A HOSPITAL BASED STUDY ON THE ROLE OF CRP AS A BIOMARKER IN PLEURAL EFFUSION

Dissertation submitted to
THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY
In fulfilment of the regulations for the award of the degree

M.D
TUBERCULOSIS AND RESPIRATORY DISEASES

DEPARTMENT OF RESPIRATORY MEDICINE

PSG INSTITUTE OF MEDICAL SCIENCES AND RESEARCH
THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY
COIMBATORE

2016
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TUBERCULOSIS AND RESPIRATORY DISEASES

GUIDE
DR. ANUPAMA MURTHY, MD (CHEST)
DEPARTMENT OF RESPIRATORY MEDICINE

PSG INSTITUTE OF MEDICAL SCIENCES AND RESEARCH

THE TAMILNADU DR. M. G. R. MEDICAL UNIVERSITY
COIMBATORE

2016
To
Dr Arun R Thomas
Postgraduate
Department of Respiratory Medicine
PSG IMS & R
Coimbatore

The Institutional Human Ethics Committee, PSG IMS & R, Coimbatore -4, has reviewed your proposal on 13th June, 2014 in its expedited review meeting held at IHEC Secretariat, PSG IMS&R, between 10.00 am and 11.00 am, and discussed your study proposal entitled:

“A hospital based study on role of CRP as a biomarker in pleural effusion”

The following documents were received for review:

1. Duly filled application form
2. Proposal
3. Informed Consent Forms (Ver 1.1)
4. Proforma
5. Permission letter from the concerned Heads of Department
6. CV
7. Budget

After due consideration, the Committee has decided to approve the study.

The members who attended the meeting at which your study proposal was discussed are as follows:

<table>
<thead>
<tr>
<th>Name</th>
<th>Qualification</th>
<th>Responsibility in IHEC</th>
<th>Gender</th>
<th>Affiliation to the Institution</th>
<th>Present at the meeting</th>
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The approval is valid for one year.

Proposal No. 14/192
We request you to intimate the date of initiation of the study to IHEC, PSG IMS&R and also, after completion of the project, please submit completion report to IHEC.

This Ethics Committee is organized and operates according to Good Clinical Practice and Schedule Y requirements.

Non-adherence to the Standard Operating Procedures (SOP) of the Institutional Human Ethics Committee (IHEC) and national and international ethical guidelines shall result in withdrawal of approval (suspension or termination of the study). SOP will be revised from time to time and revisions are applicable prospectively to ongoing studies approved prior to such revisions.

Kindly note this approval is subject to ratification in the forthcoming full board review meeting of the IHEC.

Yours truly,

Dr S Bhuvaneshwari
Member - Secretary
Institutional Human Ethics Committee
INTRODUCTION

Pleural effusion is defined as the abnormal collection of pleural fluid in between the two layers of the pleura as a result of imbalances in the homoeostatic factors that govern the rate of pleural fluid formation and absorption. The goal incidence of pleural effusion is estimated to be around 3 million per annum. Thus, it is important to exactly diagnose the cause of pleural fluid formation and thereby reducing the mortality and morbidity associated with the same. Pleural fluid originates from the capillaries of the parietal pleura at a rate of 0.01 ml/kg/h and is cleared at a rate of 0.4 ml/kg/hour. In normal individuals, the approximate amount of pleural fluid present is 85–43 ml and the normal pleural fluid composition shows that the mean total cell count is 1715 cells/mm3 and mean red cell count being 300 cells/mm3 in humans. Approximately 75% cells in pleural fluid are macrophages, 25% being lymphocytes and mesothelial cells and finally eosinophils and neutrophils totally comprising 25% of the cellular population of pleural fluid analysis. Pleural fluid accumulation occurs when the pleural fluid formation exceeds the rate of pleural fluid absorption. Various theories have been proposed for the same, of which three basic mechanisms have been identified:

1. Increased hydrostatic pressure
2. Increased capillary permeability
INTRODUCTION

Pleural effusion is defined as the abnormal collection of pleural fluid between the two layers of the pleura as a result of irritation in the hematocrit factors that govern the rate of pleural fluid formation and absorption. The total incidence of pleural effusion is estimated to be around 2 million per annum; thus, it is important to accurately diagnose the cause of pleural fluid formation and then try reducing the morbidity and mortality associated with it. Pleural fluid originates from the capillaries of the parietal pleura and is drained at a rate of 1-3 ml/hr in normal individuals: the approximate amount of pleural fluid produced is 4.4–4.3 ml and the normal pleural fluid composition shows that the mean total cell count is 179 cells/mL and mean red cell count being 756 cells/mL in humans approximately 15% in pleural fluid are macrophages, 2% being lymphocytes and mesothelial cells and finally eosinophils and neutrophils usually comprising 0% of the cellular population of pleural fluid analysis. Pleural fluid accumulation occurs when the pleural fluid formation exceeds the rate of pleural fluid absorption.
CERTIFICATE

This is to certify that the thesis entitled “HOSPITAL BASED STUDY ON THE ROLE OF CRP AS A BIOMARKER IN PLEURAL EFFUSION” is a bonafide work of DR. ARUN R THOMAS done under the guidance and supervision of DR. K. ANUPAMA MURTHY MD (CHEST) in the Department of PSG Institute of Medical Sciences and Research, Coimbatore in fulfillment of the regulations of Dr. MGR Medical University for the award of M.D. Degree in Tuberculosis and Respiratory Diseases.

DR. K. ANUPAMA MURTHY
Professor & Head of Dept.
Dept. of Respiratory Medicine

DR. RAMALINGAM
DEAN
DECLARATION

I hereby declare that this study dissertation entitled “HOSPITAL BASED STUDY ON THE ROLE OF CRP AS A BIOMARKER IN PLEURAL EFFUSION” was prepared by me under the direct guidance and supervision of Professor of Respiratory Medicine, DR.K.ANUPAMA MURTHY, MD (CHEST), PSG Institute of Medical Sciences & Research, Coimbatore.

This dissertation is submitted to the Tamil Nadu Dr. MGR Medical University in fulfillment of the University regulations for the award of M.D. Degree in Tuberculosis and Respiratory Diseases. This dissertation has not been submitted for the award of any other Degree or Diploma.

DR. ARUN R THOMAS
CERTIFICATE BY THE GUIDE

This is to certify that the thesis entitled “HOSPITAL BASED STUDY ON THE ROLE OF CRP AS A BIOMARKER IN PLEURAL EFFUSION” is a bonafide work of DR. ARUN R THOMAS done under my direct guidance and supervision in the Department of Respiratory Medicine, PSG Institute of Medical Sciences and Research, Coimbatore in fulfillment of the regulations of DR. MGR Medical University for the award of M.D. Degree in Tuberculosis and Chest Diseases.

DR. K. ANUPAMA MURTHY
Professor & Head of Dept.
Dept. of RESPIRATORY MEDICINE
ACKNOWLEDGEMENTS

I shall forever remain indebted to my beloved teachers, Dr. Anupama Murthy and Dr. Karthikeyan Ramaraju for their constant valuable inputs, guidance, patience, support without which this thesis would have been impossible.

I would also like to thank my co guides in the department of Microbiology for their support

A special mention to the Radiology, Medical Oncology, Cardiology, Nephrology and Gastroenterology departments for their unyielding support and providing a good number of cases for this study. I take this opportunity to thank all the above mentioned departments

Finally I thank all my patients, who cooperated at every step and provided me the opportunity to conduct the study.

Thank You

Dr. Arun R Thomas
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ABBREVIATION

CONSENT FORM

CASE PROFORMA

MASTER SHEET
INTRODUCTION

Pleural effusion is defined as the abnormal collection of pleural fluid in between the two layers of the pleural as result of imbalance in the homeostatic factors that govern the rate of pleural fluid formation and absorption. The global incidence of pleural effusion is estimated to be around 3 million per annum. Thus it is important to exactly diagnose the cause of pleural fluid formation and there by reducing the mortality and morbidity associated with the same. Pleural fluid originates from the capillaries of the parietal pleura at a rate of 0.01ml/kg/hr and is cleared at a rate of 0.4ml/kg/hour.

In normal individuals the approximate amount of pleural fluid present is 8.4 ± 4.3ml and the normal pleural fluid composition shows that the mean total cell count is 1716 cells/mm3 and mean red cell count being 700 cells/mm3. In humans approximately 75% cells in pleural fluid are macrophages, 25% being lymphocytes and mesothelial cells and finally eosinophils and neutrophils totally comprising of 2% of the cellular population of pleural fluid analysis. Pleural fluid accumulation occurs when the pleural fluid formation exceeds the rate of pleural fluid absorption. Various theories have been proposed for the same, of which three basic mechanisms have been identified;

1. Increased hydrostatic pressure
2. Increased Capillary permeability
3. Decreased oncotic pressure.
These three basic underlying pathogenic process have been implicated in the formation of pleural effusion due to any cause (either systemic or localised pathology). Thus a knowledge about the underlying pathogenic process gives an idea about the etiology of the pleural effusion. Generally pleural effusions were classified as transudates (secondary to systemic causes like CCF, renal failure, decompensated liver diseases) or exudates (infectious causes). Exudative effusions further classified into parapneumonic, tubercular and malignant effusions. This sub classification of exudative effusions is important as the line of management differs for each.

Traditionally the classification into exudative and transudative effusions were based on pleural fluid and serum proteins which had a lot of disadvantages and led to misclassification of pleural effusions. Thus the need for a proper diagnostic criteria was essential for correctly classifying the pleural effusions. Light et al \(^{(4)}\) in 1972 proposed the Lights criteria for the same which states:

1. Pleural fluid LDH/SerumLDH >0.6
2. Pleural fluid LDH >200IU/L
3. Pleural fluid protein/Serum protein >0.5

It was further stated that in the presence of any one of the following criteria, pleural fluid was diagnosed as exudative, while failure to fulfillment of any of the above criteria, pleural fluid was said to be transudative. Lights criteria stood the test of time as the gold standard for diagnosis of pleural
effusions for nearly four decades. However several prospective studies were unable to reproduce the results of Lights criteria. It was found that in most of these studies Lights criteria had >95% sensitivity for exudates but the specificity was <78%. This led to a large number of exudates being misclassified as transudates which altered the treatment modalities for the same.

Various other characteristics of the pleural fluid such as the appearance, presence of loculations, estimation and evaluation of pleural fluid glucose, pleural fluid pH, ADA were used to further aid in the diagnosis of pleural effusions. However, all the above mentioned criteria were not specific, they had a lot of pitfalls which led to further misclassification of pleural effusion happened. This lead to the search of newer biomarkers for the same and initially the pleural fluid cholestrol measurement was seen as a likely biomarker along with the traditional Lights Criteria. Thus the Modified Lights Criteria was introduced which in turn contributed to the estimation of pleural fluid cholestrol as a biomarker along with routine Lights Criteria for classification of exudates and transudates which also had certain drawbacks. This lead to the search of newer biomarkers to aid in the classification of pleural effusions and various biomarkers were studied which included pleural fluid NT ProBNP, soluble mesothelial related proteins, pleural fluid CRP. These biomarkers when used along with the traditional Lights Criteria were found to serve as a diagnostic tool for the classification of borderline cases.
Amongst these biomarkers, pleural fluid CRP is being widely studied as an adjunct along with Lights Criteria for the classification of transudates and exudates. C Reactive Protein is an acute phase reactant which is released by the hepatocytes in the liver during an ongoing inflammatory process. It is of two types, hs CRP and ls CRP of which ls CRP is more sensitive marker for inflammatory reaction. Various prospective studies also showed the importance of pleural fluid CRP as a sensitive biomarker in differentiating exudative effusions and further it also helped in differentiating parapneumonic effusions from malignant effusions.

Further on CRP was released into the blood stream during the initial course of any inflammatory reaction in the body (infectious, malignant), this was further supported by the fact that in pleural space CRP is not normally seen and its presence in pleural fluid was a result of its diffusion from plasma. This formed the very basis of estimation of pleural fluid CRP in infectious and malignant effusions, which has good clinical reliability as shown in various publications. This reliable nature of pleural fluid CRP led to it being studied in a detailed manner through various clinical trials.

Further on estimation of pleural fluid CRP was also a cost effective procedure and required minimal man power for estimation of the same. Taking into consideration all the advantages of using pleural fluid CRP as a biomarker it was stated that pleural fluid CRP could be used a potential biomarker along with Lights Criteria for classification of pleural effusions and further on it had
a good sensitivity and specificity for the identification of parapneumonic effusions and thus it helped differentiate parapneumonic from other effusions. An intense inflammatory process like a parapneumonic effusion had a higher pleural fluid CRP than tubercular or a malignant effusion. Thus pleural fluid CRP helped in discriminating transudates from exudates as well as separating infectious from non-infectious causes.

Thus taking into consideration the need for newer biomarker for pleural effusion and the benefits of pleural fluid CRP, it was considered as reliable adjunct along with Lights Criteria. In this study we evaluate the role of CRP in differentiating transudative from exudative effusions and further on to differentiate between the different types of exudative effusions.
Aims & Objectives
AIM OF THE STUDY

Primary Aim

1. To study the diagnostic use of pleural fluid CRP as a biomarker in differentiating exudative from transudative effusions

Secondary Aim

2. To correlate the value of pleural fluid CRP with the clinic radiological picture and to differentiate exudative effusions of varying etiology
OBJECTIVE

Primary Objective

To categorize pleural effusions as transudates or exudates based on pleural fluid CRP values

Secondary Objective

To assess the diagnostic value of pleural fluid CRP in exudative effusions of different etiology
Materials and Methods
MATERIALS AND METHODS

The study aims at justifying the use of pleural fluid CRP as a diagnostic marker in the differentiation of pleural effusion of varying etiology

Study Type

Prospective Observational Study

Study Duration

12 months

Study Locale

PSG Institute of Medical Sciences and Research

Study Method:

Convinient Sampling

Sample Size:

60 subjects
**Inclusion Criteria**

1. Age 18 years and above
2. Willingness to participate
3. All cases of pleural effusion: Radiological evidence significant for diagnostic thoracocentesis

**Exclusion Criteria**

1. Pregnant and Lactating Women
2. Mentally challenged who are unable to give consent
3. All conditions which are contraindication for performing a diagnostic thoracocentesis

**DIAGNOSTIC CRITERIA FOR SPECIFIC PLEURAL EFFUSION**

1. **Tubercular Effusion**
   a. Exudative pleural effusion with predominantly lymphocytic prominence and a few mesothelial cells
   b. Fever, cough, pleuritic chest pain, toxemia which are compatible with the diagnosis of a tubercular pleural effusion
   c. Response to antitubercular therapy
2. Malignant Pleural Effusion

a. Demonstration of mesothelial cells on cytological examination of pleural fluid
b. Demonstration of malignant tissue in a pleural biopsy specimen
c. Histologically proven primary malignancy with the exclusion of any other cause known to be associated with the pleural effusion

3. Parapneumonic Effusion

a. Exudative effusion with neutrophilic or lymphocytic predominance
b. Pleural fluid LDH > twice the serum LDH values and pleural fluid ADA < 30 mg/dL
c. Pleural fluid cytology negative for malignant cells
d. Positive response to antibiotic therapy

4. Transudative Effusion

a. Clinical evidence of other system failure such as congestive heart failure, chronic liver disease or chronic renal failure
b. Lymphocytic predominance in pleural fluid cytology
c. A positive response to diuretic therapy as evidenced by clearance of pleural effusion
STUDY METHODOLOGY

STEP 1:
Fulfilment of the inclusion criteria

STEP 2
Clinical and radiological profile for assessing the pleural effusion

STEP 3
Diagnostic Thoracocentesis

STEP 4
Routine pleural fluid parameters assessed and classified as exudates / transudates based on Lights criteria

STEP 5
Pleural fluid CRP assessed using nephelometric method (BECK MANN COULTRE IMMAGE 800 and calculated in mg/dL)

STEP 6
Classifying the pleural effusion

Data Analysis

Spss Software Version 20
Review of Literature
REVIEW OF LITERATURE

Pleural effusion is a common occurrence seen during routine clinical practice, which is a result of varied systemic and local inflammatory pathology.

Steven A Sahn (1) in a study concluded that the global incidence of pleural effusion to be 3.5 million per annum. A detailed clinical history, a careful physical examination, appropriate blood investigations, a systematic interpretation of the chest radiographs goes a long way in the diagnosis and further management of a pleural effusion prior to diagnostic thoracocentesis itself. For eg: a massive effusion with no shift of mediastinum to the opposite side with features of grade 4 MMRC dyspnea is likely that it may be a malignant effusion.

Physical findings however depends on the volume of pleural fluid and degree of lung compensation due to the same .In a pleural fluid measuring approximately 500ml the above mentioned typical findings can be elicited, but this is not always the case in patients with minimal pleural effusion wherein a diagnostic thoracocentesis can be helpful in further confirming the diagnosis A diagnostic thoracocentesis and pleural fluid analysis further adds to the likely diagnosis or will help the clinician to rethink and search for an alternative diagnosis for the same. Also helping further diagnosis is the colour and characteristics of the pleural fluid during thoracocentesis.
Porcel et al\textsuperscript{(2)} in a study stated that malignancy as a cause for a frank blood stained pleural fluid, further on added the same to be seen in case of effusion due to pulmonary embolism also. However he stated that in reality only 11\% of the malignant pleural effusions were bloody. Contrary to the belief that transudates were watery in appearance, Porcel et al\textsuperscript{(2)} proved through a large multicentric study involving 766 patients where in 67\% of the transudative effusions were straw coloured, 11\% were bloody effusions and around 9\% were turbid in nature. Thus the pleural fluid appearance and characteristics were not conclusive of the exact etiology of pleural effusion.

Pleural fluid originates in the capillaries of the parietal pleura, normally at rate of 0.01ml/kg/hr and is cleared at a rate of 0.4ml/kg/hr. This steady clearance of pleural fluid results in achieving normal homoeostasis between pleural fluid production and pleural fluid absorption thereby ensuring that there is adequate layer of pleural fluid between the parietal and the visceral pleura, so as to avoid the friction between the two surfaces during normal respiration. The normal amount of pleural fluid is $8.4+/-4.3$ml between the two pleural surfaces.

Pleural fluid tends to accumulate when the rate of pleural fluid formation exceeds the rate of pleural fluid absorption and varied medical conditions are known for causing the same via different but similar mechanisms. These include (1)-increased pleural membrane permeability, (2)-increased pulmonary capillary pressure, (3)-Decreased oncotic pleural pressure.
and (4)-lymphatic obstruction. Varied factors have been implicated in the same ranging from localized pathology to systemic causes. This wide spectrum of the causes for pleural effusion presents a daunting task to the clinician in determining the exact pathology for the same. The initial step in evaluation of any pleural effusion is the basic separation into transudative and exudative effusions. This is a vital step as once the pleural effusion is found to be transudative no specific further management is required and treatment with diuretics will suffice as more than 80% of the transudative effusions were due to congestive heart failure as stated in a study by Theodoros et al\(^{(3)}\).

However a pleural fluid being exudative further detailed clinical methods and further exhaustive work up was necessary to exactly the determine cause for any exudative effusion as it goes a long way in the management of the same. Pleural effusions as a result of pleural disease more closely resembles that of plasma concentration. This is based on the concept that any inflammatory condition of the pleural fluid membrane leads to increase permeability of the capillaries thereby leading to transport of high molecular weight compounds along the concentration gradient.

While a transudative effusion occurred in the presence of a normal pleural membrane which was caused due to hemodynamic or the oncotic changes and is an ultrafiltrate of the plasma. The transudation of plasma through an intact serous membrane as in transudative effusions leads to transport of water and lower molecular weight compounds
(sodium, glucose, urea) and at the same time prevents the protein molecules to permeate through the intercellular pores of the normal pleural endothelium.

However a pleural effusion with lymphatic obstruction also lead to a high concentration of proteins in the pleural fluid and was an example for an exudative effusion with an intact pleural membrane. The most important step in discriminating exudates and subcategorizing was to differentiate malignant from non malignant effusions. Further on non malignant effusions were classified as tubercular or effusions due to bacterial causes.

Thus over the years various methods for the differentiation of pleural effusion was studied and different studies performed varied parameters for segregating the same. Historically the initial method for assessing the same was via pleural fluid specific gravity. A pleural fluid specific gravity of >3mg/dl was considered equivalent to that of pleural fluid proteins. This was used for a certain time period for the classification of exudates and transudative pleural effusion.

However the major drawback being this method wrongly classified around 30% of the effusions as quoted by Paddoc FK in 1940. Later on Leuallen and Carr in 1955 in a study comprising 436 patients claimed that pleural fluid protein was a better parameter in differentiating pleural effusions. This study too had certain drawbacks in the form of misclassification of pleural effusions. Further on 14 years later in 1958 Wroblewski, described that pleural fluid protein criterion alone was not significant to distinguish pleural effusions
and thus stated that pleural fluid protein to serum protein as a more reliable criteria for the same. He further observed that pleural fluid LDH of malignant effusions were higher than the simultaneous serum LDH level. Following which various studies in the subsequent years also quoted that pleural fluid LDH can be raised in exudative effusions, however no concrete data was found for the same and no study citing the combination of pleural fluid protein to serum protein and pleural fluid LDH to serum LDH were found till 1972.

In 1972 Light et al\cite{4} studied the correlation between serum LDH to pleural fluid LDH and serum protein to pleural fluid protein levels to effectively discriminate between transudates and exudates. Lights criteria stated as follows

1. Pleural fluid protein /Serum protein >0.5
2. Pleural fluid LDH/Serum LDH >0.6
3. Pleural fluid LDH > 2/3 of upper limit of serum LDH

Light et al showed that pleural effusion to be classified as exudates any one of the three criteria was to be satisfied and on the other hand a transudative effusion met none of the above mentioned criteria. Lights Criteria stood the test of time for nearly four decades and it accurately classified pleural effusions and was regarded the very basic step in evaluation of patients with pleural effusions.

Till date Lights criteria is widely accepted as the initial step in the management of pleural effusions. However studies done subsequently stated
that though Lights criteria had a good sensitivity for classifying exudative effusions i.e 98% sensitivity, almost 30% of the transudates were misclassified as exudates and analysis of pleural fluid of patients with transudative effusions with congestive heart failure post diuretic therapy met the exudative Lights criteria.

Another important drawback of the Lights criteria was that other than the initial classification of pleural fluid into exudates and transudates, it failed to further sub classify and attach a specific label to exudative effusions. Similar studies by Porcel et al\(^{(2)}\) using the standard Lights criteria further confirmed its draw backs as in the misclassification of transudates. Despite these drawbacks pleural effusion classification via Lights Criteria still remains the gold standard in the initial evaluation of patients.

Thus in the following years, studies were carried on for the search of newer biomarkers for pleural effusion, and almost all studies concluded that a single biomarker was not sufficient for discriminating pleural effusions. A direct quote by Richard Light echoed the same which states that “A single chemical test or a set of chemical tests is rarely 100% effective in separating two sets of populations of pleural effusions, but increasing the number of tests results in a reliable separation”.

Various biomarkers were studied subsequently and few reliable ones with positive outcomes were as follows. This was in concurrence with a study by Muzaffer et al\(^{(5)}\) were in 93 patients were recruited for the study of which 21
were transudatives and 72 were exudatives and studied the following parameters for their separation. Study concluded that

1. Pleural fluid cholestrol - 77% sensitivity
2. Serum–fluid albumin - 67% sensitivity
3. Pleural fluid/serum alkaline phosphate - 83% sensitivity
4. Pleural creatinine kinase - 83% sensitivity
5. Pleural fluid uric acid - 71% sensitivity

However of the above mentioned only a pleural fluid cholesterol/serum cholesterol and pleural fluid to serum bilirubin and pleural fluid pre albumin were statistically significant to the Lights Criteria which were further studied in detail. Hamm et al(6) in 1987 in a prospective study conducted in Germany, studied the importance of pleural fluid protein, pleural fluid LDH and pleural fluid cholesterol and examined their investigatory utility in the differentiation of transudates and exudates. In the 70 patients enrolled in the study, only 62 patients had an underlying diagnosis of which 31 were transudates and rest 31 were exudates.

Study showed that elevated pleural fluid cholesterol was independent of serum cholesterol levels and further on pleural fluid cholesterol levels when used along with the traditional Lights Criteria was an excellent indicator for the discrimination of the pleural effusions.

Results showed that effusions associated with CHF/other transudative pleural effusions had a mean cholesterol gradient of 30+-12mg/dl was
statistically significant and malignant effusions had a mean cholesterol gradient of 94+/-25 mg/dl (mean range between 62-155). Further on there was no overlap between the two study groups.

They also evaluated the ratio of pleural fluid to serum cholesterol ratio in various type of effusions and concluded that both absolute levels of pleural fluid cholesterol and concentration ratio were diagnostic indicators for separation of pleural effusions when used along with traditional Lights Criteria in border line cases. This lead to the origin of Modified Lights Criteria in the diagnosis of pleural effusions. Further on the study stated that using a cut off value of 60mg/dL there was complete separation between transudative and exudative effusions and effusions of inflammatory origin had a mean pleural fluid cholesterol of 76 mg/dL, transudates had a cut off of 30 mg/dL and the pleural fluid cholesterol levels for malignant was 94mg/dL.

A similar study done by Guleria et al(7) in 2003 in India were in 50 patients with exudative (25 tubercular, 25 non tubercular) and 25 patients of transudative effusions were studied. The study concluded that a mean pleural fluid cholesterol of 60 mg/dL, pleural fluid to serum cholesterol of 0.4 were characteristic of exudates and assessing the pleural fluid cholesterol and the pleural fluid to serum cholesterol ratio had a sensitivity of 98% and a specificity of 100% for exudates and cited that the results yielded were superior to Light et al (sensitivity of 92%, specificity-80%) and they concluded stating
pleural fluid cholesterol as a simple and cost effective biomarker in differentiating an exudate from a transudative effusion.

Mainly two hypothesis were explained for the diagnostic accuracy of pleural fluid cholesterol stating that

a. Cellular degradation of both WBCs and RBCs as assumed for chylous effusions

b. Serum leakage hypothesis-which explains for high pleural fluid cholesterol seen in exudative effusions as a result of increased permeability of the pleural membrane.

However it was noted that chylous effusions also had similar pleural fluid cholestrol level, but the actual different ion between chylous effusions and exudates were based on the demonstration of chylomicrons and elevated Triglycerides in the former. Further on the reliability of pleural fluid cholesterol in differentiation of exudative from transudative effusions diminished and was loosing its importnace.

Thus search for other biomarkers continued and in 1990 Simcha et al(8) in Israel demonstrated that pleural fluid to serum bilirubin ratio for the separation of transudates from exudates. The study conducted on 51 patients concluded that pleural fluid to serum bilirubin ratio helped in differentiation of pleural effusions and a ratio of 0.6 or more in the presence of an exudative effusion(as met by the Lights criteria) was statistically significant with good sensitivity and specificity and a positive predictive accuracy, overall sensitivity
being around 90%. Similar results were found for transudative effusions were the pleural fluid to serum bilirubin gradient of 0.6 or less were significant for a transudative effusion. Another similar study too proved the efficacy of pleural fluid to serum bilirubin ratio by concluding that a ratio of 0.6/more had a sensitivity of 96.2% for discriminating exudative pleural effusions.

Similarly other biomarkers such as Vascular Endothelial Growth Factor (VEGF) which is a endothelial biomarker and a net result of angiogenesis were further studied for identification of exudates as increased capillary permeability is an important characteristic of an exudative effusion. Thus study for newer biomarkers continued and no single biomarker was found to be superior to the traditional Lights Criteria.

Newer biomarkers were needed for primarily diagnosing the etiology of a pleural effusion and to further differentiate a malignant from a non malignant effusion. Porcel et al[2] in a study described an ideal biomarker as one which can be defined as a biological molecule that is found in blood, other body fluids or tissues that is a sign of a normal or an abnormal process or of a condition or a disease such as malignancy, infection or heart failure. He further on stated that an ideal biomarker as one which can be measured easily at a reasonable cost (analytical validity), should provide information which is new and is not already available from a routine clinical assessment (clinical validity) and finally should be helpful in aiding the clinical diagnosis (clinical usefulness). Thus the search for this ideal biomarker ensued and studies for
the same concurrently started thus gradually moving beyond the Lights Criteria

As per the Infectious Disease Biomarker Data approximately around 611 biomarkers were involved for 66 Infectious Diseases and 70 pathogens, that was roughly estimated to be 8-9 biomarker/pathogen. Thus amongst this varied biomarkers available it was needed to estimate the most reliable biomarker in the suitable setting given the limited resources available for the same. The following studies stated were in view of identifying the best biomarker in each type of effusion.

Bielsa S et al\(^9\) in a study involving cardiac and hepatic transudates analyzed the role of pleural fluid to serum protein, LDH and albumin concentrations in 364 cardiac effusions and 102 Hepatic transudates which concluded that heart failure related transudates were more often misclassified by Lights Criteria than hepatic transudates\(29\%\) to \(18\%\), \(p=0.002\). Similarly an albumin gradient of >1.2 g/dL had a sensitivity of 83\% for cardiac transudates and 62\% for hepatic transudates. The study concluded that in the setting consistent with heart failure, the pleural fluid meets the Lights criteria, measuring the albumin gradient than the protein gradient is considered the best.

Similar other studies were carried out to classify the wrongly misplaced cardiac transudates as per the Lights criteria were in post diuretic therapy the cardiac transudates met the criteria for exudates as per Lights
Criteria by a narrow margin. Amongst this the vastly studied biomarkers were Natriuretic Peptides which included the Brain Natriuretic Peptide and the amino terminal fragment ie; NT proBNP and the mid regional pro atrial natriuretic peptide(MR-pro ANP). Natriuretic peptides are defined as those neurohormones which in response to increased pressure in the hear chambers are secreted by the cardiomyocytes.

Initial study in 2004 by Porcel et al\(^2\) analyzed its usefulness and concluded that measurement of NT pro BNP and BNP helped in differentiating cases of effusion caused by heart failure. Further on it stated that a serum level of BNP > 500 pg/mL and serum level of 450-1800pg/mL of NT pro BNP were highly suggestive of heart failure in an acute setting. Since 2004 various other studies have analyzed the importance of BNP and NT pro BNP and in meta analysis of 10 studies which included 429 cardiac and 691 non cardiac patients a combined sensitivity and specificity of 94% was observed and a value of >1500 pg/ml for NT pro BNP confirmed heart failure.

Measurements of pleural fluid MR pro ANP was studied to have properties similar to that of NT pro BNP. Further on in those 80% of HF associated effusions which were misclassified based on Lights criteria,NT pro BNP evaluation was found to be superior to BNP. Thus calculation of NT pro BNP values were found to be significant in the clinical suspicion of
effusion due to heart failure were other methods failed to give a diagnostic accuracy for the same.

Similarly newer biomarkers were studied for infectious effusions (non tubercular effusions) as this presented a varied list of causes for the same. Thus it was of great difficulty to identify accurately the precise biomarker which can pin point the accurate nature of an infectious effusion. Inflammatory effusions were initially divided based on the duration to acute, sub acute and chronic.

Acute conditions begins immediately and lasted for a few days, while sub acute and chronic effusions had an insidious process and lasted for months together. It was proved that in the initial stages (ie-acute infection) a combination of neutrophil predominant pleural fluid cytology with a low pleural fluid glucose (<40 mg/dL) and low pleural fluid pH (<7.2) were indicators for an acute infection along with the presence of band forms in peripheral smear.

This has been related to the hypothesis which states that in an acute type of pleural injury initially neutrophils were attracted to the pleural space by the production of chemo tactic factor that is Interlukin 8 (IL8), as the nature of the illness progresses this neutrophil predominance was replaced by an lymphocytic exudate which yielded a diagnosis of sub acute or chronic inflammatory pathology. Certain other biological parameters were also studied by Hassan et al (10) to differentiate
an acute presentation from an sub acute presentation which included soluble triggering receptor expressed on myeloid cells (STREM-1), lipo polysaccharide binding protein (LBP), C reactive protein (CRP), tumor necrosis factor (TNF alpha), myeloperoxidase of $>$ 3000 microgm/L, matrix metalloproteinase 2 $\leq 343$ ng/ml, neutrophil elastase, interleukin 8 etc. Each biomarker reflected the different stages of an inflammatory process and were easily measured by immuno assays.

In a study by Theodoros et al (3) in 2006 analyzing the various biomarkers for infectious effusion concluded that CRP, IL6 and TNF alpha measurements gave an accurate diagnosis in the setting of a parapneumonic effusion. Other studies by Perlat et al (11) analyzing the biomarkers of acute inflammation stated that a pleural fluid CRP of $>$ 30 mg/L had diagnostic evidence towards parapneumonic effusions. Another prospective study by MG Alexandrakis et al in (12) Greece in 2000 analyzed the importance of alpha 2 macroglobulin and alpha 1 acid glycoprotein in differentiation of pleural fluid and suggested that both AAG and AMG were significantly higher in the exudative group.

Further on differentiation between complicated parapneumonic effusion and uncomplicated parapneumonic effusions were needed, as a CPPE required a tube thoracostomy. Skouras V et al (13) in a study conducted over 54 patients in Greece were in 23 patients had CPPE and analysis of pleural fluid CRP of $>$ 78.5 mg/L and a serum CRP of $>$ 83 mg/L gave a
sensitivity and specificity of 65% and 87% respectively. Further on they stated that a serum CRP >150 mg/L had a 91% specificity and 61% sensitivity for prediction of a residual pleural thickening (RPT).

The study concluded that pleural fluid CRP and serum CRP when used along with the traditional Lights criteria had a role in differentiating complicated parapneumonic effusions from the non complicated parapneumonic effusions. Further other tests of less significance have been studied in a background of low income settings which stated the use of Leukocyte Esterase Reagent Strips. A study tested its efficacy in 42 patients with bacterial infections, 15 with tuberculosis and in 71 patients with non infectious causes which stated that a positive test yielded 42% sensitivity and 100% specificity.

Similarly another studied biomarker in similar settings of the previous study was the Rapid Pneumococcal Antigen Test which was found to be positive in cases of pneumococcal pneumonia complicating with effusion (71% sensitivity). However the clinical reliability of this test was not significant to discriminate infectious from non infectious causes.

Tubercular effusions was responsible for nearly 50% of all cases of effusions in an endemic country like India. Thus the correct identification and early treatment of a tubercular effusion helped in preventing the mortality and morbidity due to the same. The need for newer biomarkers exclusively for tuberculosis were due to the fact that the conventional
methods for the same were time consuming and concurrently the yield was low.

They included the identification of mycobacterium tuberculosis in pleural fluid and this was further complicated by the low yield for the same. In retrospective analysis of 214 patients with pleural tuberculosis the conventional solid culture media for mycobacterium were just positive in only 28% of the sputum samples and was further low in pleural fluid samples (around 15%), further on AFB staining which is considered as more rapid diagnostic method had a sensitivity (14%) and specificity of 3%. Further the demonstration of granulomas by pleural biopsy was found to confirm diagnosis in around 80% of cases but due to the invassiness of the procedure and the dependence of the operator skills it was also considered as less likely diagnostic method for the same.

This further increased the urgent need for a novel biomarker for tubercular effusions which was easily reproducible less expensive and non invasive. This led to the study of adenosine deaminase, interferon gamma for the same. Further a raised lymphocytic effusion in the presence of raised ADA (>40) with clinical features were considered suggestive for tuberculosis in an endemic country like India. In a study by Porcel et al(14), Jiemenez DC et al(36) ADA levels were evaluated in the pleural fluid of 2104 patients in whom 221 had tubercular effusion.
The pleural fluid ADA level were > 35 U/L in 93% of the cases. However the study concluded that a very high ADA (>250 U/L) were significant of empymas rather than tubercular effusions. The ADA molecule occurs in mainly 2 isoenzyme forms that is ADA 1 and ADA 2. ADA 1 is found to be commonly seen in all cells while ADA 2 is specifically isolated from patients with tubercular effusions and is found to be elevated.

In a meta analysis of 63 studies, ADA was reported to have a sensitivity of 92% and specificity of 90%. Thus the measurement of ADA along with clinical features was concluded to have an excellent diagnostic value with a sensitivity and specificity rates of 95% and 97% respectively. Interferon gamma which is cytokine which is derived from lymphocytes has also been studied in the diagnosis of tubercular effusions.

However the sensitivity and specificity of this biomarker was found inferior to ADA measurements. But when combined along with the routine clinical parameters it yielded a sensitivity of 96% and specificity of 93% which was quoted in a study by Greco 2003. Other studies such as the commercially available QUANTIFERON TB GOLD, T SPOT TB were found to be poor biomarkers when compared to interferon gamma assay.

The nucleic acid amplification and detection of mycobacterium tuberculosis in pleural fluid have yielded a specificity of 95% and sensitivity of 60%. However it is not of significance.
Malignant effusions account for nearly 40-60% of all types of pleural effusions globally and the diagnosis of a malignant effusion is established by the presence of malignant or atypical cells in pleural space. But the pleural fluid cytology has been found to be positive in only 60% of the cases and it is said that at least a large amount of pleural fluid to be necessary for a confirmatory diagnostic yield.

Further on confirming the presence of a malignant tissue via biopsy has a sensitivity of 80% in clinching the diagnosis, but owing to the invasiveness of the procedure and the skills of the operator it is found to be less significant in limited resource settings. These made the need for newer biomarkers for diagnosis of malignant pleural effusions.

The following biomarkers were studied which was described in a metanalysis of 45 studies, which included 2834 patients with malignant and 3251 patients with non malignant effusions and it summarized that pleural fluid CEA as a biomarker had a sensitivity of 54% and specificity of 94%. Other biomarkers studied in the respective metanalysis were CA 125, CA 15-3, CA 19-9, cytokeratin fragment(CYFRA). Further on high pleural fluid CA 125 was found to be observed in squamous and adenocarcinomas and had a poor prognostic role.

Pleural fluid CEA was one of the first biomarkers to be studied for malignant pleural effusions and was specifically elevated for metastatic adenocarcinomas and had a prognostic significance in terms of median
survival and treatment response. CYFRA 21 a cytokeratin has found to have a role in both prognostic as well as diagnostic role in non small cell lung cancers which was studied in prospective study by Wagner in Spain. malignant pleural effusion was found to be seen in approximately 50% of the cases with lung cancer.

Further on the diagnosis of mesothelioma related pleural effusions were difficult as the number of studies were few. However the identification of pleural fluid mesothelin was found to be significant for the same. Other biomarkers for diagnosis of malignant pleural effusions included soluble mesothelin receptor protein (SMRP) which is significant of mesotheliomas. Immunohistochemistry was also performed on cytological pleural fluid samples and the following immunohistochemical markers were found to be significant which included Thyroid transcription factor 1 (TTF1) for differentiating epithelial mesothelioma from adenocarcinoma, desmin, calretnin, CK 5/6, MOC 31, WT 1, Napsin A, BG8 (Lewis) were the other studied immunohistochemical markers in pleura fluid cytology. It is said that when used in together with routine pleural fluid parameters, the biomakers for malignant pleural effusion assumed significance. Also other molecular tests like fluorescent insitu hybridization (FISH), gene expression have found to aid and improve the cytological diagnosis of the same and is yet to be included in routine clinical practice.
Among all the varied biochemical markers analyzed in the setting of pleural fluid analysis along with traditional Lights criteria only a few biomarkers have shown to be promising as a reliable biomarker in the near future and of the following included C reactive protein (CRP) which has been studied in the backdrop of various clinical settings and various etiologies of pleural effusion. It was found to be a simple and cost effective method for classification of pleural effusions and also further aided in the separation of malignant from non malignant effusions. Due to these above mentioned characteristics, pleural fluid CRP measurement was studied in detail.

As the clinical symptoms were overlapping and with other constraints such as lack of specificity of pleural fluid cultures and increase turnaround time, it was important to study one particular biomarker which can be helpful in the above setting. CRP is an acute phase protein which is synthesized in the hepatocytes in the backdrop of an inflammatory setting. It is helpful in monitoring changes in any inflammatory condition such as trauma, malignancy which are the usual inflammatory scenarios seen in an hospital setting.

The increase in CRP in these conditions is mainly due to the production of Interlukin 6(IL 6) which is in turn released by the activation of macrophages and adipocytes as a result of immune stimulation. CRP plays a key role in inflammatory process by binding to phosphocholine on
the microbial organisms and thereby leading to its intracellular destruction by macrophages. Further CRP also activates the complement system via the C1q complex. Thus it is said that CRP is an effective initiator of an inflammatory reaction in the body, thereby significantly adding to its weightage in determining the disease progression and effectiveness in its treatment.

These characteristics of CRP coupled with ease of investigation and the diagnostic reliability of the test made it a biomarker of choice for the differentiation of pleural effusions. Numerous studies worldwide have supported the use of pleural fluid CRP as a useful adjunct in the differentiation of pleural effusions.

Sanjose et al\(^{(15)}\) in a large prospective study conducted in 2002 in 233 patients with pleural effusion evaluated the clinical significance of pleural fluid CRP. Of the 233 patients studied, they were further sub divided into 5 groups as Parapneumonic (28 cases), Tubercular (n=49), Malignant (N=57), Traumatic (n=53) and Mixed etiology (n=46). Study concluded that pleural fluid CRP was higher in the parapneumonic group as compared to that of other groups (with a statistical significance of \(p<0.0001\)) also low levels of CRP were significant in the malignant and miscellaneous group with a P value between 0.001-0.004.

In another cross sectional study done on 166 patients with pleural effusion in 2005 in Thailand they studied the clinical use fullness of and the
validity of ratio of pleural fluid to serum CRP in the differentiation of tubercular from malignant effusions in a back ground of lymphocytic exudative effusions. Of the 148 patients with lymphocytic exudative effusion, 55 were tubercular effusions, 60 were malignant effusions and 33 effusions were of unknown etiology. The study concluded that the ratio of pleural fluid to serum CRP were higher in tubercular than in malignant pleural effusion (54.58 ± 4.5 mg/L and 106.93 ± 9.54 mg/L with a P < 0.001) and that the ratio of pleural fluid to serum CRP was higher in the tubercular group as compared to the malignant group.

A cut off value for pleural fluid CRP > 30 mg/dL had a sensitivity of 72% and a specificity of 93% and a pleura fluid to serum CRP ratio of 0.45 had a sensitivity of 60% and specificity of 89% in differentiating tubercular effusions from the malignant counterparts.

Yadav et al (16) in a study conducted on 187 patients with exudative pleural effusions concluded that pleural fluid CRP can be used as a diagnostic tool in specifically differentiating effusions of acute and chronic origin as well as differentiating infectious from non infectious group and suggested that a pleural fluid CRP value > 30 mg/L excluded malignant effusion. Patients included in the study were categorized into 5 groups which were malignant, chronic non specific inflammation, parapneumonic effusions, tubercular pleural effusions and miscellaneous group.
In differentiating tubercular effusions from non tubercular effusions, pleural fluid CRP had a good sensitivity of 97.05% and a specificity of 71.76%. Similarly for differentiating parapneumonic from malignant effusions, pleural fluid CRP had a sensitivity of 100% and a specificity of 98%.

Hoda Abu et al\(^{(17)}\) in a study in Egypt in 2010 highlighted the importance of the diagnostic value of pleural fluid CRP in the etiological diagnosis of pleural effusion and concluded that pleural fluid CRPs were higher in tuberculosis than malignant effusions than that in parapneumonic effusions and the lowest for a transudative effusion. The study included 10 patients with transudative pleural effusion, 12 patients with tubercular effusions, 14 patients with malignant pleural effusions and 4 patients with bacterial parapneumonic effusions.

Huang et al\(^{(18)}\) in a study conducted amongst 209 patients with pleural effusion evaluated the diagnostic significance of pleural fluid CRP and prealbumin in the differential diagnosis of infectious from malignant effusions, concluded that pleural fluid prealbumin levels were high in malignant effusions as compared to parapneumonic effusions and the combination of pleural fluid prealbumin and pleural fluid CRP had a combined sensitivity of 61.7% and specificity of 90.3%.

Garcia et al\(^{(19)}\) studied the importance of pleural fluid CRP in lymphocytic pleural effusions and evaluated its significance in the diagnosis of tubercular effusions. 144 patients with lymphocytic predominant pleural
effusion were recruited of which 93 were men and 51 were women, further classified the lymphocytic effusion of which 20 were tubercular and 69 were malignant effusions and transudates and other benign exudates formed other 55 effusions. Conclusion of the study was that pleural fluid CRP was higher in patients of tubercular effusion (54 +/- 24 mg/l) than compared to lymphocytic effusions of other origin (21 +/- 16 mg/l, p<0.001). The study also stated that high pleural fluid CRP (>=50 mg/L) had a high specificity for tuberculosis and low levels (<30 mg/L) had a high sensitivity for excluding tubercular effusions.

As most of the studies applied pleural fluid CRP in the differentiation of parapneumonic effusions, its similar beneficial effects for discrimination of malignant effusions were also studied through various trials. The importance of raised pleural fluid CRP in malignant effusions lies in the fact that a malignant condition is basically an inflammatory condition where in various mediators of inflammation are released which in turn increased CRP levels. Also increased production of cytokines by the tumor tissue was responsible for increased CRP production which was another hypothesis which correlated the importance of CRP analysis in malignant effusions.

Scott et al (21) in a publication in the year 2002 highlighted the importance of the catabolic effects of CRP on metabolism and stated that increased CRP in a malignant state was involved in increase in resting energy expenditure and loss of fat free mass in patients with carcinoma which were in turn key factors for determining cancer survival and in these sub set of
patients no significant difference was found in the total counts, frequency of bacterial culture growth in pleural fluid samples and in sputum samples between the high and the low pleural fluid CRP patients indicating that raised CRP is not an indicator of infection alone.

Park et al\(^{(20)}\) in a study conducted in 2012 in Korea evaluated the diagnostic and prognostic significance of CRP in lung cancer patients with pleural effusions. A total 68 patients were recruited for the study and the pleural fluid to serum ratio of CRP was evaluated. It showed that differentiating malignant from infectious effusions pleural fluid CRP was of greater significance than serum CRP and higher pleural fluid CRP levels correlated with shorter overall survival time\((p=0.006)\). Overall the study concluded that the evaluation of pleural fluid CRP superior to serum CRP in cases of malignant effusions and the quantitative measurement of pleural fluid CRP helped in predicting the overall survival outcome in lung cancer patients and stated that the risk of death for lung cancer patients with a high CRP was 3.909\((95\% \text{ confidence interval})\).

Nusarth et al\(^{(22)}\) in a study conducted among 100 patients showed that pleural fluid CRP analysis could differentiate transudate from an exudative effusion and further on pleural fluid CRP helped to differentiate inflammatory from non-inflammatory effusions. Study concluded that a mean CRP of\(>6\text{mg/dl}\) was significant for a parapneumonic effusion, patients of tubercular effusion had CRP\(>2\text{mg/dl}\) and pleural fluid CRP for malignant and
transudative effusion was <2mg/dl. Further on gross appearance of the pleural fluid like hemorrhagic (malignant, embolism), milky white (lymphatic duct obstruction), straw colored (tubercular effusions) also helps in some extent in differentiating the varied causes of effusions.

Castano et al\(^{(23)}\) in a study comprising 72 patients proved that high pleural fluid CRP as an accurate method of differentiating parapneumonic effusions from other effusions. Further on malignant effusions were proved by the demonstration of atypical cells in pleural fluid, or via the demonstration of malignant tissue in a biopsy specimen. Tubercular effusions were predominantly exudative with lymphocytic cells and presence of mesothelial cells along with presence of clinical features such as cough, fever which aids in the clinical diagnosis of tubercular effusions. Parapneumonic effusions were highly exudative with neutrophil predominance and pleural fluid cytology negative for malignant cells and patients had a positive response to antibiotic therapy.

Alexandra et al\(^{(12)}\) in a study comprising 84 patients of which 65 were exudates, of which 27 were malignant and 23 were of infectious etiology and 19 were transudative. In the 65 exudative effusions (46 were men, 19 were women with a mean age of 60 years, in the transudative group of 19, 12 were males and 7 were females with a mean age of 70 years). This study concluded that exudative effusions had a significantly higher CRP than transudative effusions and CRP > 1mg/dl had a good sensitivity and specificity for differentiating
transudates from exudates. Study also showed that pleural fluid CRP was a useful marker when used along with the Lights criteria in the diagnosis of borderline cases.

Waffa et al.\(^{(24)}\) in a study conducted on 100 patients correlated the value of pleural fluid CRP with the nature of the effusion and concluded that a mean pleural fluid CRP of 0.4-2 was suggestive of a transudative effusion, while a parapneumonic effusion had a higher range of pleural fluid CRP levels ranging from 1.8-20, tubercular effusions had a CRP between 1.01-6.8, thereby concluding that higher values of pleural fluid CRP was significant for pleural effusions of inflammatory causes (i.e. parapneumonic and tubercular), while lower CRP levels were significant of malignant and transudative effusions.

Thus from the above mentioned studies it was noted that pleural fluid CRP as a reliable indicator for the differentiation of both malignant as well as non malignant pleural effusions (parapneumonic) and when used along with the Lights Criteria had a good specificity and sensitivity for separation of the pleural effusions and it ranked above other biomarkers studied in terms of its clinical utility to clinch a diagnosis and being cost effective and a simple test. However the limitation of pleural fluid CRP being in its inability to separate transudates and also the inability of the pleural fluid CRP in differentiating tubercular from malignant effusions from the parapneumonic variant was also noted as another drawback.
Despite these important drawbacks of pleural fluid CRP it has shown promising outcomes in the differentiation of parapneumonic pleural effusions in research trials and the same has to be replicated in routine clinical practice and is hopeful of the same in the near future.
Results
RESULTS

We present our study results under the following description

1. Distribution of study variables
2. Comparison of the variables between transudative and exudative effusions
3. Comparison of the variables between exudative effusions of varying etiology

A. DISTRIBUTION OF STUDY VARIABLES:

Sixty subjects were recruited in our study. Out of the sixty subjects 39 were males as compared to 21 female study participants (65 and 35% respectively). The age of the study participants ranged from 30-80 years of age with a mean of 52.85 ± 17.77 years with a mean BMI of 25.38 ± 1.54 kg/m2. Of the sixty study subjects 54 consumed mixed diet (90%). In the sixty subjects studied, 24 had a history of smoking (40%) while 10 had a history of alcohol consumption (16.7%)

Symptomatology studied amongst the sixty subjects revealed that majority of the subjects presented with breathlesness (41.68.3%) and cough (41.68.3%) as the cardinal symptoms, chest pain was seen in 19 patients with pleural effusion (31.7%), followed by fever which was noticed in 20 patients at 33.3% followed by hemoptysis which was seen only in 2 cases (3.3%). Amongst the comorbidities studied in the sixty study subjects, Diabetes Mellitus was seen
in 20 cases (33.3%), followed by systemic hypertension (13, 21.7%), coronary artery disease seen in 11 cases (18.3%) and COPD and renal impairment contributed to seven cases each amongst the study subjects (11.7%) as demonstrated in (Table 1)

**Table 1** This table compares the sociodemographic and clinical variables between subjects with transudative and exudative effusions

<table>
<thead>
<tr>
<th>Sociodemographic and clinical variables</th>
<th>N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td>52.85 ±17.77</td>
</tr>
<tr>
<td>Gender –Males</td>
<td>39 (65%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.38 ±1.54</td>
</tr>
<tr>
<td>Socioeconomic status (Family Income in Rs)</td>
<td>6050 ±3307</td>
</tr>
<tr>
<td>Mixed Diet</td>
<td>54(90%)</td>
</tr>
<tr>
<td>Smoking status(current /past)</td>
<td>24(40%)</td>
</tr>
<tr>
<td>Alcohol intake(current/past)</td>
<td>10(16.7%)</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td>Breathlessness</td>
<td>41(68.3%)</td>
</tr>
<tr>
<td>Cough</td>
<td>41(68.3%)</td>
</tr>
<tr>
<td>Fever</td>
<td>20(33.3%)</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>19(31.7%)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>2(3.3%)</td>
</tr>
<tr>
<td>Comorbid condition</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>7(11.7%)</td>
</tr>
<tr>
<td>DiabetesMellitus</td>
<td>20(33.3%)</td>
</tr>
<tr>
<td>Systemic</td>
<td>13(21.7%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>11(18.3%)</td>
</tr>
<tr>
<td>Renal Disease</td>
<td>7(11.7%)</td>
</tr>
</tbody>
</table>
COMPARISON OF STUDY PARTICIPANTS IN TRANSUDATIVE AND EXUDATIVE GROUP

FIG 1: This chart compares the number of study participants in transudative and exudative group

n = 13
n = 47
COMPARISON OF BMI IN SUBJECTS WITH TRANSUDATIVE AND EXUDATIVE EFFUSIONS

Table 2: This table compares the BMI (Kg/m²) in subjects with transudative and exudative effusions

<table>
<thead>
<tr>
<th>EFFUSION TYPE</th>
<th>BMI(Kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRANSUDATIVE</td>
<td>25.95±1.51</td>
</tr>
<tr>
<td>EXUDATIVE</td>
<td>25.22±1.52</td>
</tr>
</tbody>
</table>

There was no statistical difference noted in the age group of the study participants in each group with the mean BMI in the transudative group being (25.95±1.51) and the mean BMI in the exudative group being (25.22±1.52) with a p value of 0.134. None of our study population belonged to the obese category.
COMPARISON OF THE AGE AND GENDER DISTRIBUTION AMONGST THE STUDY GROUP

Table 3: This table compares the age and gender distribution amongst the study group

<table>
<thead>
<tr>
<th>TYPE OF EFFUSION</th>
<th>AGE/GENDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRANSUDATIVE</td>
<td>59.62±16.50/ 7 –MALES</td>
</tr>
<tr>
<td></td>
<td>6-FEMALES</td>
</tr>
<tr>
<td>EXUDATIVE</td>
<td>50.98±17.80 / 32-MALES</td>
</tr>
<tr>
<td></td>
<td>15-FEMALES</td>
</tr>
</tbody>
</table>

The mean age group of the patients in the transudative group was 59.62±16.50 years, the mean age group of the patients in the exudative group was 50.98±17.80 years. In the transudative group, seven were males and six were female participants (53.8% and 46.2% respectively). In the exudative arm off the 47 study participants, 32 were males and 15 were females (68.1% and 31.9% respectively). There was no statistical significance between the age and gender distribution for transudative and exudative groups (P=0.122 and 0.34 respectively)
SMOKING STATUS AND ALCOHOL INTAKE:

Table 4: This table compares the alcohol and smoking status between the transudative and exudative effusions

<table>
<thead>
<tr>
<th>EFFUSION TYPE</th>
<th>ALCOHOL</th>
<th>SMOKING</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRANSUDATIVE</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>EXUDATIVE</td>
<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>

In the transudative and exudative effusions, when smoking and alcohol intake was calculated, there was no significant difference between the two groups and no significant correlation was found on the same. The total number of smokers in the transudative group were 4(30.8%), and only 1 person had a history of alcohol consumption in the transudative group (7.7%) which had no statistical significance (P=0.443). Similarly when smoking history was reviewed in the exudative group 20 of the 47 study participants were smokers (42.6%) while there 9 study participants with history of alcohol intake amongst the 47 exudative effusions (19.1%) which again had no statistical significance (P=0.327)
COMPARISON OF THE SOCIO DEMOGRAPHIC VARIABLES IN THE STUDY GROUP WITH P VALUE

Table 5: This table compares the socio demographic variables in the study group

<table>
<thead>
<tr>
<th>SOCIO DEMOGRAPHIC VARIABLES</th>
<th>TRANSUDATIVE EFFUSIONS (N=13)</th>
<th>EXUDATIVE EFFUSIONS (N=47)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE (YEARS)</td>
<td>59.62±16.50</td>
<td>50.98±17.80</td>
<td>0.122</td>
</tr>
<tr>
<td>GENDER (MALES)</td>
<td>7 (53.85)</td>
<td>32 (68.1%)</td>
<td>0.341</td>
</tr>
<tr>
<td>BMI (KG/M2)</td>
<td>25.95±1.51</td>
<td>25.22±1.52</td>
<td>0.134</td>
</tr>
<tr>
<td>SMOKING STATUS</td>
<td>4 (30.8%)</td>
<td>20 (42.6%)</td>
<td>0.443</td>
</tr>
<tr>
<td>ALCOHOL</td>
<td>1 (7.7%)</td>
<td>9 (19.1%)</td>
<td>0.327</td>
</tr>
</tbody>
</table>
This table compares the clinical variables (symptoms) between the exudative and transudative effusions

Table 6

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>TRANSUDATIVE</th>
<th>EXUDATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>COUGH</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>BREATHLESNESS</td>
<td>9</td>
<td>32</td>
</tr>
<tr>
<td>CHESTPAIN</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>FEVER</td>
<td>1</td>
<td>19</td>
</tr>
</tbody>
</table>

In the exudative and transudative arms studied, breathlessness was the predominant symptom seen in 9 of the 13 study participants in the transudative group (69.2%) followed by cough (6, 46.2%), chest pain (4, 30.8%), fever (1, 7.7%). In the exudative group cough was seen in majority of the patients (35, 74.5%), followed by breathlessness (32, 68.1%), fever (19, 40.4%), chest pain (15, 31.9%) and hemoptysis in 2 cases. There was no statistical significance between the symptoms and the nature of the effusion.
COMORBIDITIES

Table 7: This table depicts the relation between comorbidities and exudative and transudative effusions

<table>
<thead>
<tr>
<th>COMORBID CONDITION</th>
<th>TRANSUDATIVE</th>
<th>EXUDATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>DM</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>SHT</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>CAD</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>RENAL DISEASE</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

Comorbidities had a statistical significance in transudative effusion as compared to an exudative effusion. Off the comorbid conditions in the 13 transudative study participants, 8 had coronary artery disease (61.5%, p=0.0001), followed by diabetes mellitus (8, 61.5%, p=0.015), systemic hypertension (53.8%, 7) and renal disorder seen in 5 cases (38.5%). In the exudative group comorbidities played no role in the disease outcome and was not statistically significant. Thus there was positive correlation between comorbidities and a transudative effusion.
Table 9: This table compares the clinical variables in the study group.

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>TRANSDUATIVE</th>
<th>EXUDATIVE</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>BREATHLESNESS</td>
<td>9 (69.2%)</td>
<td>32 (68.1%)</td>
<td>0.957</td>
</tr>
<tr>
<td>CHEST PAIN</td>
<td>4 (30.8%)</td>
<td>15 (31.9%)</td>
<td>0.937</td>
</tr>
<tr>
<td>COUGH</td>
<td>6 (46.2%)</td>
<td>35 (74.5%)</td>
<td>0.052</td>
</tr>
<tr>
<td>FEVER</td>
<td>1 (7.7%)</td>
<td>19 (40.4%)</td>
<td>0.027</td>
</tr>
<tr>
<td>HEMOPTYSIS</td>
<td>0</td>
<td>2 (4.3%)</td>
<td>0.449</td>
</tr>
<tr>
<td>CO MORBID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONDITIONS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>0</td>
<td>7 (14.9%)</td>
<td>0.139</td>
</tr>
<tr>
<td>DM</td>
<td>8 (61.5%)</td>
<td>12 (25.5%)</td>
<td>0.015</td>
</tr>
<tr>
<td>HTN</td>
<td>7 (53.8%)</td>
<td>8 (12.8%)</td>
<td>0.001</td>
</tr>
<tr>
<td>CAD</td>
<td>8 (61.5%)</td>
<td>3 (6.4%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>RENAL</td>
<td>5 (38.5%)</td>
<td>2 (4.3%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
COMPARISOM OF THE HEMATOLOGICAL VARIABLES BETWEEN SUBJECTS WITH TRANSUDATIVE AND EXUDATIVE EFFUSIONS

Table 10: This table compares the hematological variables between subjects with transudative and exudative effusions

<table>
<thead>
<tr>
<th>HEMATOLOGICAL VARIABLES</th>
<th>TRANUSDATIVE EFFUSION (n=13)</th>
<th>EXUDATIVE EFFUSIONS (n=47)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEMOGLOBIN (Mg/dl)</td>
<td>9.64±1.69</td>
<td>11.37±2.51</td>
<td>0.023</td>
</tr>
<tr>
<td>TOTAL LEUCOCYTE COUNTS (per mm3)</td>
<td>9746±2641</td>
<td>13,289±12070</td>
<td>0.30</td>
</tr>
<tr>
<td>PLATELETS</td>
<td>2,35,620±87,602</td>
<td>31,3530±128618</td>
<td>0.045</td>
</tr>
<tr>
<td>ESR (mm)</td>
<td>41.54±15.88</td>
<td>60.28±32.14</td>
<td>0.006</td>
</tr>
</tbody>
</table>

On comparison of hematological variables between the exudative and the transudative group, only ESR was found to be statistically significant between the two study groups, with a mean ESR of (60.28±32.14) in exudative effusions and a mean of (41.54±15.88) in transudative effusions with a P value <0.006. Exudative effusions being a condition of intense inflammation, ESR was expected to be higher in the exudative group.
COMPARISON OF THE BIOCHEMICAL VALUES BETWEEN EXUDATIVE AND TRANSUDATIVE EFFUSIONS

Table 11: This table compares the biochemical values between exudative and transudative effusions

<table>
<thead>
<tr>
<th>BIOCHEMICAL VALUES</th>
<th>TRANSUDATIVE</th>
<th>EXUDATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL PROTEINS</td>
<td>6.23±0.74</td>
<td>6.75±0.55</td>
</tr>
<tr>
<td>ALBUMIN</td>
<td>3.13±0.39</td>
<td>3.33±0.50</td>
</tr>
<tr>
<td>GLOBULIN</td>
<td>2.99±0.48</td>
<td>3.41±0.44</td>
</tr>
</tbody>
</table>

It is found that serum globulin had a positive correlation in separating transudates and exudates with a mean serum globulin of (2.99±0.48) for transudative effusions and a mean serum globulin of (3.41±0.44) for exudative effusions with a P value of 0.005. Serum proteins and serum albumin was found to have no statistical significance in differentiating between the two study arms.

Thus in comparing the both the biochemical and the hematological parameters, It was found through our study that only ESR with a P value 0.006 and serum globulin with a P value of 0.005 were statistically significant in differentiating exudates from transudates.
COMPARISON OF THE PLEURAL FLUID PROTEINS BETWEEN THE TRANSUDATIVE AND EXUDATIVE EFFUSIONS.

Table 12: This table compares the pleural fluid characteristics between the transudative and exudative effusions.

<table>
<thead>
<tr>
<th>PLEURAL FLUID CHARACTERSTICS</th>
<th>TRANSUDATIVE</th>
<th>EXUDATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLEURAL FLUID PROTEINS(mg/DL)</td>
<td>1.60±0.50</td>
<td>4.72±1.00</td>
</tr>
</tbody>
</table>

In comparison of pleural fluid characteristics of transudative and exudative effusions, it was found that pleural fluid protein in the transudative group was (1.60±0.50) and mean pleural fluid protein in the exudative group was (4.72±1). This had a positive statistical significance in differentiating exudates from transudative effusions with a P value=0.0001. This is also regarded as one of the criteria in differentiating transudates from exudates as per Lights Criteria.

This table depicts the importance of assessing pleural fluid protein in differentiating exudates from transudates. The mean pleural fluid protein of 1.60±0.50 was statistically significant for a transudative effusion while a mean pleural fluid protein of 4.72±1.00 was statistically significant for an exudative effusion with a P =0.0001. This was one of the Lights Criteria for the differentiation of transudates from exudates.
COMPARISON OF THE PLEURAL FLUID CHARACTERISTICS IN DIFFERENTIATING EXUDATIVE FROM TRANSUDATIVE PLEURAL EFFUSIONS WITH P VALUE

Table 13: This table depicts the pleural fluid characteristics in differentiating exudative from transudative pleural effusions

<table>
<thead>
<tr>
<th>PLEURAL FLUID CHARACTERSTICS</th>
<th>TRANSUDATIVE EFFUSIONS</th>
<th>EXUDATIVE EFFUSIONS</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTEINS (mg/dL)</td>
<td>1.60+_0.50</td>
<td>4.72+_1.00</td>
<td>0.0001</td>
</tr>
<tr>
<td>GLUCOSE (mg/dL)</td>
<td>136.23±55.18</td>
<td>4.72±1.00</td>
<td>0.094</td>
</tr>
<tr>
<td>LDH</td>
<td>103.23±65.76</td>
<td>1566.23±4939.29</td>
<td>0.293</td>
</tr>
<tr>
<td>ADA (u/l)</td>
<td>4.20±2.38</td>
<td>44.71±68.78</td>
<td>0.039</td>
</tr>
<tr>
<td>TOTAL COUNTS</td>
<td>647.69±591.34</td>
<td>3914.89±4013.42</td>
<td>0.0001</td>
</tr>
<tr>
<td>DIFFERENTIAL COUNT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LYMPHOCYTES</td>
<td>78.15±21.84%</td>
<td>55.30±39.21</td>
<td>0.009</td>
</tr>
<tr>
<td>NEUTROPHILS</td>
<td>21.77±21.84%</td>
<td>42.17±38.76</td>
<td>0.019</td>
</tr>
</tbody>
</table>

The above table highlights the importance of mainly pleural fluid ADA, and pleural fluid total counts in differentiating between exudative and transudative effusions. A mean ADA of 44.71±68.78 U/ml was significant for an exudative effusion as compared to a transudative effusion (4.20±2.38) with a p=0.039. Similarly, a mean pleural fluid total counts of (3914.89±4013.42) was significant for an exudative effusion as compared to a transudative effusion with a P=0.0001. Other values such as pleural fluid LDH, pleural fluid Glucose was not found to be statistically significant in differentiating exudates from transudative effusions.
COMPARISON OF THE PLEURAL FLUID CRP IN DIFFERENTIATING EXUDATES FROM TRANSUDATES

In differentiating transudates from exudates a mean pleural fluid CRP of 1.03±1.20 was significant for a transudative effusion, while a pleural fluid CRP of 5.71±7.33 was significant for an exudative effusion with a positive statistical significance with P =0.0001. The result of our study was in accordance with other similar studies and pleural fluid CRP proved to be a useful adjunct in differentiating exudative from transudative effusions.
<table>
<thead>
<tr>
<th>PLEURAL FLUID CHARACTERS</th>
<th>TRANSUDATIVE</th>
<th>EXUDATIVE</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>1.03±1.20</td>
<td>5.71±7.33</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Table 14
In analysing the test results, a pleural fluid CRP of 1.05 had a ROC of 0.82 with sensitivity of 74.5% and specificity of 76.9% for differentiating between transudative and exudative effusions.
COMPARISON OF THE CLINICAL VARIABLES AMONG THE SUBJECTS WITH EXUDATIVE PLEURAL EFFUSION

Table 15: This table draws comparison of clinical variables among the subjects with exudative pleural effusion

<table>
<thead>
<tr>
<th></th>
<th>MALIGNANCY</th>
<th>PARAPNEUMONIC</th>
<th>TUBERCULAR</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE (YEARS)</td>
<td>57.60±13.7</td>
<td>51.93±15.51</td>
<td>42.6±21.09</td>
<td>0.063</td>
</tr>
<tr>
<td>GENDER (males)</td>
<td>8 (53.3%)</td>
<td>12 (80%)</td>
<td>11 (73.3%)</td>
<td>0.260</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>25.26±1.57</td>
<td>25.78±1.39</td>
<td>24.37±1.22</td>
<td>0.03</td>
</tr>
<tr>
<td>SMOKING</td>
<td>5 (33.3%)</td>
<td>9 (60%)</td>
<td>6 (40%)</td>
<td>0.310</td>
</tr>
<tr>
<td>ALCOHOL</td>
<td>0</td>
<td>6 (40%)</td>
<td>3 (20%)</td>
<td>0.024</td>
</tr>
<tr>
<td>SYMPTOMS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BREATHLESNESS</td>
<td>12 (80%)</td>
<td>9 (60%)</td>
<td>5 (67.7%)</td>
<td>0.734</td>
</tr>
<tr>
<td>CHEST PAIN</td>
<td>5 (33%)</td>
<td>4 (26.7%)</td>
<td>6 (40%)</td>
<td>0.741</td>
</tr>
<tr>
<td>COUGH</td>
<td>12 (80%)</td>
<td>8 (53.3%)</td>
<td>13 (86.7%)</td>
<td>0.092</td>
</tr>
<tr>
<td>FEVER</td>
<td>2 (13.3%)</td>
<td>9 (60%)</td>
<td>8 (53.3%)</td>
<td>0.02</td>
</tr>
<tr>
<td>HEMOPTYSIS</td>
<td>0</td>
<td>2 (13.3%)</td>
<td>0</td>
<td>0.123</td>
</tr>
<tr>
<td>COMORBID CONDITIONS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>3 (20%)</td>
<td>3 (20%)</td>
<td>1 (6.7%)</td>
<td>0.508</td>
</tr>
<tr>
<td>DM</td>
<td>2 (13.3%)</td>
<td>6 (40%)</td>
<td>3 (20%)</td>
<td>0.209</td>
</tr>
<tr>
<td>SHT</td>
<td>3 (20%)</td>
<td>2 (13.3%)</td>
<td>0</td>
<td>0.207</td>
</tr>
<tr>
<td>CAD</td>
<td>0</td>
<td>2 (13.3%)</td>
<td>0</td>
<td>0.123</td>
</tr>
<tr>
<td>RENAL</td>
<td>0</td>
<td>1 (6.7%)</td>
<td>0</td>
<td>0.360</td>
</tr>
</tbody>
</table>

The above table compares all the clinical variables in different exudative pleural effusions. On analysing the different clinical variables in different exudative pleural effusions, there was found to be no statistically significant clinical variable between the three groups. In short, our study concluded that using only the clinical variables differentiation between the three exudative groups were not possible.
COMPARISON OF THE AGE AND GENDER BETWEEN EXUDATIVE PLEURAL EFFUSION

Table 16: This table depicts average age and gender distribution between malignant, parapneumonic and transudative effusions

<table>
<thead>
<tr>
<th>SOCIO DEMOGRAPHIC VARIABLES</th>
<th>PARAPNEUMONIC</th>
<th>MALIGNANT</th>
<th>TUBERCULAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE(YRS)</td>
<td>51.93+_15.51</td>
<td>57.60+_13.7</td>
<td>42.6+_21.09</td>
</tr>
<tr>
<td>GENDER(MALES)</td>
<td>12</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>FEMALES</td>
<td>3</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

No significant difference between the variables were found on analysis.
COMPARISON BETWEEN THE HEMATOLOGICAL VARIABLES AMONG THE EXUDATIVE EFFUSIONS

Table 17: The following table depicts the various hematological parameters compared between the various exudative effusions.

<table>
<thead>
<tr>
<th>HEMATOLOGICAL VALUES</th>
<th>MALIGNANCY</th>
<th>PARAPNEUMONIC</th>
<th>TUBERCULAR</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HB</td>
<td>12.11±3.06</td>
<td>11.18±1.77</td>
<td>11.43±2.16</td>
<td>0.548</td>
</tr>
<tr>
<td>TLC</td>
<td>10266±4591</td>
<td>16480±5722</td>
<td>13086±20088</td>
<td>0.394</td>
</tr>
<tr>
<td>ESR</td>
<td>48.8±34.56</td>
<td>75.5±32.75</td>
<td>59.67±24.43</td>
<td>0.067</td>
</tr>
<tr>
<td>PLATELETS</td>
<td>311533±126186</td>
<td>271666±113933</td>
<td>339666±142565</td>
<td>0.572</td>
</tr>
</tbody>
</table>

The above table depicts the basic hematological parameters assessed between the various exudative pleural effusions. Though non of the hematological parameters have been proved to be significant in differentiating the exudative effusions. Serum ESR with a mean value (75.5±32.75) has been found to be significant in parapneumonic effusion when compared to tubercular and malignant effusion with a statistical significance of 0.067. This is in accordance to other similar studies which has found a higher ESR in the parapneumonic category as compared to malignant and tubercular effusions.
COMPARISON OF BIOCHEMICAL VALUES (SERUM PROTEINS) AMONGST EXUDATIVE EFFUSIONS

Table 18: The below mentioned table signifies that no significant difference in serum proteins were noted in the different exudative effusions

<table>
<thead>
<tr>
<th>BIOCHEMICAL VALUES</th>
<th>MALIGNANT</th>
<th>PARAPNEUMONIC</th>
<th>TUBERCULAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL PROTEINS (mg/dL)</td>
<td>6.92+_0.46</td>
<td>6.58+_0.50</td>
<td>3.52+_0.27</td>
</tr>
<tr>
<td>ALBUMIN</td>
<td>3.51+_0.59</td>
<td>3.21+_0.43</td>
<td>3.37+_0.42</td>
</tr>
<tr>
<td>GLOBULIN</td>
<td>3.43+_0.33</td>
<td>3.36+_0.64</td>
<td>3.52+_0.27</td>
</tr>
</tbody>
</table>

In comparing serum proteins amongst the different exudative effusions, there was found to be no statistical correlation between serum protein and exudative effusions and they had no statistical significance when compared to the various exudative effusions.

This is in accordance to other similar studies which found no significant difference amongst the various exudative effusions based on serum proteins.
COMPARING PLEURAL FLUID CHARACTERISTICS AMONGST DIFFERENT EXUDATIVE EFFUSIONS

In comparing the pleural fluid characteristics amongst various exudative effusions it was noted that not all pleural fluid parameters were correlating with the nature of the effusion. The parameters with statistical significance were pleural fluid differential counts were in a mean lymphocyte predominance (74±32.56) and neutrophils (19.20±25.71) were significant for a malignant effusion, parapneumonic effusions had a mean neutrophil predominance (85.60±17.79) and a lymphocyte predominance of (14.13±17.81) and in tubercular effusions the mean lymphocyte predominance was (76.53±31.25) and neutrophil predominance of (23.20±30.71) all of which had a P=0.0001 which was statistically significant. This was in accordance with other studies which showed similar results. Other pleural fluid parameters that were studied include pleural fluid proteins, glucose, LDH, ADA and total counts. Off which a pleural fluid ADA of (59.75±115.46) and a mean pleural fluid ADA (57±25.48) had a P=0.274 for parapneumonic and tubercular effusions respectively. This is also in accordance with studies which states that high ADA (80) were more significant for a parapneumonic effusion as compared to a tubercular effusions were in ADA (40).
Table-19 : The following table analysis the significance of pleural fluid parameters in the exudative effusions.

<table>
<thead>
<tr>
<th>PLEURAL FLUID CHARACTERSTICS</th>
<th>MALIGNANCY</th>
<th>PARAPENUMONIC</th>
<th>TUBERCULAR</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTEIN(MG/DL)</td>
<td>4.76±0.96</td>
<td>4.28±0.98</td>
<td>5.3±0.76</td>
<td>0.013</td>
</tr>
<tr>
<td>LDH</td>
<td>713.07±726.2</td>
<td>3433.2±8561.05</td>
<td>740.8±901.04</td>
<td>0.241</td>
</tr>
<tr>
<td>GLUCOSE</td>
<td>98.66±32.07</td>
<td>113.72±82.93</td>
<td>101.2±79.32</td>
<td>0.815</td>
</tr>
<tr>
<td>ADA</td>
<td>22.66±20.37</td>
<td>59.75±115.46</td>
<td>57±25.48</td>
<td>0.274</td>
</tr>
<tr>
<td>TOTAL COUNTS</td>
<td>1970±2767</td>
<td>6722±4324</td>
<td>3361±3588</td>
<td>0.003</td>
</tr>
</tbody>
</table>

This table also shows that a mean pleural fluid LDH(3433.2±8561.05) was significant for a parapneumonic effusion with a P =0.241. However the pleural fluid LDH values were not significant to distinguish between tubercular and malignant effusions. This has been studied in other studies too which reflected on the importance of pleural fluid LDH as one of the parameters for assessing a parapneumonic effusion.
COMPARISON BETWEEN PLEURAL FLUID DIFFERENTIAL COUNT AND EXUDATIVE EFFUSIONS.

The following table highlights the importance of pleural fluid differential count in differentiating between exudative effusions.

In the first table, neutrophil predominance was assessed with the exudative effusions and higher pleural fluid neutrophils were associated with a parapneumonic effusion (85%) as compared to malignant and tubercular effusion.

<table>
<thead>
<tr>
<th>PLEURAL FLUID DIFFERENTIAL COUNT (cells/mm³)</th>
<th>MALIGNANT</th>
<th>TUBERCULAR</th>
<th>PARAPNEUMONIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEUTROPHILS</td>
<td>19.2 ± 25.71</td>
<td>23.20±30.71</td>
<td>85.60±17.79</td>
</tr>
</tbody>
</table>
This below mentioned table depicts the lymphocyte predominance assessed within the exudative effusions and higher pleural fluid lymphocytes were seen in malignant and tubercular effusions as compared to a parapneumonic effusion.

<table>
<thead>
<tr>
<th>PLEURAL FLUID DIFFERENTIAL COUNT(cells/mm3)</th>
<th>MALIGNANT</th>
<th>PARAPNEUMONIC</th>
<th>TUBERCULAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>LYMPHOCYTES</td>
<td>74±32.56</td>
<td>14.13±17.81</td>
<td>76.53±31.25</td>
</tr>
</tbody>
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The above mentioned results are in accordance with the similar results obtained from other studies.
COMPARISON OF PLEURAL FLUID CRP BETWEEN EXUDATIVE EFFUSIONS

On comparing the pleural fluid CRP values amongst the exudative effusions of varying etiology, it was observed that a mean pleural fluid CRP of (1.68±2.24) was observed in malignant effusions, in parapneumonic effusions the mean pleural fluid CRP was (12±9.86) and in tubercular effusions the mean pleural fluid CRP was observed to be (3.90±3.04) with a statistical significance of P=0.006. This was in accordance with other similar results obtained from other studies.

The following graph highlights the importance of pleural fluid CRP and various exudative effusions
On further analysis of pleural fluid CRP by ROC it was found that for parapneumonic effusions, analysis of pleural fluid CRP with ROC=0.88, and P=0.0001 had a sensitivity of 80% and specificity of 80% in discriminating parapneumonic from malignant and tubercular effusions.
Similarly pleural fluid CRP was not obtained for the differentiation of tubercular and malignant effusions were ROC=0.477 and 0.136 respectively.

Similar results were obtained from other studies which concluded that pleural fluid CRP was an useful adjunct with Lights Criteria for initially differentiating exudates from transudative pleural effusions and further on can be used to differentiate between parapneumonic from tubercular and malignant in the exudative group which was a similar finding which was noted in our study.
Discussion
DISCUSSION

The important findings in our study were as follows

1. Pleural fluid CRP was an useful adjunct to the Lights Criteria for differentiating between transudative and exudative effusions

2. In case of exudative effusions, pleural fluid CRP was helpful in differentiating parapneumonic effusions from tubercular and malignant effusions

Pleural effusion is primarily characterized by accumulation of fluid between the pleural surfaces. Approximately 3 million cases of pleural effusion are detected worldwide per annum. Diagnosis of pleural effusion provides a challenge to the clinician in routine clinical practice. Initial step in management includes differentiation of pleural effusions as exudates and transudates, which is done by the Lights criteria, in case of transudates no further management is needed, other than treating the underlying pathology (CHF, DCLD, Renal disease). In case of an exudative effusion, further diagnostic modalities are required to clinch a diagnosis which is time consuming and expensive and this goes a long way in the management of the same.

The aim of our study was to evaluate the role of pleural fluid CRP as a reliable biomarker in separating pleural effusion. We found that a pleural fluid CRP value of 1.05 had a good sensitivity and specificity (74.5%, 76.9% respectively) in separating transudative from exudative pleural effusions with a
Further on amongst the exudative effusions a pleural fluid CRP of (5.25 mg/dL and above) had 80% sensitivity and 80% specificity in differentiating parapneumonic from tubercular and malignant effusions with a ROC of 0.888 and a P=0.0001. Thus pleural fluid CRP when used along with the Lights Criteria was an useful adjunct in differentiating transudates from exudates and to further differentiate parapneumonic from tubercular and malignant effusions amongst the exudative group.

Further on pleural fluid CRP is relatively inexpensive, non invasive, less time consuming when compared with the other biomarkers in differentiating pleural effusions and has proved to be useful as an ideal biomarker in low income settings were the use of other invasive diagnostic modalities for the same will be difficult.

SOCIODEMOGRAPHIC CHARACTERS:

In our study 60 subjects were recruited off which 39 were males and 21 were females with a mean age of 52.85±17.77 years. This was comparable to another study by Ahemad et al \(^{(25)}\) were in 100 patients were recruited of which 60 were males and 40 were females with a mean age of 54.5±10.7 years. A study by Wafaa et al \(^{(24)}\) conducted on 54 patients, in which 36 patients were males and 18 were female participants with a mean age of 55±10.4 years was also comparable to our study.
It was found that there was no significant difference between the age and gender distribution characteristics in both the studies were the P value=0.9 was not statistically significant. Our study yielded a P =0.341 on comparing the age and gender variables. Gabhale et al\(^{(26)}\) in another study on 187 patients with pleural effusion highlighted the importance of gender in pleural effusions were in males had a higher incidence of malignant and tubercular effusions as compared to females(77.6% and 67% respectively as compared to 22.4% and 33.3% respectively) with P=0.005 which was statistically significant.

Similarly their study highlighted the importance of age in differentiating pleural effusions were the mean age of the study population was 44.12±16.5 years as compared to the age group of malignant effusions which was higher(59.8±11.86 years) which was statistically significant (P<0.001), attributing the same to malignancy occurring in the fifth – seventh decade of life. This was in accordance to our study which had a similar age group of patients in the malignant group(57.6±13.7 years with a P=0.063).

Qiaoying et al\(^{(27)}\) in a study conducted in 209 patients were in 122 were males and 87 were females with a mean age of 56 years found no statistical significance between age and gender distribution amongst the study groups.

On assessing the BMI amongst study participants in our study, it was found that the mean BMI amongst the study population was 25.38±1.54 kg/m2 which was not statistically significant(p=0.134). Gabhale et al\(^{(26)}\) found no statistical correlation between BMI and the nature of pleural effusion amongst
the study groups were the mean BMI-24.56±1.82 kg/m². This was in accordance with our study. Yadav et al\textsuperscript{(16)} in study conducted amongst 187 patients with pleural effusion also found no significant correlation between BMI and the study groups. Similarly no studies till date have proven the role of BMI in assessing patients with pleural effusion and correlating its significance in the same.

Assessing the significance of smoking and alcohol intake in our study it was found that, off the 47 exudative effusions, 20 were smokers and in 13 transudative effusion 4 were smokers which was not statistically significant with P =0.443. Similarly alcohol intake was correlated with pleural effusion in our study which showed that off the 47 exudative effusions, 9 participants had a history of alcohol intake while amongst the 13 patients with transudative effusion only 1 patient had a history of alcohol intake. No significant correlation was found between alcohol intake and study groups with P=0.327.

Waffa et al\textsuperscript{(24)} also reported similar findings that there was no positive correlation between smoking and alcohol and the study groups. Similarly no study has analyzed the relation between these parameters and pleural effusion. Thus concluding that on individual basis smoking and alcohol had no significance in differentiating pleural effusions and their presence could not be taken as a reliable indicator for the classification of pleural effusion.

On analyzing the symptomatology and nature of pleural effusion, our study found that off the 13 patients with transudative effusion- breathlessness
was seen in 9 patients (69.2%), cough in 6 patients (46.2%), chest pain in 4 patients (30.8%) and fever in 1 patient (7.7%). Similarly in 47 patients with exudative pleural effusion, 32 patients had breathlessness (68.1%), cough in 35 patients (74.5%), 19 patients had fever (40.4%), chest pain 15 patients (31.9%). Correlating the symptomatology with pleural effusion it was found that symptomatology had no positive statistical significance to delineate the nature of pleural effusion (P=0.957).

Gabhale et al.\(^{(26)}\) analyses the symptomatology with nature of pleural effusion and found that chest pain as the most common symptom (80.74%), followed by cough (77%). However no statistical significance was seen with nature of the symptom and pleural effusion, further on stated that none of the patients of pleural effusion were without any chest symptom.

These results were consistent with our study were similar findings were noted. Amitabha et al.\(^{(28)}\) in a study conducted on 110 patients with pleural effusion found variation as compared to our study were cough (40.2%) and dyspnea (33%) were less commonly observed, while chest pain (86.8%), fever (68.4%) were observed as the next common complaints. However all the above mentioned studies concluded that symptomatology was not conclusive enough for differentiating pleural effusions. Similarly our study assessed the prevalence of co-morbidities and nature of pleural effusion. Amongst the 13 transudative effusions, CAD and diabetes were the most commonly associated
co morbid conditions both having 8 patients in each group(61.5%), followed by Hypertension(7,53.8%) and renal involvement in 5 cases(38.5%), were in there was a positive correlation between CAD, DM and transudative effusions (P=0.0001 and 0.015 respectively). In the exudative effusions off the 47 patients, there was no significance between nature of the effusion and the co morbid condition.

This is in contrast to a study by Mansour et al(25) who found no statistical significance between nature of co morbid condition and the study population. The fact that there was a positive relation between co morbid conditions and transudative effusions highlight the importance of the same in differentiating transudative from exudative effusions as we have done in our study. Similarly there was no positive correlation between exudative effusions and the comorbid conditions as highlighted by our study which further emphasize on the fact that predominantly co morbid conditions were seen in transudative effusions and thereby increasing the need to effectively treat the underlying pathology in a transudative effusion.

On analyzing the hematological variables in our study, it was found that for the transudative group the mean values for hemoglobin (9.64±1.69), TLC (9746±2641), platelets (235620±87602) and ESR (41.54±15.88) had no statistical significance in differentiating pleural effusion. Similarly in the exudative group the mean Hb (11.37±2.51), TLC (13289±12070), platelets (313530±128618) and ESR (60.28±32.14). There was no positive correlation
between the study groups on determining the hematological variables as was evidenced by our study (P=0.30).

Similar findings were noted by Qiayoying et al (27) in study conducted in 209 patients. Thus it was proved that analysis of hematological parameters had no significant impact on the nature of pleural effusion. Other biochemical parameters total protein, serum albumin and serum globulin were analyzed in our study which showed no statistical significance between these biochemical parameters and pleural effusion with a p=0.199. Similarly no studies have individually analyzed the importance of serum proteins and classification of pleural effusion and thus it can be concluded that the analysis of serum proteins had no significance in the differentiation of pleural effusion as stated in our study.

COMPARISON OF PLEURAL FLUID PARAMETERS BETWEEN THE STUDY GROUPS:

In our study we analyzed the importance of each pleural fluid parameter and its importance in individually differentiating a pleural effusion. Amongst the 13 patients with transudative pleural effusion the mean pleural fluid protein was (1.6±0.50) which when compared with the exudative group had a statistical significance of P=0.0001 were the mean pleural fluid protein was (4.72+_1). Similarly pleural fluid LDH levels were significantly elevated in the exudative group (1566±4939) as compared to the transudative group (103.23±65.76) with a P =0.293.
Pleural fluid total count was also noted to be elevated in the exudative group were the mean was $(3914.89 \pm 4013.42)$ as compared to the transudative group $(647 \pm 591.34)$ with a $P=0.0001$. These values obtained by our study is in direct consensus with Lights Criteria in differentiating transudative effusions from exudative effusions were importance was given to the pleural fluid LDH and pleural fluid protein level for the classification of pleural effusion. Similar findings were noted in a study conducted by Hassan et al$^{(10)}$ which concluded that assessing the pleural fluid LDH and pleural fluid protein levels had a positive statistical correlation in differentiating exudative from transudative effusions $(p=0.000)$.

Other studies also quoted the significance of assessing pleural fluid LDH, pleural fluid proteins and pleural fluid total count in differentiating transudative from exudative effusions and found positive correlation between both. Other pleural fluid parameters like pleural fluid glucose, and pleural fluid differential counts were assessed and their correlation with the classification of pleural fluid transudates or pleural fluid exudates were considered insignificant $(P=0.094$ and $0.019$ respectively). Our study was in accordance with other studies which obtained similar in significant results in comparing pleural fluid glucose and pleural fluid differential count in the differentiating exudates from transudative pleural effusion.
COMPARISON OF PLEURAL FLUID CRP IN DIFFERENTIATING PLEURAL FLUID EXUDATES FROM TRANSUDATES:

Our study analyzed 60 subjects with pleural effusion of which based on clinico radiological and pleural fluid biochemical properties they were separated into transudates and exudative pleural effusion. Amongst the 60 pleural effusions, 13 were transudates and 47 were exudates. On analysis of pleural fluid CRP between the two groups, it was found that a pleural fluid CRP of 1.05 mg/dL had 75% sensitivity and 77% specificity in differentiating exudative from transudative effusions with a ROC=0.825 which was statistically significant and thus proved that pleural fluid CRP can be used as an adjunct with the Lights criteria in classification of transudative and exudative pleural effusion. Our results were similar to other studies which showed similar findings.

Waffa et al\(^{(24)}\) in a study conducted on 54 patients showed that the mean pleural fluid CRP in a transudative effusion(1.113+_0.574 mg/dL) which was statistically significant with P=0.002. Mansour et al\(^{(25)}\) in a similar study conducted on 110 patients found similar but slightly higher values for pleural fluid CRP in differentiating pleural fluid transudates from exudates were a mean pleural fluid CRP for a transudative effusion was(5.7±0.9) and similarly for an exudative effusion was(16.1±7.2) with a P=0.0001.
Hoda et al\(^{(17)}\) also published similar reports in a study stating higher pleural fluid CRP in exudative effusions as compared to transudative effusion with a P value <0.003. Alexandris et al\(^{(12)}\) in a study conducted on 84 patients with pleural effusion, found similar results as to our study, where in a pleural fluid CRP of 1mg/dL had a sensitivity and specificity of 74% in differentiating exudative from transudative pleural effusions with a P value<0.001 and concluded that pleural fluid CRP as a good biomarker in differentiating transudative from an exudative pleural effusion. In another similar study by Castano et al\(^{(23)}\), were 72 patients were recruited for the study, a mean pleural fluid CRP of 1mg/dL had a positive correlation with p<0.001 in differentiating exudative from transudative pleural effusion.

Rezaeetalab in a study too proved that pleural fluid CRP were higher in exudates as compared to transudates with a p<0.05. Thus our study is in accordance with all the above mentioned studies in concluding that lower level of pleural fluid CRP was found in transudative effusions as compared to exudative effusions with a strong statistical correlation. This proves that pleural fluid CRP can be a useful adjunct with the Lights criteria in differentiating exudates from transudates which is the initial step in the management of pleural effusion.
COMPARISON OF SOCIODEMOGRAPHIC VARIABLES IN EXUDATIVE PLEURAL EFFUSION.

Our study correlated the socio demographic variables in the classification of exudative effusions. With respect to age there was a significant correlation between the exudative groups. The mean age for the malignant group was \(57\pm13.7\), for parapneumonic group \(51.93\pm15.51\) and tubercular group was \(42.6\pm21.09\) were the \(P=0.063\).

Gabhale et al\(^{(26)}\) too found higher incidence of age in the malignant group with a mean age \(59.8\pm11.86\) years as compared to a mean age of \(44.12\pm16.5\) years in other effusions. This was attributed to the higher incidence of malignancy seen in the fifth-seventh decade of life. In relation to BMI and the classification of an exudative effusion there was no significant relation between the same were the mean BMI for malignant \(25.26\pm1.57\), for parapneumonic group was \(25.78\pm1.39\) and for tubercular group was \(24.37\pm1.22\) with a \(P\) value of 0.03 which was insignificant. Similar results were obtained by El shimy et al\(^{(24)}\) and Mansour et al\(^{(25)}\) in their respective studies. In our study we found that on analysing gender with exudative pleural effusions, male predominance was noted for each of the exudative effusion. Off the 15 malignant effusion, 8 were males \(53.3\%\) in the parapneumonic group 12 were males \(80\%\) and 11 were males in the tubercular effusion category \(73.3\%\) with a \(p=0.260\).
This was directly correlated to the smoking incidence which was observed amongst the male gender. On similar assessment of the 8 malignant effusion which were males 5 were smokers(62.5%) there by showing a positive correlation between smoking and malignancy.

Gabhale et al\(^{(26)}\) in a similar study showed the higher incidence of malignant effusion in the male population as compared to females(78% and 22% respectively) and attributed this to the smoking and alcohol habits in the male population. Concluded that risk of malignancy was three times increased in the male population. They found a similar increase in the number of males in the parapneumonic category with male to female ratio being 3:1.

This was in accordance to similar findings noted in our study were off the 15 parapneumonic effusions,12 were males(80%).In assessing the symptomatology amongst exudative effusions, our study noted that breathlessness was a common finding in twelve of the 15 cases of malignant effusion, followed by cough which was seen in 12 cases of the 15 malignant effusion with a \(P=0.092\).Similar findings were noted by Gabhale et al\(^{(26)}\) in a study which concluded that the most common symptom in a malignant effusion was chest pain(80.74%) followed by cough(77%) which is in accordance with our study.

Also other studies have quoted variable frequency of chest symptoms amongst exudative effusions to which our study was not in accordance with. However in our study, we found that there was no significant difference when
other symptomatology was assessed between other exudative effusions with an insignificant correlation with P=0.734.

Other sociodemographic variables assessed in our study included the distribution of co morbid conditions and nature of exudative effusions. The comorbidities analyzed were COPD, DM, HTN and CAD all of which had no predominance amongst the exudative effusions with a P=0.508. Similar studies have analysed the prevalence of co morbid conditions and exudative effusion and have found no statistical significance for the same. There by concluding that comorbidities were not a criteria for analysing the exudative effusions, unlike the transudative effusions were comorbid conditions play a role as proved by our study previously.

ANALYSIS OF HEMATOLOGICAL VARIABLES IN EXUDATIVE EFFUSION:

On analyzing the hematological variables with respect to exudative effusion, our study concluded that apart from ESR there was no significant correlation between other hematological variables and exudative effusions. ESR when analysed was found to be significantly higher in the parapneumonic category (75.5±32.75) as compared to malignant or tubercular effusions (48.8±34.56 and 59.67±24.43 respectively).

Similarly TLC was analyzed in our group and only a marginal difference was noted amongst the exudative effusions which was in accordance
with Gabhale et al (26) were TLC was found to be elevated in parapneumonic group followed by tubercular and malignant were the \( p=0.70 \) which was insignificant. This was attributed to the inflammatory process on going in a parapneumonic effusion. On reviewing other hematological variables, their correlation with the exudative effusion was considered insignificant. Other variables analyzed in our study were platelets and Hb which were insignificant with \( p=0.548 \) and \( 0.572 \) respectively. Similarly assessment of serum proteins were also insignificant in the differentiation of exudative effusions as demonstrated by our study. Similar findings were also observed in other studies.

**ANALYSIS OF PLEURAL FLUID PARAMETERS AMONG SUBJECTS WITH EXUDATIVE EFFUSION**

The various pleural fluid parameters analyzed in our study were pleural fluid LDH, ADA, protein, glucose, total and differential counts. Our study concluded that on analysing certain parameters like pleural fluid LDH, ADA, total and differential counts there was a significant difference between the exudative effusions of different etiology and was also proved in studies quoting similar results. In our study, the mean pleural fluid LDH in parapneumonic, malignant, tubercular effusions were \((3433.2 \pm 8561.05)\), \((713 \pm 726.20)\), \((740.8 \pm 901.04)\) respectively with a \( p=0.24 \).

Though parapneumonic effusions had a larger range of pleural fluid LDH, no similar differences amongst tubercular and malignant effusions were
noted. Similar studies have proved that a higher range of pleural fluid LDH was noted in parapneumonic effusion as compared to tubercular and malignant effusion was noted in our study

Another pleural fluid variable assessed was the pleural fluid ADA amongst exudative effusions. It was found that pleural fluid ADA was lowest in the malignant group (22.66±20.37) as compared to parapneumonic and tubercular effusions (59.75±115.46) and (57±25.48) respectively with p=0.27. It was seen that there was no difference in pleural fluid ADA when compared between the parapneumonic and tubercular group.

Nusrath et al\(^{22}\) in a study concluded the effectiveness of pleural fluid ADA and stated that a ADA(40) had a good sensitivity and specificity in differentiating tubercular effusions from other exudative effusions with a P<0.001. This was in accordance to our study which had near similar results on comparing pleural fluid ADA.

Motoki S\(^{35}\) et al gave a similar report regarding pleural fluid ADA wherein an ADA of <50IU/L had a good sensitivity and specificity in differentiating tubercular from malignant and parapneumonic effusions.

Wipa et al\(^{29}\) reported that when a pleura fluid ADA with cut off 48U/L was estimated, it had a sensitivity of 80% and a specificity of 80.5% respectively. Similarly Burgess et al\(^{30}\) showed 90% sensitivity and 89% specificity for an ADA of 50 U/L in differentiating tubercular from malignant
and parapneumonic effusions. In a report by E. Garcia et al\(^{(31)}\) which showed contrasting views on pleural fluid ADA from the above mentioned studies, concluded that a higher pleural fluid ADA(73 U/L) was associated with mesotheliomas and quoted as one third of the patients with mesotheliomas to have a higher pleural fluid ADA value. Similar observation was also noted by Verma et al\(^{(32)}\) were the ADA for malignant effusion was(87.6±18.5 U/L) which was contrasting to our study. Verma et al\(^{(32)}\), Arun G et al\(^{(39)}\) also stated that high pleural fluid ADA were also noted in patients with rheumatoid arthritis, fungal infections and in cases of empyma apart from malignant effusions. Rafael LL\(^{(40)}\) highlighted the over implication of pleural fluid ADA in the diagnosis of tubercular effusion.

On analysis of pleural fluid total counts in our study it was found that parapneumonic effusions had a higher pleural fluid counts as compared to tubercular and malignant effusions (6722±4324), (3361±3588) and (1970±2767) respectively with a statistical significance P=0.03. In turn attributing the increase in total counts to the ongoing inflammatory condition associated with a parapneumonic effusion. Huang et al\(^{(27)}\) quoted similar findings in their study were in a higher pleural fluid leukocyte levels were seen associated with parapneumonic effusions as compared to tubercular and malignant effusions.

Gabhale et al\(^{(26)}\) also found similar findings in their study, and concluded that pleural fluid leukocyte count was higher in parapneumonic
effusions as compared to tubercular and malignant effusion, though the
difference in the total counts were insignificant=0.70. Further analysis of
differential counts in the exudative group in our study found significant
differece in differential count between paraneumonic as compared to tubercular
and malignant effusions. The mean pleural fluid differential count found a
neutrophil predominance in parapneumonic effusion as expected(85.60±17.79 )
and a mean lymphocyte count(14.13±17.81) as compared to a lymphocyte
predominant tubercular effusion(76±31.25) with a P value=0.0001 which was
statistically significant. However no significant differential count
predominance was seen in the malignant group in our study.

The neutrophil predominance was seen in parapneumonic effusions as
they were acute onset and a neutrophil predominant cell population was
expected in the initial course of an acute inflammation. As the on going
inflammation continues further, the neutrophil predominance gives way to a
lymphocytic predominant effusion which was evident as proved by a
lymphocyte predominant effusion as seen in our tubercular effusion and
malignant effusion. This was in accordance to San jose et al(15) who highlighted
the importance of cell counts in differential diagnosis of pleural effusion and
stated that a total neutrophil count had sensitivity of 64.3% and a specificity
of 93.4% in the diagnosis of a parapneumonic effusion with a ROC=0.836
which was statistically significant. In another study by Perlat et al(11), the
presence of a neutrophilic cell predominance, leucocytosis were significant of a
pleural effusion of an infectious origin (parapneumonic effusion) and went to state that a lymphocytic predominant effusion were seen in a sub acute to chronic condition there by explaining the lymphocytic predominant tubercular and malignant effusion as in our study.

A similar study by Trajman A et al\(^{(33)}\) in diagnosis of a tubercular effusion quoted as saying that a pleural fluid lymphocyte level of (>90%) were significant for tuberculosis or lymphoma while a neutrophilic level of more than 80% was significant of a parapneumonic effusion which was in accordance with our study.

Porcel at al\(^{(2)}\) too justified a similar finding stating that a lymphocytic predominant effusion was more in favor of tubercular or malignant effusion while a neutrophilic predominant effusion was significant of a parapneumonic effusion which is again in accordance to our study results .

Hassan et al\(^{(10)}\) too yielded similar results stating the importance of cell group predominance in identifying the nature of an exudative effusion. The other pleural fluid parameter which was analyzed in our study was pleural fluid glucose which was found to be increased in parapneumonic effusions (113±82.93) and was insignificant variable in the differential diagnosis of an exudative effusion with a p=0.815 as per our study. This was not in accordance to other studies which proved that pleural fluid glucose was the lowest in a parapneumonic effusion (46±5.3 mg/dL) and highest in a malignant effusion (85.6±42) and a glucose of <60 mg/dL was seen in
complicated parapneumonic effusion with a statistical significance of 0.006. No other study has highlighted the importance of pleural fluid glucose as a parameter in differentiating between exudative pleural effusions.

**COMPARISON OF PLEURAL FLUID CRP WITH EXUDATIVE EFFUSIONS:**

CRP is an acute phase reactant which is generated by the hepatocytes in response to the inflammatory process. In case of an inflammatory effusion, due to the increased permeability of the pleural membranes, CRP diffuses through the same and is found in the pleural fluid there by signifying an increased pleural fluid CRP which is associated with an exudative effusion especially of the parapneumonic variety. Further studies have correlated the importance of pleural fluid CRP in a malignant effusion stating that since malignancy is an inflammatory condition, this explains the increase in pleural fluid CRP in a malignant effusion. Further on the prognostic value of pleural fluid CRP was evaluated by Scott et al(21) who proved that higher CRP levels indicated a poor overall survival rate, attributing to the fact that increased CRP levels were corresponding to cachexia and poor mineral bone density there by contributing to the poor overall survival rate. Similar studies by Garcia et al(37) and Okamura et al(38), too evaluated clinical applications of CRP in differential diagnosis of exudative pleural effusion.

In our study we analyzed the significance of pleural fluid CRP in the different exudative effusions and found that parapneumonic effusions had a
higher pleural fluid CRP(12+_9.86), followed by tubercular effusion(3.90±3.04) and malignant effusion(1.68±2.24) with a p=0.006 which was statistically significant. Further on our study showed that on using a pleural fluid CRP of 5.25 and above there was 80% sensitivity and specificity in discriminating parapneumonic from the malignant and tubercular effusions with ROC=0.888 which was highly significant. This was in accordance to the above mentioned path physiology of increased pleural fluid CRP which was associated with a parapneumonic effusion.

San jose et al(15) in a study correlated the pleural fluid CRP in parapneumonic effusions and stated that higher pleural fluid CRP was observed in the parapneumonic group as compared to the other groups with a p<0.001-0.004) which was statistically significant. Similar study by Perlat et al(11) too found similar results in using pleural fluid CRP as a differentiating factor and found that a mean level of 57±33.7 mg/L had a sensitivity of 94.7% in differentiating a parapneumonic from other exudative effusions and concluded that pleural fluid CRP values were highest for a parapneumonic effusion, followed by tubercular and malignant effusion. Gabhale et al(26) too found high values of pleural fluid CRP(134±22.9 mg/L) in parapneumonic group as compared to the lowest levels seen in the malignant group with mean of(26.8±18.7 mg/L).

This difference was found to be statistically significant with a P <0.001 and in the tubercular group the mean pleural fluid CRP was (66.75±10.77 mg/l)
which was also in accordance to our study. In ROC analysis for analyzing the significance of pleural fluid CRP, they said that it gave the largest area under ROC curve(1.00) for differentiating parapneumonic effusion from non parapneumonic effusion. They also stated that the slightly higher level in pleural fluid CRP in a malignant effusion was due to an infectious component super imposed on a malignant effusion. Further on the study concluded that for an accurate clinical diagnosis of a parapneumonic effusion, a pleural fluid neutrophil predominance, and a high pleural fluid CRP had a ROC=0.85 and 0.82 respectively which was a similar finding which was seen in our study.

El Shimy et al (24) too proved that a pleural fluid CRP level was lower in a malignant effusion(2.49±1.69 mg/dL) as compared to a parapneumonic effusion(6.85+_1.658 mg/dL) and tubercular effusions had a pleural fluid CRP(6.992±3.72 mg/dL) with a p=0.003 and 0.002 respectively. This was different to our study as a higher mean pleural fluid CRP was obtained in the tubercular group when compared to the same in our group. Also the study compared pleural fluid CRP in patients of malignant effusion with transudative effusion with a p=0.159 which was not correlated in our study.

Mansour et al (25) too found a higher value of pleural fluid CRP in the parapneumonic group as compared to the other exudative group with a statistical significance of p<0.001. Similarly Yilmaz et al in (34) 97 patients analyzed pleural fluid CRP and quoted that it was significantly higher in the parapneumonic group as compared to tubercular and the neoplastic group with
Castano et al\(^{(23)}\) too correlated the pleural fluid CRP in 72 patients with pleural effusion and quoted that a pleural fluid CRP (>10mg/L) had a sensitivity of 82% and specificity of 87.5% in the diagnosis of parapneumonic effusions from other effusions.

Hoda et al\(^{(17)}\) also concluded that pleural fluid CRP was higher in the parapneumonic group as compared to the other exudative group, however a contradiction to the fact that a higher pleural fluid CRP level was observed in the tubercular group as compared to the parapneumonic group as was found in our study. Other studies also reported that the highest sensitivity and specificity in differentiating exudates from transudates was a pleural fluid CRP >30 mg/dL which had a sensitivity of 93.7% and a specificity of 76.5%.

From comparing our study to the other above mentioned studies it was found that a higher pleural fluid CRP was a useful parameter along with the clinical and radiological features in discriminating a parapneumonic effusion from other exudative effusions. A mild increase in the mean pleural fluid CRP as observed in some studies have been attributed to a super imposed inflammatory component in those cases.

Thus it is justified in concluding that pleural fluid CRP is a useful adjunct in the discrimination of transudates from exudates along with the Lights Criteria and further on a high pleural fluid CRP had a diagnostic reliability in differentiating parapneumonic effusion from neoplastic and tubercular effusion.
Summary
SUMMARY

Sixty patients with pleural effusion diagnosed by clinico radiological criteria were recruited in our study. We evaluated the socio demographic and hematological variables in transudative and exudative effusion. We compared the pleural fluid parameters like LDH, ADA, Glucose, Protein and Total counts with pleural fluid CRP values to evaluate the role of pleural fluid CRP differentiating pleural effusions. The study participants were divided into transudates and exudates and further in exudates the patients were divided into malignant, parapneumonic and tubercular effusions. Sociodemographic variables and hematological variables like total counts, platelets, Hb and ESR had no significant correlation between the study groups. We found that a pleural fluid CRP of 1.05 mg/dL had a good sensitivity and specificity in differentiating transudative effusions from exudative effusions. Further on amongst the exudative effusions, a pleural fluid CRP of 5.25 mg/dL and above had a good sensitivity and specificity in differentiating parapneumonic from tubercular and malignant effusions.
Limitations
LIMITATIONS

1. Sixty samples were only included in our study due to time constraints.

2. Though pleural fluid CRP proved a good indicator in differentiating exudates from transudates and further in differentiating parapneumonic from other exudative effusions, it was not a reliable indicator in differentiating malignant from tubercular effusions.

3. Pleural fluid glucose was not found to be a reliable indicator in differentiating parapneumonic from tubercular and malignant effusions, contradictory to other studies.

4. Apart from pleural fluid CRP, an additional biomarker needed to be analyzed to differentiate pleural effusions as no single biomarker has proven to be significant in differentiating pleural effusions.
Conclusion
CONCLUSION

Our study showed that a pleural fluid CRP of 1.05 mg/dL helped in differentiating transudates from exudative pleural effusions. In the exudative group a pleural fluid CRP of 5.25 mg/dL and above had a diagnostic significance in differentiating parapneumonic effusions from tubercular and malignant effusions.

Thereby CRP can be used as a novel biomarker to differentiate transudative from exudative effusions. It also has specificity in differentiating parapneumonic effusions from other exudative effusions.
Bibliography
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Annexures
## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>SHT</td>
<td>Systemic Hypertension</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary Artery Disease</td>
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<tr>
<td>MPE</td>
<td>Malignant Pleural Effusion</td>
</tr>
<tr>
<td>TPE</td>
<td>Transudative Pleural Effusion</td>
</tr>
<tr>
<td>CPPE</td>
<td>Complicated ParaPneumonic Effusion</td>
</tr>
<tr>
<td>PPE</td>
<td>Parapneumonic Effusion</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate Dehydrogenase</td>
</tr>
<tr>
<td>MR pro ANP</td>
<td>Mid Regional Atrial Natriuretic Peptide</td>
</tr>
<tr>
<td>AAG</td>
<td>Alpha 1 Acid Glycoprotein</td>
</tr>
<tr>
<td>AMG</td>
<td>Alpha 2 MacroGlobulin</td>
</tr>
<tr>
<td>LBP</td>
<td>Lipo polysacchride Binding Protein</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumor Necrosis Factor</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular Endothelial Growth Factor</td>
</tr>
<tr>
<td>BNP</td>
<td>Brain Natriuretic Peptide</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>N Terminal Brian Natriuretic Peptide</td>
</tr>
</tbody>
</table>
STREM-1 : Soluble Triggering Receptor Expressed on Myeloid cells-1

IL-6 : Interleukin-6

AFB : Acid Fast Bacilli

CYFRA : Cytokeratin Fragment

CEA : Carcinoma Embryonic Antigen

TTF1 : Thyroid Transcription Factor 1

CA : Carcinoma Antigen

ADA : Adenosine De Aminase

CRP : C-Reactive Protein

ls CRP : Low sensitivity CRP

hs CRP : High sensitivity CRP
I (write name of the investigator(s) here), Dr. Arun R. Thomas is carrying out a study on the topic: “A HOSPITAL BASED STUDY ON PLEURAL FLUID CRP AS A BIOMARKER IN PLEURAL EFFUSION”.

as part of our research project being carried out under the aegis of the Department of: Respiratory Medicine

(Applicable to students only): our research guide is: Dr. K. Anupama Murthy

The justification for this study is: My study aims at justifying the use of pleural fluid biomarker (CRP) in early differential diagnosis of exudative pleural effusion.

The objectives of this study are:

1. Primary Objective: To evaluate CRP as a biomarker in differentiating exudative pleural effusion.
2. Secondary Objective: To assess the diagnostic value of pleural fluid CRP with routine pleural fluid parameters in exudative pleural effusions of different etiology.

Sample size: _60_.

Study volunteers / participants are (specify population group & age group): Males & Females, 18 yrs & Above

Location: PSG IMSR.

We request you to kindly cooperate with us in this study. We propose collect background information and other relevant details related to this study. We will be carrying out:

Initial interview (specify approximate duration): ____ 5 ______ minutes.

Data collected will be stored for a period of Five years. We will use the data as part of another study.

Health education sessions: Number of sessions: ___ : ___. Approximate duration of each session: -

Clinical examination (Specify details and purpose):
- Respiratory System: To detect diminished breath sounds,
- Chest X-Ray PA View: To detect pleural fluid
- Diagnostic thoracocentesis: To aspirate pleural fluid for diagnosis

Blood sample collection: Specify quantity of blood being drawn: ______ 5 _____ ml.

No. of times it will be collected: ____ NA ____.

Whether blood sample collection is part of routine procedure or for research (study) purpose:
1. **Routine procedure ✓**

   Specify **purpose**, discomfort likely to be felt and side effects, if any: **Mild discomfort at the time of diagnostic aspiration**

   Whether blood sample collected will be stored after study period: Yes / **No, it will be destroyed ✓**

   Whether blood sample collected will be sold: Yes / **No ✓**

   Whether blood sample collected will be shared with persons from another institution: Yes / **No ✓**

   **Medication** given, if any, duration, side effects, purpose, benefits: **NIL**

   Whether medication given is part of routine procedure: Yes / **No (If not, state reasons for giving this medication)**

   Whether alternatives are available for medication given: Yes / **No (If not, state reasons for giving this particular medication)**

   **Final interview** (specify approximate duration): **NA** mts. If **photograph** is taken, purpose:

   1. **Benefits** from this study: Helps in early differential diagnosis of pleural fluid effusions.
   2. **Risks** involved by participating in this study: **Minimal Risk during Diagnostic thoracocentesis**

   How the **results** will be used:

   If you are uncomfortable in answering any of our questions during the course of the interview / biological sample collection, **you have the right to withdraw from the interview / study at anytime**. You have the freedom to withdraw from the study at any point of time. Kindly be assured that your refusal to participate or withdrawal at any stage, if you so decide, will not result in any form of compromise or discrimination in the services offered nor would it attract any penalty. You will continue to have access to the regular services offered to a patient. You will **NOT** be paid any remuneration for the time you spend with us for this interview / study. The information provided by you will be kept in strict confidence. Under no circumstances shall we reveal the identity of the respondent or their families to anyone. The information that we collect shall be used for approved research purposes only. You will be informed about any significant new findings - including adverse events, if any, – whether directly related to you or to other participants of this study, developed during the course of this research which may relate to your willingness to continue participation.

   **Consent:** The above information regarding the study, has been read by me/ read to me, and has been explained to me by the investigator/s. Having understood the same, I hereby give my consent to them to interview me. I am affixing my signature / left thumb impression to indicate my consent and willingness to participate in this study (i.e., willingly abide by the project requirements).

   Signature / Left thumb impression of the Study Volunteer / Legal Representative:

   Signature of the Interviewer with date: 

   **Witness:**

   **Contact number of PI:** 9677398350

   **Contact number of Ethics Committee Office:** 0422 2570170 Extn: 5818
அதிகார வழியானது ஆங்கிலத்தில் PSG புதுக்கோட்டைக்கு கீழ் உள்ள வேளாண்மைகளின் மூலமாக மத்தியக்கட்டுரைகள் குறிக்கப்பட்டது. "சிலரே, பிறந்த ஆண்டு தோன்றிய புலியான ஆராய் நேராக வரும் செயல்வாடியல்களும்" என்று உரையானது ஆங்கிலத்தில் பதப்புக்குத் தலைசெய்க்கின்றார்.

ஆனால் பாரம்பரியக் கலைஞர்கள் இரண்டு ஸ்தப்பா புதுக்கோட்டை வழியாக செல்ல வேண்டும் என்று பிற வேளாண்மைகள் குறிக்கப்பட்டது. இது கீழக்கரை தலைசெய்தியாகப் புதுக்கோட்டை வழியாக உரையானது. கூறும் படை நம்பிக்கைகளின் செயல்வாடியல் நல்நடைபெற வேண்டும். இவை புரோப்பத்தைப் போட்டு முறை வழியாக செல்லும் வழியாக நல்நடைபெற வேண்டும் என்று சொல்லப்பட்டது.

அப்படி உரையானது
1. சிலரே புதுக்கோட்டை வழியாக ஆகஸ்டில் வரும் செயல்வாடியல்
2. இருவர் சிலரே வழியாக செல்லும் செயல்வாடியல்

அப்படி வழியாக புதுக்கோட்டை வழியாக செல்லப்பட்டது: 70 போட்டுகள்

அப்படி வழியாக செல்லப்பட்டது: வேளாண்மை வருமாற்றாக, புதுக்கோட்டை வழியாக செல்லப்பட்டது

ஆப்பளவான உரையானது அசைலம்பாண்டால் / பாதுகாப்பால்

சிறு வருமாற்றால் குறை வழியாக வரும் செயல்வாடியல் வழியாக குறை வளை பாது

காப்பால் வழியாக செல்லப்பட்டது.
இரு அமைதிகள் விளக்கத்து 12 அடுக்குகள் பார்த்தார்கள். கிளை வைக்கும் விளக்கத்து பார்த்து கிளைவைக்கும் விளக்கத்து பார்த்தார்கள். இரு அமைதிகள் சூட்டப்படுத்துகின்றன. அமைதிகளால் தொகுதியில் அமைதிகள் சூட்டப்படுத்துகின்றன. இல்லாத விளக்கத்து பார்த்தார்கள். அமைதிகள் சூட்டப்படுத்துகின்றன. அமைதிகளால் தொகுதியில் அமைதிகள் சூட்டப்படுத்துகின்றன.

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**Thesis Project**

**Title:** HOSPITAL BASED STUDY ON THE ROLE OF CRP AS A BIOMARKER IN PLEURAL EFFUSION

**Department of Respiratory medicine**

**PSG IMSR**

---

**Case Record Form**

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<th>Informant:</th>
</tr>
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<tbody>
<tr>
<td>Age / sex:</td>
<td>CRC. No:</td>
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<tr>
<td>Father’s / Husband’s name:</td>
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<td>Address:</td>
<td>Height: Weight:</td>
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<tr>
<td></td>
<td>BMI:</td>
</tr>
<tr>
<td></td>
<td>PSG OP No:</td>
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</tbody>
</table>

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**Marital status:** Married Unmarried Widow/Widower

**No. of family members:**           Adults ...... Children ...... (< 12 years)

**Dwelling** [lived for most part (>70%) of the subject’s life] Urban / Rural
**Education:**
- Illiterate
- Read & write
- Primary school
- High school
- Higher secondary
- Graduate
- Postgraduate
- Professional / Fellow / Doctorate

**Occupation:**
- employed
- unemployed
- retired
- housewife

**Present:** …………………………………………
**Duration:** …………………

**Past:**
(1) …………………………………………
**Duration:** …………………

(2) …………………………………………
**Duration:** …………………

**Total monthly family income:** …………………

What is your contribution to total monthly family income? ………………… %

**Socioeconomic status (Modified prasad's classification):**

**Personal History:**

**Diet:** vegetarian / mixed

If mixed diet how frequently you take animal food?

Daily / weekly / fortnightly / monthly / occasional

**Smoking:** Yes / No (presence of regular smoking for at least one year and / or smoked at least 100 cigarettes / beedies / others in his / her lifetime)

If yes, beedi/ cigarette/ hukka/others
No of beedies / cigarettes per day ..............................

Age at started ..........................................................

If ex-smoker, when stopped ........................................

Alcohol:  Yes / No

If yes, Quantity ....................... ml

Frequency .........................

If stopped when .........................

Other informations:  Drugs / narcotics abuse

Tobacco / pan chewing

Sexual promiscuity

Disease specific details: PLEURAL EFFUSION

Duration of illness:

Treatment details(at the time of enrollment):

Past history / Co-existing illness:

- Allergic rhinitis...........................................................................
- GERD / Acid peptic disease............................................................
- Hypertension..............................................................................
- Diabetes mellitus........................................................................
**Family History:**  (mention relationship where relevant)

- Hypo/hyperthyroidism
- Other endocrine disorders
- Lung diseases other than COPD
- Heart diseases
- Cerebro vascular diseases
- Kidney diseases
- Obstetric history / Gynecological illnesses
- Surgical illnesses
- Congenital anomalies
- Others

**Physical examination**

1. **Vitals:**

   Pulse rate: ....................  Respiratory rate: ....................

   B.P.: ....................  Temperature: ....................

   O2 saturation: ....................
2. General examination:

| Built | Pallor | cyanosis | clubbing | JVP | edema | Lymph nodes |

3. Respiratory system:

4. Cardiovascular System:

5. Others

X-ray chest PA view:

ECG:

Baseline Blood Investigations:

CBC, Serum LDH, Serum Protein

Pleural Fluid Parameters, LDH, ADA, Protein, Glucose, Cell Count, Cytology, CRP

Diagnostic Thoracocentesis at time of Recruitment
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