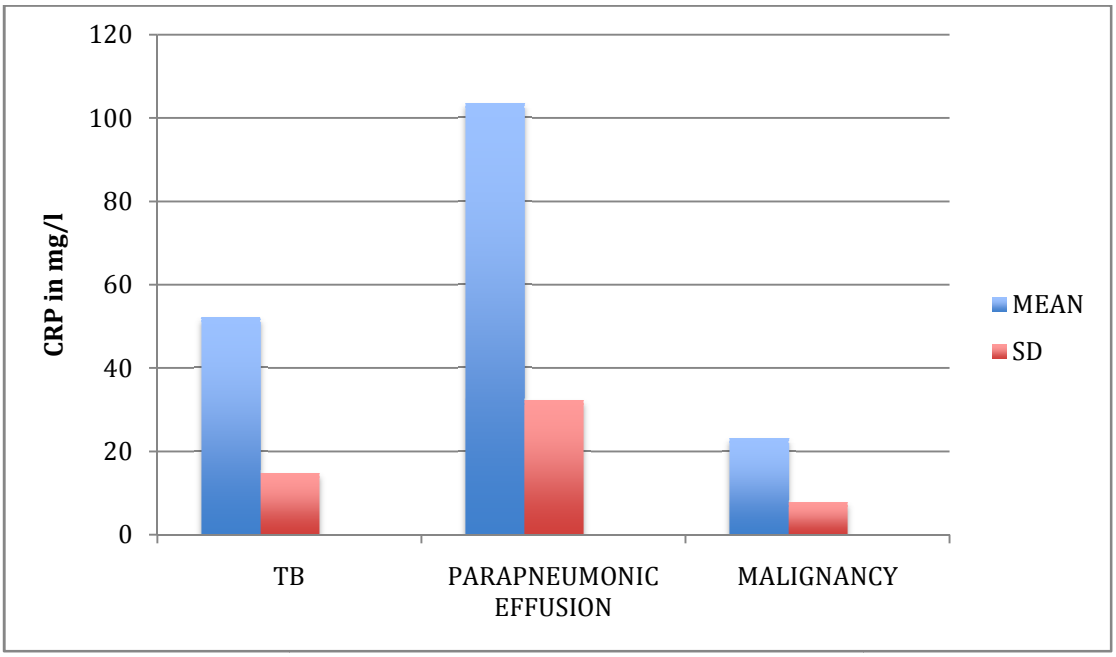


TABLE:19 ESR

	MEAN DIFFERENCE	P VALUE	95% CONFIDENCE INTERVAL
TB vs PPE	5.11	>0.05	-9.281 TO 19.501
TB vs ME	23.780	<0.01	6.107 TO 41.453
PPE vs ME	18.670	<0.05	1.5742 TO 35.766

CHART:18 ESR

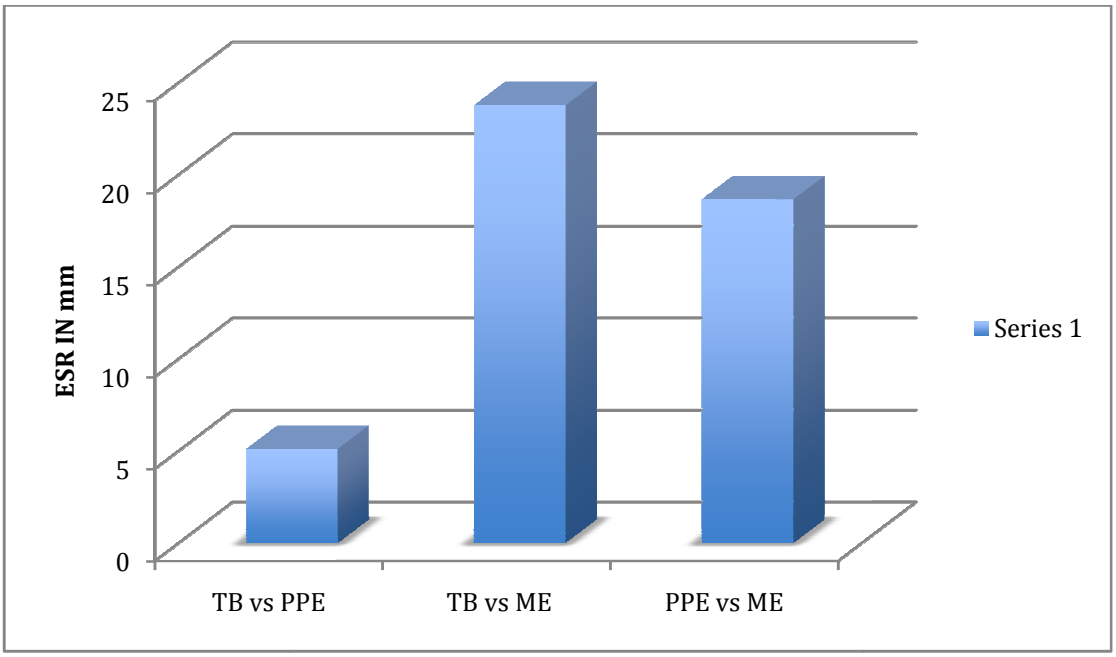


CHART:19 CRP

	MEAN DIFFERENCE	P VALUE	95% CONFIDENCE INTERVAL
TB vs PPE	51.320	<0.001	-72.08 TO -30.558
TB vs ME	+29.08	<0.05	3.583 TO 54.577
PPE vs ME	+84.40	<0.001	5.735 TO 105.06

CHART:20 CRP MEAN DIFFERENCE

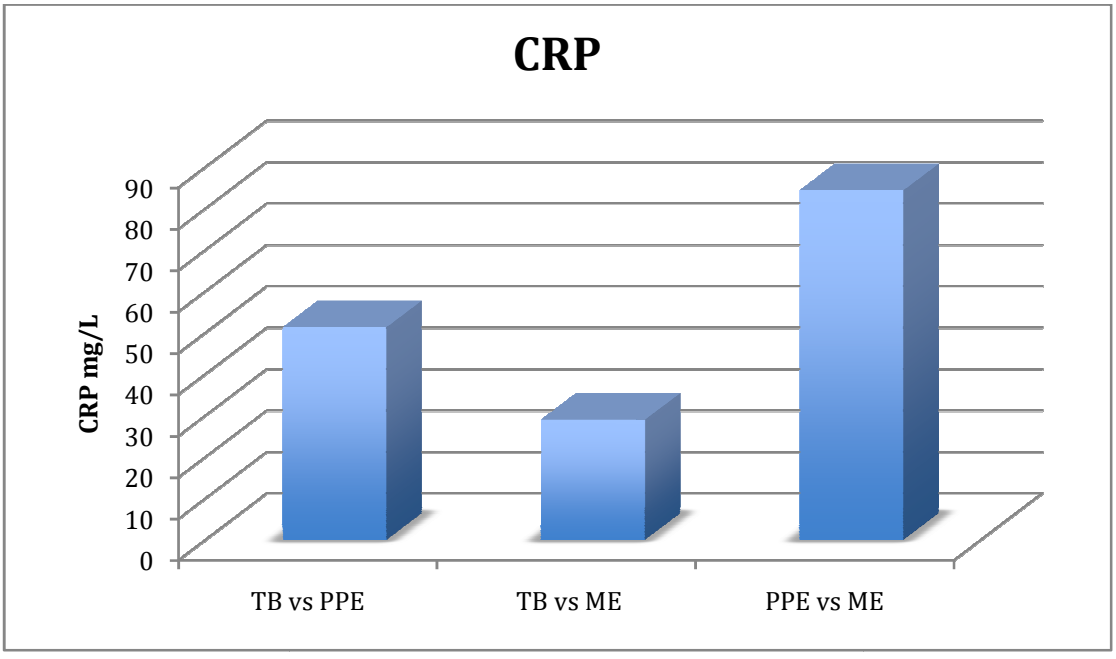


TABLE:20 PLEURAL FLUID LDH

	MEAN DIFFERENCE	P VALUE	95% CONFIDENCE INTERVAL
TB vs PPE	-75.160	>0.05	-155.86 TO 5.540
TB vs ME	-47.330	>0.05	-146.43 TO 51.772
PPE vs ME	+27.830	>0.05	-68.035 TO 123.70

TABLE: 21 PLEURAL FLUID LDH RATIO

	MEAN	P VALUE	95% CONFIDENCE INTERVAL
TB vs PPE	-0.3232	>0.05	-0.8951 TO 0.2487
TB vs ME	-0.1242	>0.05	-0.8265 TO 0.5781
PPE vs ME	0.1990	>0.05	-0.4804 TO 0.8784

TABLE:22 PLEURAL FLUID ADA

	MEAN DIFFERENCE	P VALUE	95% CONFIDENCE INTERVAL
TB vs PPE	26.800	<0.001	21.234 TO 32.366
TB vs ME	34.960	<0.001	28.125 TO 41.725
PPE vs ME	8.160	<0.05	1.548 TO 14.772

CHART 21: PLEURAL FLUID ADA

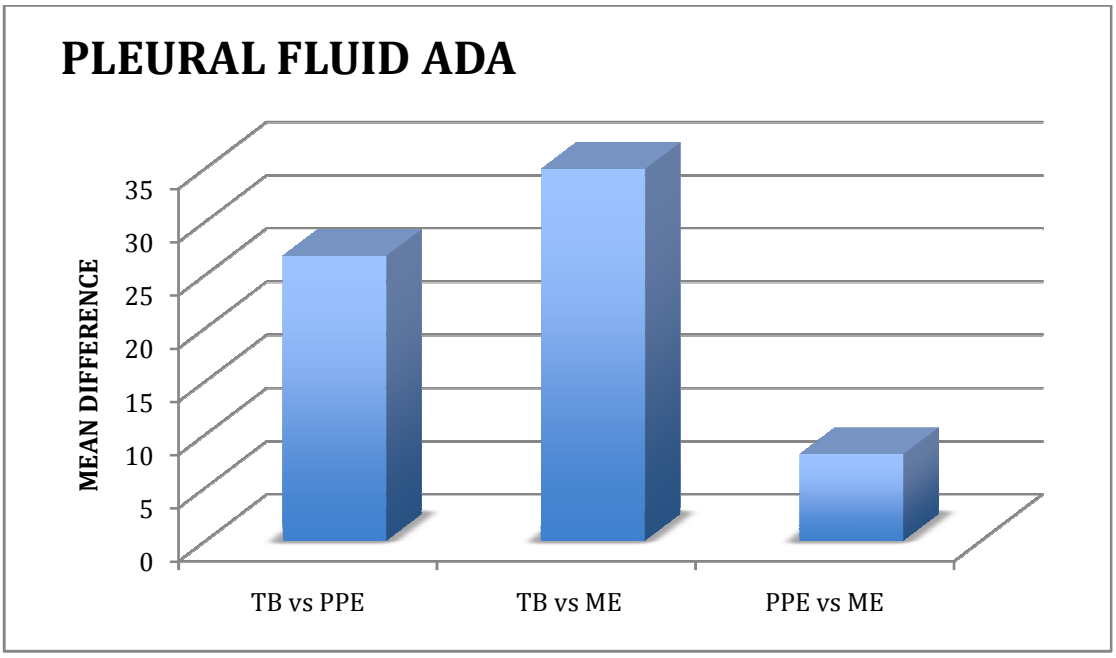
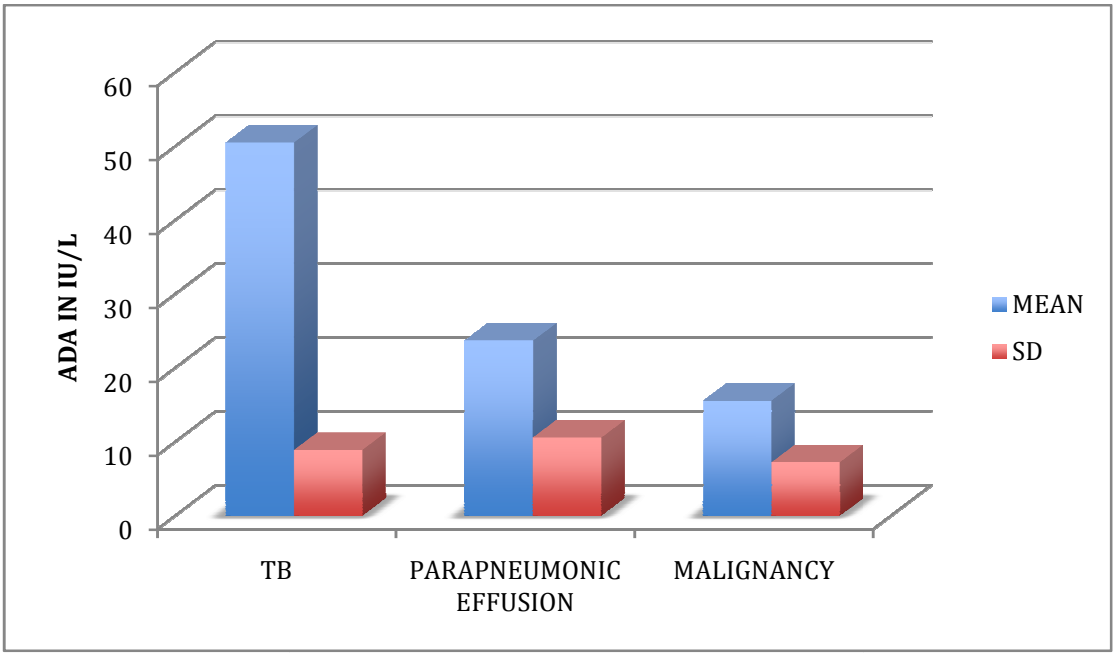


CHART:22 ADA



PLEURAL FLUID PROTEIN:

The pleural fluid protein content was significant for TB vs Malignant effusion and parapneumonic effusion vs malignant effusion.

TABLE:23 PLEURAL FLUID PROTEIN

	MEAN	P VALUE	95% CONFIDENCE INTERVAL
TB vs PPE	**-0.8100**	**<0.05**	**-1.480 TO -0.1397**
TB vs ME	**0.6550**	**>0.05**	**-0.1681 TO 1.478**
PPE vs ME	**1.465**	**<0.001**	**0.6687 TO 2.261**

PROTEIN RATIO:

The protein ratio was significant for insignificant for TB vs parapneumonic effusion and TB vs malignant effusion.

CHART:23 PLEURAL FLUID PROTEIN RATIO

	MEAN	**P VALUE**	**95% CONFIDENCE INTERVAL**
TB vs PPE	-0.330	>0.05	-0.1275 TO 0.06150
TB vs ME	0.0900	>0.05	-0.02604 TO 0.02060
PPE vs ME	0.1230	<0.05	0.01074 TO 0.2353

TB- TUBERCULOSIS

ME-MALIGNANT EFFUSION

PPE-PARAPNEUMONIC EFFUSION

S- SIGNIFICANT

NS – NOT SIGNIFICANT

DISCUSSION

DISCUSSION

ETIOLOGY OF PLEURAL EFFUSION:

In our study the most common etiology of pleural effusion is parapneumonic effusion, next in frequency is tuberculous. Exudative pleural effusion is more common than the transudative pleural effusion. According to western literature, congestive cardiac failure is the most common cause of pleural effusion but several studies do not include congestive cardiac failure in the study of pleural effusion, so the true incidence of the cardiac failure is not known. Our study shows incidence of tuberculous effusion is 28%vs 32.5% in other studies.

Parapneumonic effusion is 34% vs 19% in other studies. Having taken consecutive patients heart failure associated pleural effusion is surprisingly when compared to other studies. In a study done in India titled “Exudative pleural effusions in patients over forty years of age” malignant effusion is the most common cause followed by tuberculosis. All patients with malignant effusions were more than 40 years of age. The incidence of hepatic hydrothorax in our study is 4% vs 3% in an other study. Our study though evaluated fifty consecutive patients it did not find any rare cause of pleural effusion such as pleural effusion in hypothyroidism, lupus, rheumatoid arthritis, nephrotic syndrome.

AGE(yrs) AND SEX:

Mean age of exudative pleural effusion is 43.61yrs(SD-12.77). The mean age of transudative effusion is 43(SD-8.60). The mean age of tuberculous effusion is 47.5 vs 33.7 in other study. The mean age of parapneumonic effusion is 39.82 vs 43.3 in other studies. In our study tuberculous effusion is ten years more than the previous study, but tuberculous effusion typically occursin20-40 age group in Indian subcontinent.

The mean age of malignant effusion is 44.87yrsvs 53.4 in previous study. In our study males were 33 in number and females were 17 in number. This does not vary with other studies and not statastically significant. There was no statistical significance in the age between the transudate and exudate category.

SYMPTOM ANALYSIS:

The symptoms that were analyzed were cough, sputum production, hemoptysis, fever, loss of weight.

Cough was the most common symptom present. Followed by fever and sputum production. Hemoptysis was present only in 6% of patients. Interestingly, tuberculous patients did not have any hemoptysis and this shows pleural effusion as a primary modality of presentation in patients with tuberculosis by hypersensitivity reaction to tubercular proteins rather

than the extension of caseating focus in the lung. Fever was present in only 35.7% of tuberculous effusion patient whereas 94% of patients with parapneumoniceffusion had fever during the presentation. In a study published by BansalPankaj et al. where they studied 250 cases of tuberculous effusion the common symptoms were fever, cough, breathlessness followed by chest pain. Fever is important in the diagnosis of parapneumonic effusion and the persistence of fever more than fourty eight hours of therapy indicates complicated parapneumonic effusion. The absence of fever or chest pain should not stop us from considering parapneumonic effusion. Sahn et al. reported cases where empyema caused by aerobes did not have fever. Patients with anaerobic bacterial effusion need not have the dramatic presentation of the aerobic organisms and disease any have a subacute illness.

Malignant pleural effusion is second most common cause of exudative pleural effusion in many series. The most common symptom of malignant effusion is breathlessness and in one study, weight loss was about 32% whereas in our study the incidence of weight loss is 100%. Hemoptysis was present in 25% of malignant effusion when compared to other series where hemoptysis was present in more than 40% of patients.

ERYTHROCYTE SEDIMENTATION RATE(ESR):

ESR of the transudate group is 15.6mm/hr(SD-7.52), tuberculosis has an ESR of 39.28mm/hr(SD-25.17), parapneumonic effusion ESR-34.17mm/hr(SD-8.71) and Malignant effusion has an ESR of 15.5mm/hr(SD-6.11)

The normal upper value of ESR in male is 15mm in first hour and that of females is 20mm in first hour. Many studies have proven the value of ESR in the diagnosis of tuberculosis. In our study ESR in tuberculosis is significantly higher than in other effusions, it can also be used for follow up of treatment. The ESR is significant in our study differentiating tuberculous from malignant effusion with a P value of <0.01.

PLEURAL FLUID LDH(IU/L) AND LDH RATIO:

The mean of pleural fluid LDH is 34.72IU/L(SD-16.56) in transudate group and when compared with exudate it is extremely significant.

Pleural fluid LDH in tuberculosis, parapneumonic effusion, and malignancy is 194.42IU(SD-83.10), 420.29IU(SD-231.05), and 245.75IU(SD-99.42) respectively.

It is highest in parapneumonic effusion. In comparison with our study exudative pleural effusion has LDH value more than 200 IU/L.

In a study done by Manuel Vives et al LDH more than 300IU/L had a sensitivity of 87.4% and specificity of 87.2% and a positive predicitive value of 96.3% and diagnostic accuracy of 87.4%. Differentiating between LDH based on the LDH alone is not significant according to our study. LDH ratio was also not useful in differentiating different types of exudate but it is statistically significant in differentiating exudate and transudate effusion. LDH ratio has 94.2% diagnostic accuracy according to various studies. Though our study did not have absolute LDH value more than 1000IU/L, presence of this high value indicates high tumor burden or empyema.

PLEURAL FLUID TOTAL PROTEIN (g/dL) AND PROTEIN RATIO:

The pleural fluid protein in transudate is 1.65g/dL(SD-0.64) and in parapneumonic effusion is 4.59g/dL(SD-0.97), malignant effusion is 3.125g/dL(SD-0.575), tuberculous effusion is 3.78g/dL(SD-0.51). As expected pleural fluid protein is higher in exudates when compared to transudate,and statistically significant for comparing the two.

PROTEIN RATIO:

The protein ratio in transudate is is 0.30(SD-0.09). In tuberculosis ratio is 0.71(SD-0.07), in parapneumonic effusion, ratio is 0.743(SD-0.12) in malignancy the ratio is 0.62(SD-0.13). All three exudative effusion satisfy the lights criteria.

PLEURAL FLUID ADA (IU/L):

The mean pleural fluid ADA in transudate group is15.54 IU (SD-2.27). The mean pleural fluid ADA in tuberculosis, parapneumonic effusion, and malignancy is 52.15IU(SD-14.83),23.70IU(SD10.57)), and 23.O75 IU(SD-7.83) respectively. ADA level was significantly higher in tuberculosis and more than the diagnostic cut off of 40 IU/L. In various studies done both in India and western countries ADA remains cost effective diagnostic modality for tuberculous effusion. IN study done in Nepal mean pleural fluid ADA was about 90.29IU(SD-54.80). Our study had lesser ADA than the study done at Nepal. ADA level is defined only in the pleural fluid and the measurement of ADA in other body fluid needs further validation.

PLEURAL FLUID CRP:

Our study aimed at bringing out the significance of CRP in the etiological diagnosis of pleural effusion. Comparing the mean CRP between the transudative and exudative effusion is extremely significant with the P value of <0.0001. Study conducted by us had a mean CRP-7.21mg/L(SD-2.27) in transudative group. Study conducted by Castano et al. showed mean pleural fluid CRP around 5.3mg/L(SD-7.8) in transudate group and it was significantly lower than the exudate group. Our study was extremely significant differentiating the two.

In study conducted by Hoda et al. the mean serum value was 0.30(SD-0.11) and the stastical significance with P<0.0039.

The exudate group had mean CRP value of 68.55mg/dL(SD-40.04).The mean pleural fluid CRP in exudative group in an other study is 67.6mg/L(SD-6.74). Most of the studies also attempted also attempted to measure the corresponding CRP in the serum and determined the CRP ratio. The mean of the CRP ratio in transudative group is 0.14mg/dL(SD-0.11) and the exudative pleural fluid CRP 0.39(SD-0.34)

But the pleural fluid to serum CRP ratio was not significant in this study. In other study done, CRP ratio in transudative effusion had median value of 0.34 and mean is 0.36(SD-0.19).

CRP IN EXUDATIVE PLEURAL EFFUSION:

The mean CRP in pleural fluid among different groups of exudate in our study is tuberculosis-52.15mg/L(SD-14.83), Parapneumonic effusion-103.47mg/L(SD-32.23), malignancy-23.07mg/L(SD-7.83). In a study conducted in Spain the mean CRP in malignant process is 29.3mg/L(SD-16.1), parapneumonic effusion-122.7mg/L(SD-48) and in tuberculosis group the mean CRP is 67.8mg/L(SD-32.1).

Parapneumonic effusion had the highest CRP in exudative group and it is more than tuberculosis. Malignant pleural effusion had lower CRP level in pleural fluid compared to others in exudative group.

COMPARISON OF CRP IN TUBERCULOUS AND PARAPNEUMONIC EFFUSION:

Statistics done by one way ANOVA (Analysis of variance). The mean difference between tuberculosis vs parapneumonic effusion is –51.320. The P value is significant and <0.001.

COMPARISON OF CRP IN TUBERCULOUS EFFUSION AND MALIGNANT EFFUSION:

The mean difference between tuberculosis and malignancy group is +29.080 and p value is significant <0.05%

COMPARISION OF PARAPNEUMONIC EFFUSION AND MALIGNANCY:

The P value is <0.001 and highly significant.Various other studies performed with CRP in pleural effusion are in concurrence with our study results. From the above analysis of CRP, it is evident that CRP has a discriminating role in not only exudative from transudative effusion. It also has a significant role in differentiating role in parapneumonic effusion from malignant effusion and tuberculous effusion from malignant effusion.

CONCLUSIONS

CONCLUSION

- Pleural fluid CRP levels are useful in differentiating exudative and transudative effusion.
- Pleural fluid CRP level is elevated in all types of exudative effusion
- Among the exudative group CRP level is highest in parapneumonic effusion.
- If the pleural fluid CRP is more than 7.21 $\pm$ 2.27 transudative effusion is unlikely.
- If the pleural fluid CRP is more than 103.47 $\pm$32.23 parapnemonic effusion is more likely.
- If the Pleural fluid CRP is more than 52.15 $\pm$ 18.83 the diagnosis of tuberculous effusion is strongly considered.
- Pleural fluid CRP can be used to differentiate tuberculous from malignant pleural effusion.
- CRP can be incorporated in algorithm of pleural fluid evaluation in routine practice.

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PROFORMA

ROLE OF PLEURAL FLUID C-REACTIVE PROTEIN ESTIMATION IN ETIOLOGICAL DIAGNOSIS OF PLEURAL EFFUSION

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	**Chronic kidney disease**	**Tuberculosis**
Hypertension	Liver disease	Malignancy
Coronary artery disease/CCF	Drug intake	Collagen vascular disease

Personal history:

- Smoking
- Alcoholism
- Occupation

General examination:

PULSE:

BLOOD PRESSURE:

GENERAL EXAMINATION:

SYSTEMIC EXAMINATION:

CVS: RS: ABDOMEN: CNS:

INVESTIGATIONS:

Hemogram			**RFT**		
TC		cells/mm^3	Glucose (F)		mg/dl
DC			Glucose (PP)		mg/dl
ESR		mm/hr	Urea		mg/dl
Hb		g/dl	Creatinine		mg/dl
PCV		%	Na+		mEq/l
Platelets		lakhs/mm^3	K+		mEq/l
RBCs		million/mm^3	**Others**		
Liver function tests					
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's stain
Cytology	ADA
Cell count	CRP

CHEST X RAY

CT CHEST

PLEURAL/TISSUE BIOPSY

ULTRASONOGRAM OF KIDNEYS:

ECG:

ECHO CARDIOGRAM:

PATIENT CONSENT FORM

Study Detail	:	ROLE OF PLEURAL FLUID C-REACTIVE PROTEIN ESTIMATION IN ETIOLOGICAL DIAGNOSIS OF PLEURAL EFFUSION
Study Centre	:	Rajiv Gandhi Government General Hospital, Chennai.
Patient's Name	:	
Patient's Age	:	
Identification Number	:	

Patient may check (☑) 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's Name and Address:Signature of Investigator

Study Investigator's name:

Dr. R. VICKRAM VIGNESH

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No: 04425305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. Vickram Vignesh .R
PG in MD General Medicine
Madras Medical College, Chennai

Dear Dr. Vickram Vignesh .R

The Institutional Ethics Committee of Madras Medical College reviewed and discussed your application for approval of the proposal entitled " Role of Pleural fluid C- Reactive Protein estimation in etiological diagnosis of pleural effusion" No. 16052012.

The following members of Ethics Committee were present in the meeting held on 30.05.2012 conducted at Madras Medical College, Chennai -3.

1.	Prof. S.K. Rajan, MD	-- Chairperson
2.	Prof. Pregna B. Dolia MD Vice Principal , Madras Medical College, Chennai -3 Director , Instt.of Bio Chemistry, MMC, Ch-3	-- Member Secretary
3.	Prof R. Nandhini, MD Director, Institute of Pharmacology, MMC, Ch-3	-- Member
4.	Prof. P. Karkuzhali MD Director i/c Prof & Head , Dept. of Pathology, MMC, Ch-3	-- Member
5.	Prof.A. Radhakrishnana MD Prof. of Internal Medicine, MMC, Ch-3	-- Member
6.	Prof. P. Raghumani MS Prof. of Surgery, Dept. of Surgery, MMC, Chennai -3	-- Member
7.	Thiru. S. Govindasamy . BA.BL	-- Lawyer
8.	Tmt. Arnold Soulina MA	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd /. Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report

Member Secretary, Ethics Committee

S.NO	AGE	SEX	COUGH	SPUTUM	HEMOPTYSIS	FEVER	LOW	TC	ESR	SPUTUM GM	SPUTUM CS	SPUTUM AFB	SERUM LDH	SERUM PROTEIN	Pl SUGAR	Pl PROTEIN	Pl LDH
1	25	M	P	P	A	P	P	13000	68	A	A	P	110	5	40	4	310
2	28	M	P	A	P	P	P	8000	16	A	A	A	250	6	50	3.2	360
3	32	M	P	P	A	P	A	20000	24	P	P	A	160	5.7	60	3	250
4	33	F	A	A	A	A	A	4000	20	A	A	A	47	6	90	2	20
5	23	F	A	A	A	A	P	9000	76	A	A	A	172	4.6	50	3.1	298
6	60	F	A	A	A	A	P	13500	30	A	A	A	200	6	50	3.2	320
7	34	M	P	P	P	P	A	23600	46	P	P	A	400	7	59	5.3	1000
8	45	M	P	P	A	A	A	4800	24	A	A	A	78	4.6	110	1.2	25
9	56	M	A	A	A	A	A	5200	16	A	A	A	110	6	80	2.1	45
10	56	M	A	P	A	P	A	11020	8	A	A	A	230	5.6	40	4.1	290
11	58	M	P	P	A	P	A	28300	30	P	P	A	456	5.7	59	5	239
12	39	M	P	P	A	P	A	32300	32	P	P	A	342	6.1	70	5	609
13	50	M	P	P	A	P	A	19100	40	A	A	A	432	4.9	67	3	807
14	45	M	A	A	A	P	A	20400	20	A	A	A	342	5.6	53	4	432
15	45	M	A	A	A	A	A	6600	10	A	A	A	120	5.6	90	1.2	45
16	49	M	A	A	A	A	A	8000	20	A	A	A	29	4	110	0.6	10
17	42	F	A	A	A	A	A	6200	28	A	A	A	127	4.1	69	1.3	59
18	27	F	A	A	A	A	A	4100	14	A	A	A	120	5.8	89	2	40
19	37	F	A	A	A	P	A	11000	70	A	A	A	231	5.5	50	4.1	167
20	54	M	P	P	A	P	A	2100	40	A	A	A	243	6.1	30	4.2	399
21	35	M	A	A	A	P	A	19200	44	A	A	A	213	5.7	45	5	680
22	60	M	P	P	A	P	A	21200	34	A	P	A	159	5.7	23	3	239
23	26	M	P	P	A	P	A	22300	28	P	P	A	200	6.4	60	4.5	342
24	56	M	P	P	A	A	A	10100	50	A	A	A	134	5.8	64	3.6	204
25	60	F	P	P	A	A	A	9200	24	A	A	P	153	6.1	70	4.5	205
26	50	F	A	A	A	A	A	6200	14	A	A	A	231	5.4	60	3	45
27	52	F	A	A	A	A	A	5300	20	A	A	A	221	4.9	59	2.9	150
28	40	F	P	P	A	A	A	4100	4	A	A	A	111	5.9	98	3	35
29	55	M	P	P	A	A	A	6000	8	A	A	A	30	6	20	1.5	20
30	33	M	P	P	A	A	A	16700	32	A	A	A	264	7	59	5.7	456
31	22	M	P	P	A	P	A	13900	32	P	P	A	254	5.8	67	5	342
32	56	M	P	P	A	P	A	28000	56	P	P	A	321	7.1	70	6	432
33	45	M	P	P	A	P	A	19800	28	P	P	A	231	7	68	5.8	200
34	35	M	A	A	A	P	A	20200	32	A	A	A	150	6	50	5.4	320
35	37	M	A	A	A	P	P	4300	40	A	A	A	189	5.8	27	4.6	278
36	39	M	A	A	A	A	A	5400	8	A	A	A	48	6	89	2	23
37	56	M	A	A	A	A	P	9800	40	A	A	A	189	4.9	50	3.9	78
38	47	F	P	P	P	A	P	10000	12	A	A	A	210	5.1	86	3	290
39	58	F	A	A	A	A	P	9900	12	A	A	A	156	4	47	3.6	129
40	54	M	A	A	A	A	A	10500	20	A	A	A	187	5.5	60	3.8	156
41	54	M	A	A	A	A	A	11000	22	A	A	A	234	5.1	70	3.9	120
42	26	M	A	A	A	A	P	9600	14	A	A	A	120	3.9	54	2	256
43	25	F	P	P	A	P	A	33000	30	A	P	A	231	6.1	51	4	198
44	28	M	P	P	A	P	A	18700	33	A	P	A	253	6.6	57	4.2	200
45	59	M	A	A	A	A	P	10800	18	A	A	A	138	4.5	76	3.5	245
46	35	F	A	A	A	A	P	5500	16	A	A	A	200	4.2	89	3	342
47	45	M	P	A	A	A	P	6500	12	A	A	A	120	5.8	59	3	113
48	46	F	A	A	A	P	A	7200	80	A	A	A	110	5.4	60	4	232
49	42	F	A	A	A	A	A	8400	20	A	A	A	124	4.1	91	1.3	60
50	60	F	P	P	A	P	P	4600	12	A	A	A	174	5.6	50	4	156

	M-MALE P-PRESENT	TC-TOTAL COUNT	SP GM-SPUTUM GRAM STAIN	E-EXUDATE
	F-FEMALE ABSENT		SP CS-SPUTUM CULTURE SENSITIVITY	T TRANSUDATE
	LOW-LOSS OF WEIGHT			
	SPUTUM GS-GRAM STAIN			
	TC-TOTAL COUNT			
	S LDH-SERUM LDH			
	S PROTEIN-SERUM PROTEIN			
	Pl SUGAR-I PLEURAL FLUID LDH			
	Pl LDH-PLEURAL FLUID LDH			
	GM-GRAM STAIN			
	Pl CS-PLEURAL FLUID CULTURE AND SENSITIVITY			
	Pl-pleural fluid			
	UL LDH-UPPER LIMIT OF LDH MORE THAN 2/3 RD OF NORMAL SERUM VALUE.			
	ME-MALIGNANT EFFUSION			
	PP-PARAPNEUMONIC EFFUSION			
	TB-TUBERCULOUS EFFUSION			
	HF-HEART FAILURE			
	CLD-CHRONIC LIVER DISEASE			

Pl GM	Pl AFB	Pl CS	Pl CYTOLOGY	UL LDH	Protein RATIO	LDH RATIO	Pl ADA	PF CRP	NATURE	DIAGNOSIS
A	A	A	L	P	0.8	2.8181818	60	59.8	E	TB
A	A	A	M	P	0.533333333	1.44	20	16.2	E	ME
P	A	P	P	P	0.526315789	1.5625	23	90.7	E	PP
A	A	A	N	A	0.333333333	0.4255319	17	5	T	HF
A	A	A	N	P	0.7	1.7325581	54	60.1	E	TB
A	A	A	M	P	0.533333333	1.6	18	18.9	E	ME
P	A	P	P	P	0.757142857	2.5	9	96.1	E	PP
A	A	A	N	A	0.260869565	0.3205128	13	9.1	T	HF
A	A	A	N	A	0.35	0.4090909	19	12	T	HF
A	A	A	L	P	0.732142857	1.2608696	43	40.8	E	TB
A	A	A	P	P	0.877192982	0.5241228	20	150.9	E	PP
A	A	A	P	P	0.819672131	1.7807018	12	110.7	E	PP
P	A	P	P	P	0.612244898	1.8680556	14	78.9	E	PP
P	A	P	N	P	0.714285714	1.2631579	15	85.9	E	PP
A	A	A	N	A	0.214285714	0.375	18	6.2	T	HF
A	A	A	N	A	0.15	0.3448276	19	7.4	T	CLD
A	A	A	N	A	0.317073171	0.4645669	20	4	T	CLD
A	A	A	N	A	0.344827586	0.3333333	12	8.3	T	HF
A	P	A	L	P	0.745454545	0.7229437	47	39.9	E	TB
A	A	A	P	P	0.68852459	1.6419753	28	70.9	E	PP
A	A	A	P	P	0.877192982	3.1924883	38	102.6	E	PP
A	A	P	P	P	0.526315789	1.5031447	32	89.7	E	PP
P	A	P	N	P	0.703125	1.71	40	70.3	E	PP
A	A	A	P	P	0.620689655	1.5223881	70	70.9	E	TB
A	P	A	P	P	0.737704918	1.3398693	54	70.2	E	TB
A	A	A	P	A	0.555555556	0.1948052	42	51.7	E	TB
A	A	A	N	P	0.591836735	0.678733	48	39.1	E	TB
A	A	A	N	A	0.508474576	0.3153153	14	4.6	T	HF
A	A	A	N	A	0.25	0.6666667	17	7.1	T	HF
A	A	A	N	P	0.814285714	1.7272727	32	55.8	E	PP
A	A	A	N	P	0.862068966	1.3464567	15	79.7	E	PP
A	A	A	P	P	0.845070423	1.3457944	13	149.7	E	PP
A	A	A	P	P	0.828571429	0.8658009	13	143.8	E	PP
A	A	P	P	P	0.9	2.1333333	39	131.8	E	PP
A	A	A	L	P	0.793103448	1.4708995	41	40.1	E	TB
A	A	A	N	A	0.333333333	0.4791667	14	7.6	T	HF
A	A	A	L	A	0.795918367	0.4126984	52	31.2	E	TB
A	A	A	M	P	0.588235294	1.3809524	8	19.5	E	ME
A	A	A	M	P	0.9	0.8269231	7	37.6	E	ME
A	A	A	L	P	0.690909091	0.8342246	48	56.9	E	TB
A	A	A	L	P	0.764705882	0.5128205	63	31.4	E	TB
A	A	A	M	P	0.512820513	2.1333333	20	21.9	E	ME
A	A	A	P	P	0.655737705	0.8571429	28	90.8	E	PP
P	A	P	P	P	0.636363636	0.7905138	32	160.7	E	PP
A	A	A	L	P	0.777777778	1.7753623	44	67.8	E	TB
A	A	A	M	P	0.714285714	1.71	10	17.8	E	ME
A	A	A	M	A	0.517241379	0.9416667	17	33.1	E	ME
A	A	A	L	P	0.740740741	2.1090909	41	70.3	E	TB
A	A	A	N	A	0.317073171	0.483871	8	8.1	T	HF
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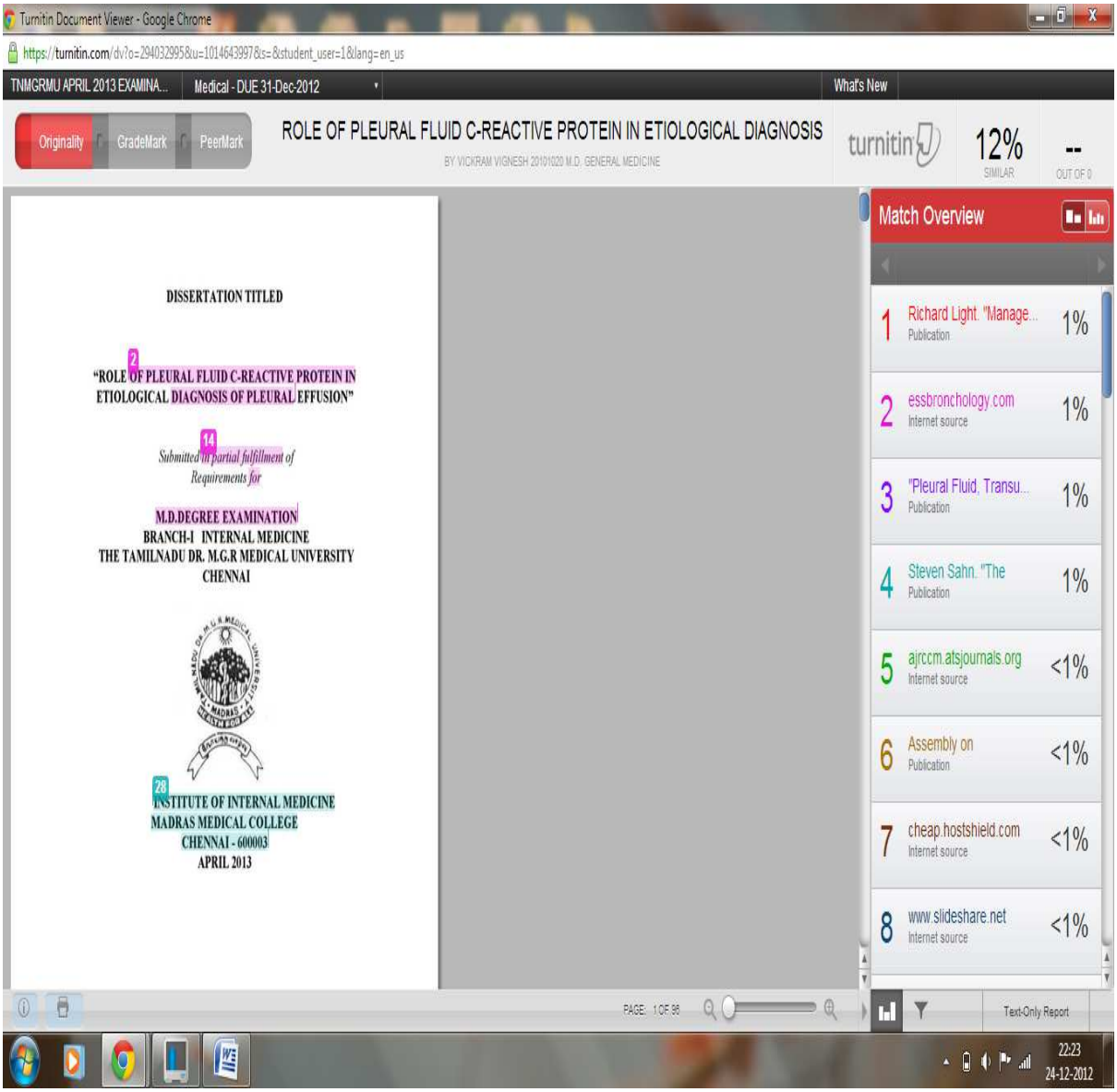
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