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

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COIMBATORE

2016

PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee

Recognized by The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER)
POST BOX NO. 1674, PEELAMEDU, COIMBATORE 641 004, TAMIL NADU, INDIA
Phone : 91 422 - 2598822, 2570170, Fax : 91 422 - 2594400, Email : ihec@psgimsr.ac.in

October 24, 2014

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:

Name	Qualification	Responsibility in IHEC	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
Dr P Sathyan	DO, DNB	Clinician, Chairperson	Male	No	Yes
Dr S Bhuvaneshwari	M.D	Clinical Pharmacologist Member - Secretary	Female	Yes	Yes
Dr Sudha Ramalingam	M.D	Epidemiologist Alt. Member - Secretary	Female	Yes	Yes
Dr Y S Sivan	Ph D	Member –Social Scientist	Male	Yes	Yes
Dr D Vijaya	Ph D	Member – Basic Scientist	Female	Yes	Yes

The approval is valid for one year.

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Phone : 91 422 - 2598822, 2570170, Fax : 91 422 - 2594400, Email : ihec@psgimsr.ac.in

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,

24.10.17

SECRETARY
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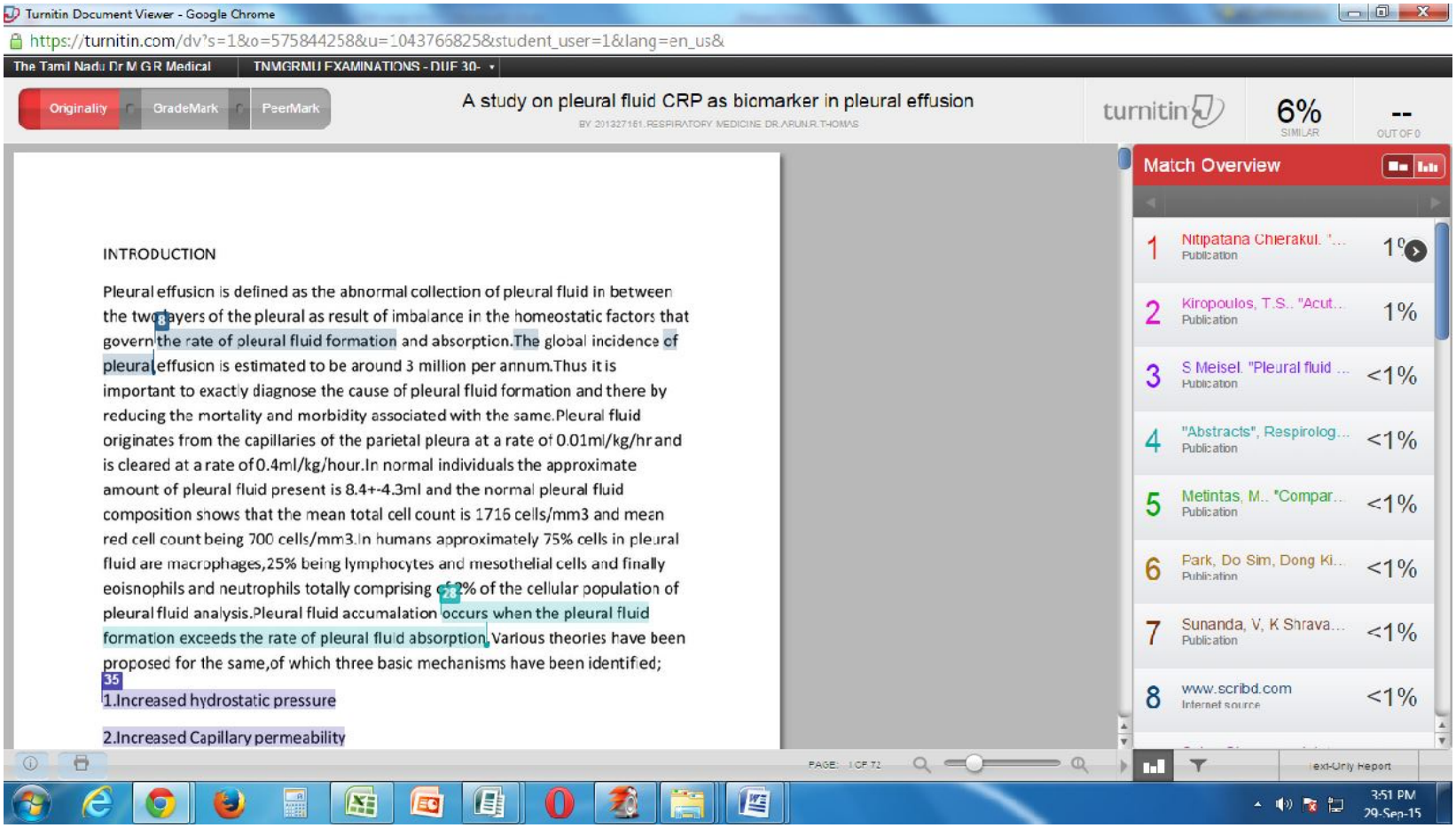
INSTITUTIONAL HUMAN ETHICS COMMITTEE

Dr S Bhuvaneshwari
Member - Secretary
Institutional Human Ethics Committee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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 eoisnophils and neutrophils totally comprising of 2% of the cellular population of pleural fluid analysis.Pleural fluid accumalation 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
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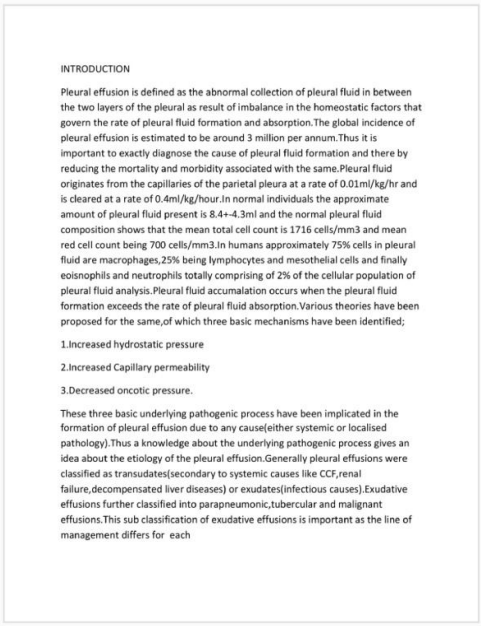

INTRODUCTION

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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

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 (**C**HEST)** 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

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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.

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A special mention to the Radiology, Medical Oncology, Cardiology, Nephrology and Gastroenterology departments for their unyeilding 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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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 perannum. 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.

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1. Increased hydrostatic pressure
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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 characterstics 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 pit falls 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 inturn 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 discrminating transudates from exudates as well as seperating 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 effuions 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 justyfing 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 Effuison

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 kown 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

STEP1:

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 assessd 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[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[2] proved through a large multicentric study involving 766 patients where in 67% of the transudative effusions were straw coloured, 11% were bloody effsuions 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+/-4.3ml 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)-lypmphatic 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 initially 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[(4)] studied the corelation 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 > 2/3rd 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 subesequently 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 seperation” .

Various biomarkers were studied subsequently and few reliable ones with positive outcomes were as follows. This was in concurence 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 seperation. 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 stuidied 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 effuions 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 sensitvity 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 effsuions.

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 bio marker / 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 mis placed 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 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>3000microgm/L , matrix mettalloproteinase 2 </equal to 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 effsuion 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 >30mg/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 un complicated 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 >83mg/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 yeild 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 invasiness 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 bio markers 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 met analysis 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 on 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 back drop 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 turn around 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 back ground 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 weight age 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 stastical 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± 4.5mg/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 parapenumonic 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 efuid CRP and pre albumin in the differential diagnosis of infectious from malignant effusions, concluded that pleural fluid pre albumin levels were high in malignant effusions as compared to parapneumonic effusions and the combination of pleural fluid pre albumin and pleural efluid 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 +/-24mg/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 (>/=50mg/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 were 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 over all survival time($p=0.006$).Over all 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 over all survival out come in lung cancer patient and stated that the risk of death for lung cancer patients with a high CRP was 3.909(95% 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>6mg/dl,was significant for a parapneumonic effusion, patients of tubercular effusion had CRP>2mg/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 diffrentiating 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 border line cases.

Waffa et a1[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 a 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.Off 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%)

Symptamatology 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 comorbdities studied in the sixty study subjects, Diabetes Mellitus was seen

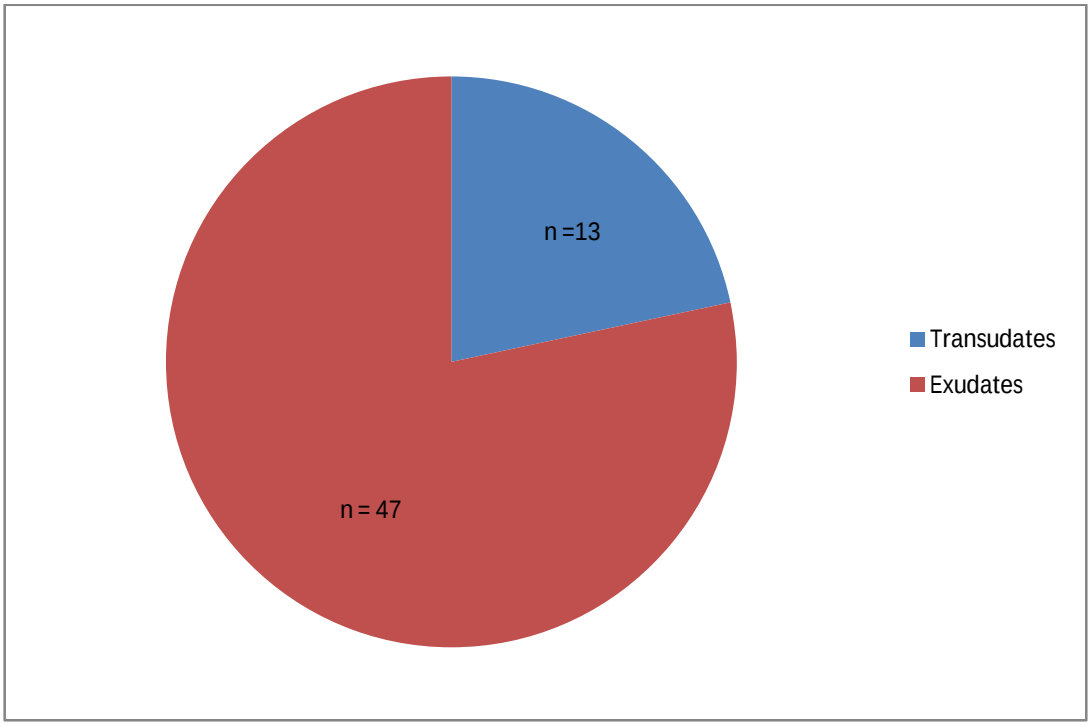
in 20 cases(33.3%),followed by systemic hypertension(13 ,21.7%),coronary artery disease seen in 11 cases(18.3%) and COPD and renal impairment contributed to seven cases each amongst the study subjcets(11.7%) as demonstrated in (Table 1)

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

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

COMPARISION OF STUDY PARTICIPANTS IN TRANSUDATIVE AND EXUDATIVE GROUP

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



COMPARISION 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

EFFUSION TYPE	BMI(Kg/m2)
TRANSUDATIVE	25.95+_1.51
EXUDATIVE	25.22+_1.52

There was no stastical 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.

COMPARISION OF THE AGE AND GENDER DISTRIBUTION AMONGST THE STUDY GROUP

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

TYPE OF EFFUSION	AGE/GENDER
TRANSUDATIVE	59.62±16.50/ 7 –MALES 6-FEMALES
EXUDATIVE	50.98±17.80 / 32-MALES 15-FEMALES

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

EFFUSION TYPE	ALCOHOL	SMOKING
TRANSUDATIVE	4	20
EXUDATIVE	1	9

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).Similary when smoking history was reviewd 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)

COMPARISION 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

SOCIO DEMOGRAPHIC VARIABLES	TRANSUDATIVE EFFUSIONS(N=13)	EXUDATIVE EFFUSIONS(N=47)	P VALUE
AGE(YEARS)	59.62±16.50	50.98±17.80	0.122
GENDER(MALES)	7(53.85)	32(68.1%)	0.341
BMI(KG/M2)	25.95±1.51	25.22±1.52	0.134
SMOKING STATUS	4(30.8%)	20(42.6%)	0.443
ALCOHOL	1(7.7%)	9(19.1%)	0.327

This table compares the clinical variables(symptoms) between the exudative and transudative effusions

Table 6

SYMPTOMS	TRANSUDATIVE	EXUDATIVE
COUGH	6	35
BREATHLESNSESS	9	32
CHESTPAIN	4	15
FEVER	1	19

In the exudative and transudative arms studied, breathlesness 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 breathlesness (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 comorbdities and exudative and transudative effusions

CO MORBID CONDITION	TRANSUDATIVE	EXUDATIVE
COPD	0	7
DM	8	12
SHT	7	8
CAD	8	3
RENAL DISEASE	5	2

Comorbdities 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 comorbdities played no role in the disease out come and was not statistically significant.Thus there was possitive correlation between comorbidities and a transudative effusion.

CLINICAL SYMPTOMATOLGY

Table 9 : This table compares the clinical variables in the study group

SYMPTOMS	TRANSUDATIVE	EXUDATIVE	P VALUE
BREATHLESNESS	9(69.2%)	32(68.1%)	0.957
CHEST PAIN	4(30.8%)	15(31.9%)	0.937
COUGH	6(46.2%)	35(74.5%)	0.052
FEVER	1(7.7%)	19(40.4%)	0.027
HEMOPTYSIS	0	2(4.3%)	0.449
CO MORBID CONDITIONS			
COPD	0	7(14.9%)	0.139
DM	8(61.5%)	12(25.5%)	0.015
HTN	7(53.8%)	8(12.8%)	0.001
CAD	8(61.5%)	3(6.4%)	0.0001
RENAL	5(38.5%)	2(4.3%)	0.001

COMPARISION 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

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

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 an condition of intense inflammation,ESR was expected to be higher in the exudative group.

COMPARISION OF THE BIOCHEMICAL VALUES BETWEEN EXUDATIVE AND TRANSUDATIVE EFFUSIONS

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

BICHEMICAL VALUES	TRANSUDATIVE	EXUDATIVE
TOTAL PROTEINS	6.23+_0.74	6.75+_0.55
ALBUMIN	3.13+_0.39	3.33+_0.50
GLOBULIN	2.99+_0.48	3.41+_0.44

It is found that serum globulin had a postive correlation in seperating 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.

COMPARISION OF THE PLEURAL FLUID PROTEINS BETWEEN THE TRANSUDATIVE AND EXUDATIVE EFFUSIONS.

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

PLEURAL FLUID CHARACTERSTICS	TRANSUDATIVE	EXUDATIVE
PLEURAL FLUID PROTEINS(mg/DL)	1.60+_0.50	4.72+_1.00

In comparison of pleural fluid characterstics 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 differentaiting 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 differentaition of transudates from exudates

COMPARISION OF THE PLEURAL FLUID CHARACTERSTICS IN DIFFERENTIATING EXUDATIVE FROM TRANSUDATIVE PLEURAL EFFUSIONS WITH P VALUE

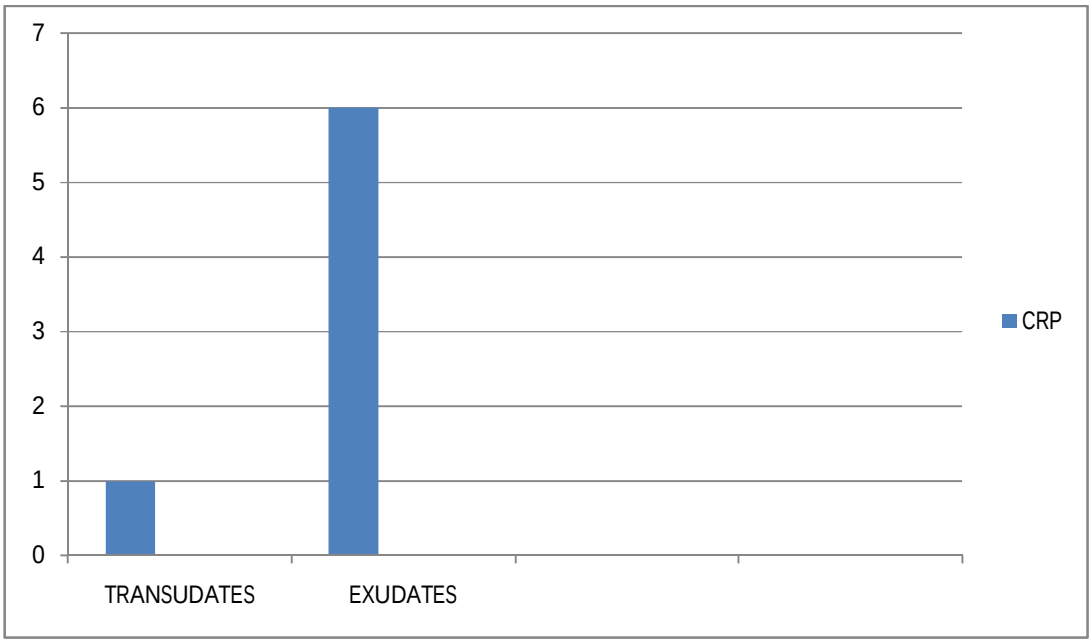
Table 13 : This table depicts the pleural fluid characterstics in differentiating exudative from transudative pleural effusions

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

The above table higlights 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.Similary 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.

COMPARISION OF THE PLEURAL FLUID CRP IN DIFFERENTIATING EXUDATES FROM TRANSUDATES

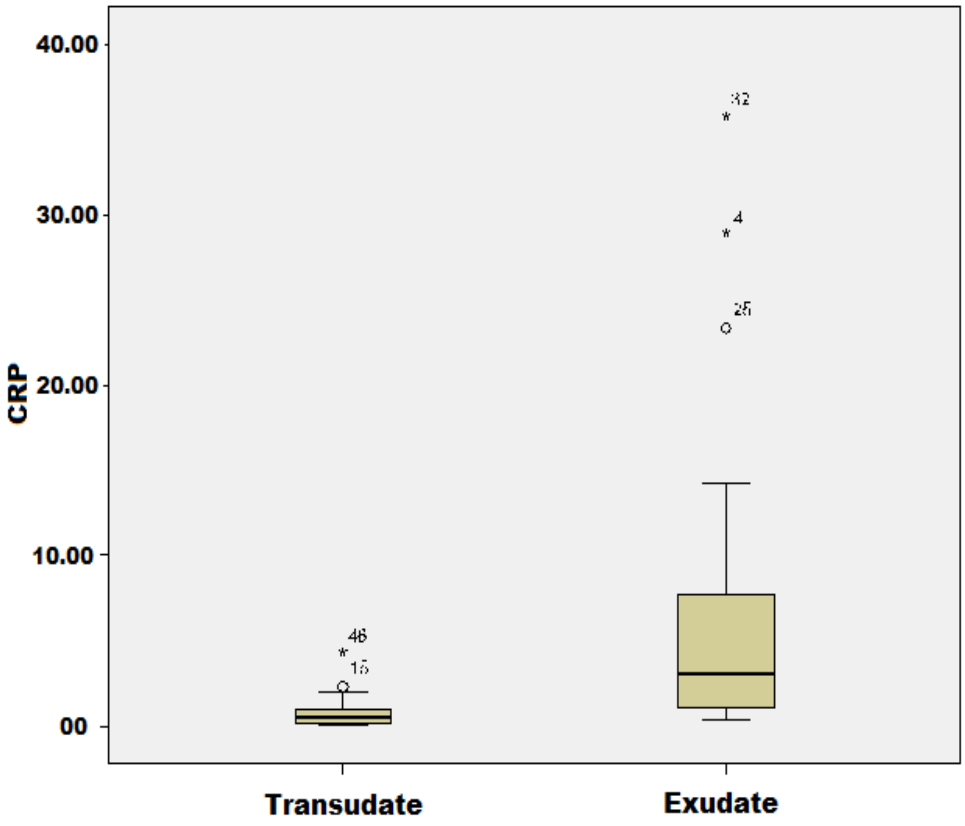
This bar diagram draws comparison of pleural fluid crp in differentiating exudates from transudates



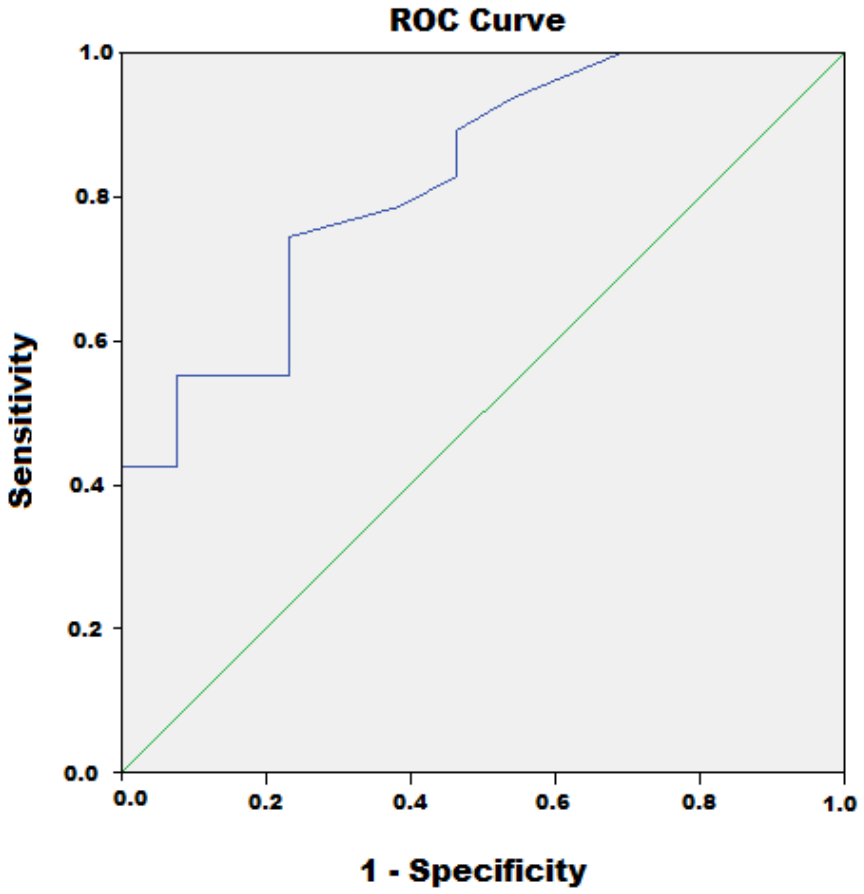
In differentaiting transudates from exudates a mean pleural fluid CRP of 1.03±1.20 was significant for a transudative effusion ,while a pleural fluid CRP of 5.71±7.33 was significant for an exudative effusion with a positive statistical significance with P =0.0001.The result of our study was in accordance with other similar studies and pleural fluid CRP proved to be a useful adjunct in differentaiting exudative from transudative effusions.

Table 14

PLEURAL FLUID CHARACTERS	TRANSUDATIVE	EXUDATIVE	P VALUE
CRP	1.03±1.20	5.71±7.33	0.0001



In analysing the test resulst a pleural fluid CRP of 1.05 had a ROC of 0.82 with sensitivity of 74.5% and specificity of 76.9% for differentaiting netween transudative and exudative effusions



COMPARISION 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

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

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 differntaition between the three exudative groups were not possible

COMPARISION 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

SOCIO DEMOGRAHIC VARIABLES	PARAPNEUMONIC	MALIGNANT	TUBERCULAR
AGE(YRS)	51.93+_15.51	57.60+_13.7	42.6+_21.09
GENDER(MALES)	12	8	11
FEMALES	3	7	4

No significant difference between the variables wer found on analysis.

COMPARISON BETWEEN THE HEMATOLOGICAL VARIABLES AMONG THE EXUDATIVE EFFUSIONS

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

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

The above table depicts the basic hematological paramaters assessed between the various exudative pleural effusions.Though non of the hematological parameters have been proved to be significant in differentaiting 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 statsistical 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

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

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 stuides which found no significant difference amongst the various exudative efuusions based on serum proteins

COMPARING PLEURAL FLUID CHARACTERSTICS AMONGST DIFFERENT EXUDATIVE EFFUSIONS

In comparing the pleural fluid characterstics 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 effusiosns 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 parapenumonic effsuion 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 .

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

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 effuion(85%) as compared to malignant and tubercular effusion

PLEURAL FLUID DIFFERENTIAL COUNT(cells/mm3)	**MALIGNANT**	**TUBERCULAR**	**PARAPNEUMONIC**
NEUTROPHILS	19.2 ± 25.71	23.20±30.71	85.60±17.79

This below mentioned table depicts the,lymphocyte predominance assessd within the exudative effusions and higher pleural fluid lymphocytes were seen in malignant and tubercular effusions as compared to a parapneumonic effusion.

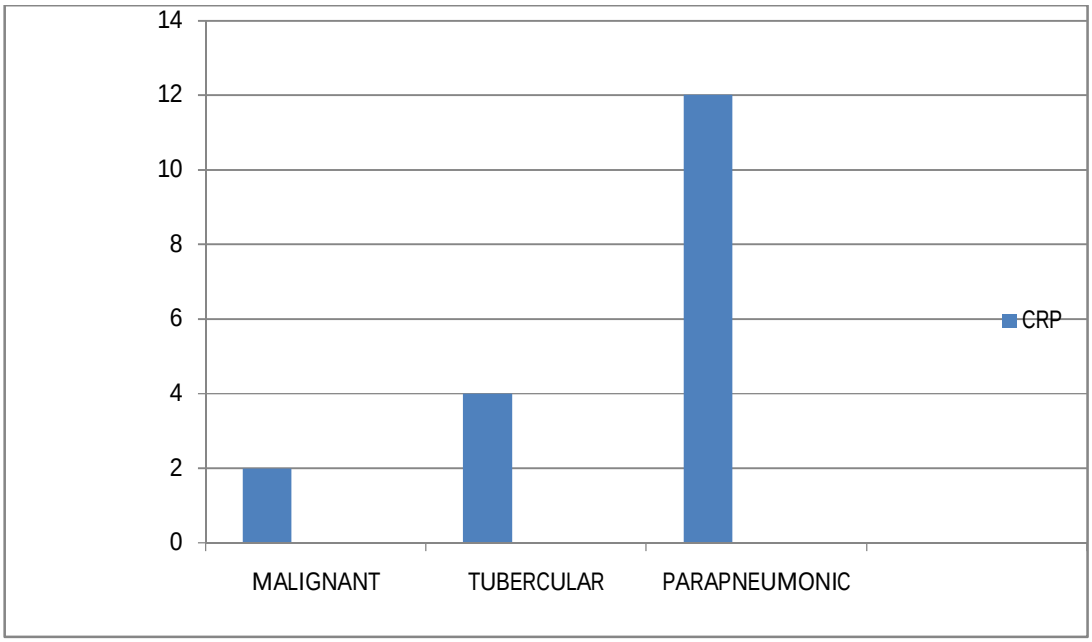
PLEURAL FLUID DIFFERENTIAL COUNT(cells/mm3)	**MALIGNANT**	**PARAPNEUMONIC**	**TUBERCULAR**
LYMPHOCYTES	74±32.56	14.13±17.81	76.53±31.25

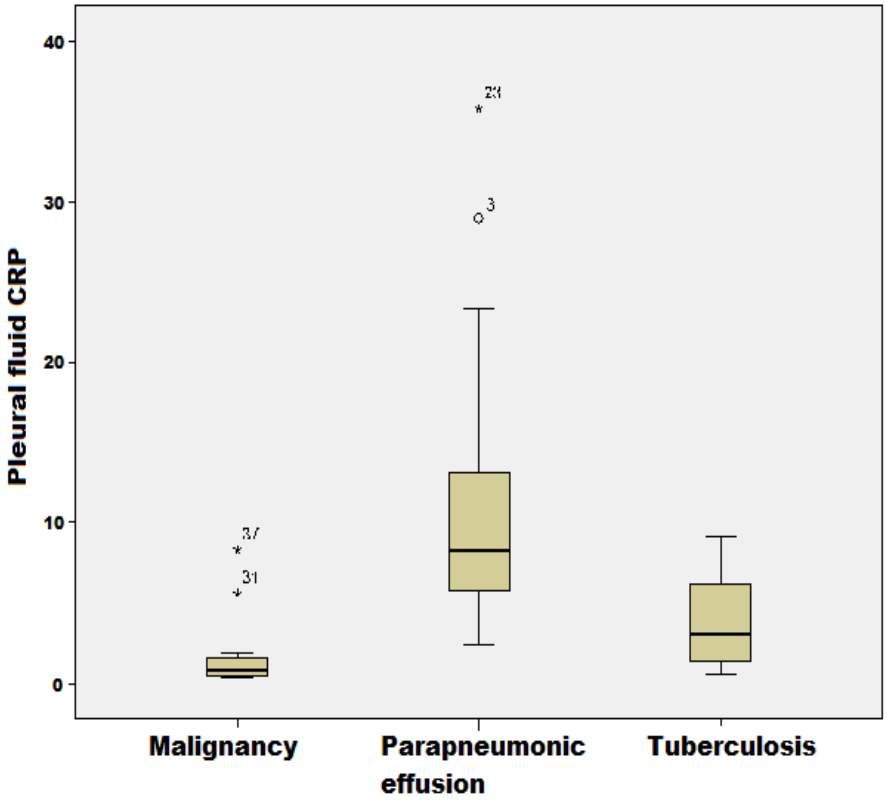
The above mentioned results are in accordance with the similar results obtained from other studies

COMPARISON OF PLEURAL FLUID CRP BETWEEN EXUDATIVE EFFUSIONS

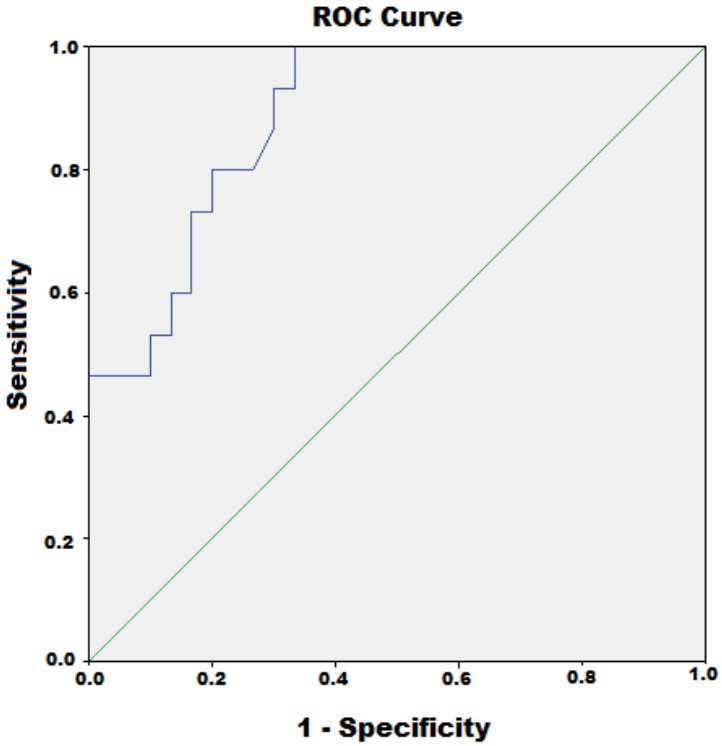
On comparing the pleural fluid CRP values amongst the exudative effusions of varying etiology,it was obsereved that a mean pleural fluid CRP of (1.68±2.24) was observed in malignant effusions,in parapneumonic effusions the mean pleural fluid CRP was (12±9.86) and in tubercular effusions the mean pleural 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 obatined 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 obatined for the differentaition of tubercular and malignant effusions were ROC=0.477 and 0.136 respectively

Similar results wer obtained from other studies which concluded that pleural fluid CRP was an useful adjunct with Lights Criteria for initially differentaiting exudates from transudative pleural effuisons 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

ROC 0.82.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 .

Similary 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[16] in study conducted amongst 187 patients with pleural effusion also found no significant correlation between BMI and the study groups. Similary 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 effsuions,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[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 symptamatology 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 with out 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 groupt 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.Similary 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 differentiaon 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±4013.42) as compared to the transudative group(647±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 ,were in a pleural fluid CRP of 1mg/dL had a sensitivity and specificity of 74% in differentiating exudative from transudative pleural effuions 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 demograhic 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±13.7),for parapneumonic group(51.93±15.51) and tubercular group was (42.6±21.09) 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±11.86 years) as compared to a mean age of (44.12±16.5 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±1.57),for parapneumonic group was(25.78±1.39) and for tubercular group was(24.37±1.22) 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 symptamatology 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 comorbdities 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 differnential 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±8561.05), (713±726.20), (740.8±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 effsuions.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 werein 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 specificty 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(73U/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 diffrence 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 paraneumonic 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 diffrerential 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 effsuions 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 out 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 oue 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

a p<0.002.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 diganosis 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 trasnsudates 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 effuions. The study participants were divded into transudates and exudates and further in exudates the patients were divded 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 differentaiting exudates from transudates and further in differentiating parapneumonic from other exudative effsuions, 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 1.05mg/dL helped in differentiating transudates from exudative pleural effuions.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

BIBLIOGRAPHY

1. Steven Shah .Evaluation of patient with Pleural Effusion *PCCSU Article 1.15.2008*
2. Jose M Porcel .Pleural fluid Biomarkers Beyond Lights Criteria. *Clin Chest Medicine 24(2013) 27-37*
3. Theodoros S,Kiropoulos,Konstantions Kostikas. Acute phase markers for differentiation of infectious and malignant pleural effusions. *Respiratory journal (2007) 101,910-918*
4. R W Light ,M I Macgregor,P.R Luchsinger and W C Ball.Pleural Effusion :the diagnostic seperation of transudates and exudates, *Annals of Internal Medicine,Vol 77,no 4,pp. 507-513,1972*
5. Muzaffer,Ozkan Comparitive analysis of biochemical parameters for differentiation of pleural exudates:Lights Criteria,cholestrol,bilirubin,albumin gradient,alkaline phosphatase, creatine kinase and uric acid . *8981:((97) 91-100*
6. H .Hamm ,Alfered,Hamburg .Cholestrol in pleural effusions,A Diagnostic Aid.*Chest Vol.92 (2) 296-307 1987.*
7. R.Guleria,S.R Agarwal.Role of pleural fluid cholestrol in differentiating transudative from exudative pleural effusion.*Natl Med J India 2003;16: 64-69*
8. Simcha Meisel, Arie Shamiss.Pleural fluid to Serum Bilribuin Concentration Ratio for The Seperation of Transudates from Exudates. *Chest 1990; 98:141-144*

9. BielsaS,Castellote.Solving the Lights criteria misclassification rate of cardiac and hepatic transudates. *Respirology Asian Pacific Society of Respirology 2012*

10. T.Hassan ,M AL Alwai.Pleural fluid Analysis:Stand still or Work in Progress? *Royal College of Surgeons Ireland 2011(9) 110-130*

11. Perlat ,Oner Dikenosoy .Acute Infalmmation Biomarkers in Pleural Effusion.*Turkey:2012 (9)15-30*

12. MG.Alexandrakis, Coulocheri .Significance of Alpha 2 Macroglobulin, Alpha 1 Acid Glycoprotein, CRP in pleural Effusion Differentiation. *Respiration 2000:67:30-35*

13. Skouras,Boultadakis Prognostic value of CRP in parapneumonic Effusions. *Respirology 2011 Feb(2) 308-314*

14. J.M Porcel.Tuberculosis pleural Effusion 2009 .*Lung Vol 187:263-270*

15. San Jose,Valdess L.Procalcitonin,CRP and cell counts in the diagnosis of parapneumonic pleural effusions.*Journal Investig Med 2010 Dec 58(8) 971-976*

16. Yadav.Usefuleness of pleural fluid CRP level in differential diagnosis of exudative pleural effusion-Pilot Study. *International Journal of Clinical Biochemistry and Research,April-June 2015(2) 97 -109*

17. Hoda Abu Yossef,Sherif.Value of CRP in Etiological Diagnosis of Pleural Effusion.*Egyptian Journal Of Bronchology Vol 4 (2) 124-130*

18. Huang .Pleural fluid CRP in diffrential diagnosis of pleural effusion. *Experimental and Thereputic Medicine 8:784-789.*

19. Garcia Pachon E,Soler.CRP in lymphocytic pleural effusions:A diagnostic aid in tuberculous pleuritis.*Chest 2006 113-120*

20. Do Sim Park,Dong Kim.Diagnostic Value and Prognostic Significance of Pleural CRP in Lung Cancer Patients with Malignant Pleural Effusions. *Yonsei Med Journal 54 (2) 396-402,2013*

21. Scott HR, Mc.Millian.The systemic inflammatory response,weight loss,performance status and survival in patients with inoperable non small cell lung cancer *Br.J Cancer 2002:87 264-267*

22. Aliya Nusarth,Maithiri.Efficacy of pleural fluid ADA and CRP in early differentiation of pleural effusions. *Journal of Evolution of Medical and Dental Sciences Vol2 Issue 22 June 3,2013*

23. Castano Vidriales.Use of pleural fluid CRP in lab diagnosis of pleural effusions. *Eur J Med.1992 Jul-Aug ;1(4) 201-207*

24. .Waffa S,ElShimy,Ghada.Diagnostic value of procalcitonin and CRP in differentiation between some benign and malignant pleural effusions. *Egyptian Journal of Chest Diseases and Tuberculosis 2014 63, 923-930*

25. Mona Mansour Ahmed.Cut Off value of pleural fuid CRP in etiological diagnosis of pleural fluid. *Egyptian Journal of Chest Diseases and Tuberculosis 2014 63,617-623*

26. Sanjay D Gabhale,Pallavi .Usefulness of pleural fluid CRP level in differential diagnosis of Exudative Pleural Effusions-A Pilot Study *International Journal of Clinical Biochemistry and Research, April June 2015:2(2) 97-109*

27. Qiaoying Ji Bifei Huang.Pleural fluid prealbumin and CRP in differential diagnosis of infectious from malignant pleural effusions. *Experimental and Therapeutic Medicine 7: 778-784 2014*

28. Amitabha Basu,Indrani C.A clinicopathological study of tuberculous pleural effusion in a tertiary care hospital .*Annals of Tropical Med.and Public Health 2012:5(3) 168-172*

29. Wipa R Theesrasuk,Yaovalak.Diagnostic Role of pleural fluid Adenosine Deaminase in tubercular pleural effusion. *South East Asia j Trop Med Public Health 2001:32(2):383-389.*

30. Burgess LJ,Martiz FJ.Use of adenosine deaminase as a diagnostic tool for tuberculous pleurisy. *Thorax 1995 50(6):672-674*

31. Garcia EP.Mesothelioma,ADA and CRP.*Arch Bronconeumol 2005:41(3):175*

32. Verma SK,Dubey AL.Adenosine levels in Tubercular pleural Effusion. *Lung India 2008:25(3):109-110*

33. Trajman. Evaluation of pleural fluid differential count in diagnosis of pleural effusion.

34. Ylimaz Turay,Yildirim Use of pleural fluid CRP in diagnosis of pleural effusions. Turkey. *RespirMed .2000 May 94(5):432-435*

35. Motoki S,Kiminikho.Pleural fluid ADA level and occult tubercular pleurisy.*Ann Thoracic cardiovascular surgery 2009:15(5):294-296*

36. Jimenez DC,Diaz .Diagnostic value of ADA in non tuberculous lymphocytic pleural effusion. *Eur. Resp Journal 2002;13(4):246-249*

37. Garcia EP.Diagnostic value of CRP in exudative pleural effusion. *Eur.Journal Internal Medicine 2002;13(4) 246-249*

38. Okamura JM,Miyagi JM.Potential clinical applications of CRP. *Journal of Clini.Lab 1990;4:231-235*

39. Arun G,Sethu MM,Surendra.Diagnosis and treatment of tubercular pleural effusion 2006 C*hest 2007:131(3):880-889*

40. Rafael LL.ADA in the diagnosis of tubercular pleural effusion.Is it really an Ideal test?A word of caution. *Chest 2005:127(2):417-418*

Annexures

ABBREVIATIONS

COPD	:	Chronic Obstructive Pulmonary Disease
DM	:	Diabetes Mellitus
SHT	:	Systemic Hypertension
CAD	:	Coronary Artery Disease
MPE	:	Malignant Pleural Effusion
TPE	:	Transudative Pleural Effusion
CPPE	:	Complicated ParaPneumonic nEffusion
PPE	:	Parapneumonic Effusion
LDH	:	Lactate Dehydrogenase
MR pro ANP	:	Mid Regional Atrial Natriuretic Peptide
AAG	:	Alpha 1 Acid Glycoprotein
AMG	:	Alpha 2 MacroGlobulin
LBP	:	Lipo polysacchride Binding Protein
TNF	:	Tumor Necrosis Factor
VEGF	:	Vascular Endothelial Growth Factor
BNP	:	Brain Natriuretic Peptide
NT-proBNP	:	N Terminal Brian Natriuretic Peptide

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 senstivity CRP
hs CRP	:	High sensitivity CRP

PSG Institute of Medical Science and Research, Coimbatore
Institutional Human Ethics Committee
INFORMED CONSENT FORMAT FOR RESEARCH PROJECTS

(strike off items that are not applicable)

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 √ 2. Research purpose

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

ஒப்பதல் படிவம்

தேதி

அருண் ஆர். தாமஸ் ஆகிய நான் PSG மருத்துவக்கல்லூரியின் **நுரையீரல் மருத்துவதுறையின்** கீழ் **"சி.ஆர்.பி. யின் அளவு கொண்டு புளூரல் எ.ீப்யூசன் என்னும் நோயை வகைப்படுத்துதல்"** என்ற தலைப்பில் ஆய்வு மேற்கொள்ள உள்ளேன்

என் ஆய்வு வழிகாட்டி : மரு. அனுபமா மூர்த்தி

ஆய்வு மேற்கொள்வதற்கான அடிப்படை

புளூரல் எ.ீப்யூசன் என்பது நுரையீரலை சுற்றி உள்ள புளூரல் மெம்பரைன் இடையே சேரும் நீர் இவற்றை எக்ஸ்யூடேட் மற்றும் பிரான்ஸ்டேட் என்று வகைப்படுத்தலாம். இதனை கண்டறியவும் எக்ஸ்யூடேட் புளூரல் எ.ீப்யூசனின் காரணத்தை கண்டறியவும் புரோட்டீன்ஸ் எல்.டி.ஹெச் என்ற பரிசோதனைகள் உள்ளது. இவ்வகைப்பாட்டினை சி.ஆர்.பி என்ற பரிசோதனை மூலமும் கண்டறியலாம் என்பதை பலர் சுட்டிக் காட்டியுள்ளனர்.

ஆய்வின் நோக்கம்

1. சி.ஆர்.பி உதவியினால் புளூரல் எ.ீப்யூசனின் எக்ஸ்யூடேட்வ் காரணங்களை வகைப்படுத்துதல்.
2. இவ்வாறு சி.ஆர்.பி.யினால் வகைப்படுத்துவதை மற்ற பரிசோதனைகளுடன் ஒப்பிடுதல்.

ஆய்வில் பங்கு பெறும் நபர்களின் எண்ணிக்கை : 70 நபர்கள்

ஆய்வு மேற்கொள்ளும் இடம் : பி.எஸ்.ஜி மருத்துவமனை,
நுரையீரல் மருத்துவ துறை

ஆய்வின் பலன்கள் :

இந்த ஆய்வின் மூலம் புளூரல் எ.ீப்யூசினனை சி.ஆர்.பி உதவி கொண்டு வகைப்படுத்தலாம்.

ஆய்வினால் ஏற்படும் அசௌகரியங்கள் / பக்க விளைவுகள் :

நீரை பரிசோதனைக்கு ஊசி மூலம் எடுக்கும போது வலி ஏற்படும் மற்றபடி வேறு பக்க விளைவுகள் இருக்காது.

இந்த ஆய்வில் கிடைக்கும் தகவல்கள் 12 வருடங்கள் பாதுகாக்கப்படும். இவை வேறு எந்த ஆய்விற்கும் பயன்படுத்தப்பட மாட்டாது. எந்த நிலையிலும் உங்களைப் பற்றிய தகவல்கள் யாருக்கும் தெரிவிக்கப்பட மாட்டாது. இவை இரகசியமாக வைக்கப்படும்.

இந்த ஆய்வில் பங்கேற்க ஒப்புக் கொள்ளுவதால் எந்தவிதமான பலனும் உங்களுக்கு கிடைக்காது. எந்த நேரத்தில் வேண்டுமானாலும் ஆய்விலிருந்து விலகிக் கொள்ளும் உரிமை உங்களுக்கு உண்டு.

ஆய்விலிருந்து விலகிக் கொள்வதால் உங்களுக்கு அளிக்கப்படும் சிகிச்சையில் எந்த வித மாற்றமும் இருக்காது.

இந்த ஆராய்ச்சிக்காக உங்களிடம் சில கேள்விகள் கேட்கப்படும் / சில இரத்த மாதிரிகள் அல்லது திசு மாதிரிகள் எடுக்கப்படும்.

மேலும் இந்த ஆய்வில் பங்கு கொள்வது உங்கள் சொந்த விருப்பம். இதில் எந்த விதக் கட்டாயமும் இல்லை. நீங்கள் விருப்பப்பட்டால் இந்த ஆய்வின் முடிவுகள் உங்களுக்குத் தெரியப் படுத்தப்படும்.

ஆய்வாளரின் கையொப்பம் :

தேதி :

ஆய்வுக்குட்படுபவரின் ஒப்புதல்

நான் இந்த ஆராய்ச்சியின் நோக்கம் மற்றும் அதன் பயன் பாட்டினைப் பற்றி தெளிவாகவும் விளக்கமாகவும் தெரியப்படுத்தப்பட்டுள்ளேன். இந்த ஆராய்ச்சியல் பங்கு கொள்ளவும் இந்த ஆராய்ச்சியின் மருத்துவ ரீதியான குறிப்புகளை வரும் காலத்திலும் உபயோகப்படுத்திக் கொள்ளவும் முழு மனதுடன் சம்மதிக்கிறேன்.

ஆய்வுக்குட்படுபவரின் பெயர், முகவரி :

கையொப்பம் :

தேதி :

மனித நெறிமுறைக் குழு அலுவலகத்தின் தொலைபேசி எண். 0422-2570170 Extn. 5818

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

Name: …….

Informant: ……..

Age / sex: ……

CRC. No : ……

Father's / Husband's name: ……

Address: ……

Height: …… Weight: ……

……..

BMI: ……

……..

PSG OP No: _____

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……

- 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……

Family History: *(mention relationship where relevant)*

- Atopic diseases……
- Hypertension……
- Diabetes mellitus……
- Hypo/hyperthyroidism……
- Other endocrine disorders……
- Lung diseases ……
- Heart diseases……
- Kidney diseases……
- Obstetric history / Gynaecological 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

Sl.No	Name	Age	Gender	BMI	FI	Diet	Smoking	Pack Years	Status	Alcohol	Quantity	Status	Dyspnea	Chestpain	Cough	Fever	Pl.Effusion	Hemoptysis	COPD	DM	HTN	CAD	Renal	P/A	TLC	Platelets	Hb	ESR	pl.LDH	ADA	Glucose	Protein	Cytology	TC	Lymphocytes	Neutrophils	CRP	T.Proteins	Alb	Glb	S.LDH	Diagnosis
1	Mrs.Ruckmani	56	0	23.3	8000	0	0	0	0	0	0	0	2	0	0	0	0	0	0	1	0	0	0	1	11,300	3,75,000	9.6	40	127	11	103	3.7	0	980	98	2	0.5	6.2	3.4	2.8		0
2	Mr.Chandran	58	1	26.6	10,000	1	1	30	2	0	0	0	3	1	1	0	1	0	1	1	0	0	0	0	9,900	2,56,000	17.3	23	454	9.7	103	4.2	2	380	99	1	0.8	7.8	4.8	3		0
3	Mrs.Sangeetha	28	0	24.2	9000	1	0	0	0	0	0	0	2	0	0	0	2	0	0	0	1	0	1	0	11,000	1,53,000	8.5	60	73	1.4	118	1.2	0	80	93	7	0.1	5.9	3.3	2.6		3
4	Mr.Vikash	28	1	25.6	10,000	1	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0	18,700	2,67,000	12.2	106	3700	97.7	90	5	2	6400	1	99	29	6.2	3.2	3		1
5	Mr.VinothKumar	27	1	25.5	7000	1	1	10	1	0	0	0	2	0	1	1	1	0	0	0	0	0	0	0	12,000	3,40,000	14.5	65	333	48.2	79	5.6	1	2820	99	1	9.1	6.2	3.2	3.8		2
6	Mrs.Kousalya	58	0	26.5	9000	0	0	0	0	0	0	0	2	1	1	0	0	0	0	0	0	0	0	0	9,300	2,99,000	13.3	36	247	12	149	4.3	2	520	98	2	0.7	6.9	4.3	2.6		0
7	Mrs.Subbathal	74	0	27.3	8000	1	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	13,200	4,46,000	6.2	18	147	5.4	110	3.3	0	2400	55	45	1.93	6.5	2.7	3.8	110	3
8	Mr.Govindaraj	50	1	26.6	4000	1	1	20	2	1	300	1	2	1	0	1	1	0	1	0	0	0	0	1	13,100	2,72,000	9.6	75	1090	27.7	296	4.1	2	13,000	10	90	9.8	6.6	3.7	2.9		1
9	Mr.Balakrishnan	49	1	28.6	3500	1	0	20	2	0	0	0	1	0	1	1	1	0	0	0	0	0	0	0	7,400	2,83,000	14.9	35	195	29.3	104	5.4	1	2500	99	1	0.4	8	4.1	3.9		0
10	Mrs.Gajalakshmi	73	0	26	8000	0	0	0	0	0	0	0	0	1	0	0	2	0	0	1	1	1	0	0	13,300	2,55,000	8.5	33	59	3.4	149	1.2	0	800	40	60	0.5	6.5	3.2	3.3		3
11	Mr.SaddikAli	37	1	28	6000	1	1	30	2	1	800	1	0	1	1	0	2	0	0	0	0	0	0	1	9,400	1,27,000	11.3	44	151	6.9	117	2.6	2	850	62	38	1	5.5	2.6	2.9	515	3
12	Mrs.Visalatchi	50	0	25.7	4500	1	0	0	0	0	0	0	1	0	0	0	1	0	0	1	1	1	1	0	8,000	2,16,000	8.4	35	50	5.8	60	1.6	0	60	85	15	0.8	6.1	3.4	2.7		3
13	Mr.Govindan	80	1	28	9000	1	0	0	0	0	0	0	1	0	1	0	2	0	0	0	1	0	0	1	7,200	2,33,000	8.6	28	108	3	101	2.5	1	600	99	1	0.2	6.8	3.7	2.6		3
14	Mr.LakshmiNarayanan	40	1	27.2	6500	1	0	0	0	0	0	0	1	0	1	0	2	0	0	1	1	1	1	0	13,900	4,46,000	7.7	52	160	4.9	102	3.5	2	780	74	17	2.8	6.5	2.6	2.9	600	3
15	Mrs.Vijayalakshmi	62	0	23.5	7000	0	0	0	0	0	0	0	1	0	1	0	0	0	0	1	1	1	1	0	9,900	2,56,000	9.9	64	123	5.6	229	2	0	780	85	15	2.32	6.5	3.8	2.6		3
16	Mr.Krishnan	52	1	24	4000	1	0	0	0	0	0	0	1	0	1	0	0	0	0	1	0	1	0	1	6,000	2,05,000	9.7	41	89	3.1	103	1.9	1	560	94	6	0.2	6	3.2	2.8		3
17	Mr.Rathinvel	54	1	25.6	9000	1	1	20	1	0	0	0	0	0	1	0	1	0	0	1	0	0	0	1	7,900	3,32,000	12.7	40	534	43	203	5.5	1	1300	83	17	0.6	8.4	4.5	3.9		2
18	Mrs.Bagarth	29	0	23.5	5800	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	8,000	4,12,000	10.8	90	542	53.1	274	5.3	2	11,500	80	20	8.7	6.5	3.3	3.5		2
19	Mr.Subramani	60	1	25.6	3500	1	1	40	2	1	800	1	1	0	1	1	2	0	0	0	0	0	0	0	5,600	6,21,000	9.2	91	409	50.9	55	4	1	650	98	2	3	6.3	3	3.3		2
20	Mr.EdwinThomas	31	1	24.4	7000	1	0	0	0	0	0	0	1	1	1	1	2	0	0	0	0	0	0	0	4,900	3,03,000	14.5	50	496	80.9	79	5.7	1	3,800	96	4	1	5.7	3.4	3.2		2

21	Mr.Nataraj	70	1	25	8000	1	1	10	1	0	0	0	1	0	0	0	2	0	0	0	0	0	0	0	10,800	4,50,000	12.3	56	110	43.4	91	5.5	1	2940	95	5	1.4	7.5	4	3.5		2
22	Mr.Murugesan	19	1	23.3	0	1	0	0	0	0	0	0	1	1	1	0	2	0	0	0	0	0	0	1	7,000	4,81,000	11.1	24	356	37.6	60	3.8	2	12,000	16	80	7.4	6.8	2.8	3.3		2
23	Mrs.Revathi	27	0	25	6000	1	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	0	0	0	4,600	3,93,000	10.5	43	277	53.3	106	5.1	1	850	96	4	1	6.7	3.1	3.6		2
24	Mr.Myilasamy	54	1	26	8000	1	0	0	0	0	0	0	1	1	1	0	2	0	0	0	0	0	0	1	5,700	2,17,000	12.3	33	3074	125	2	6.5	2	740	42	58	1.42	7.1	3.3	3.8		2
25	Mr.Palanisamy	57	1	27	4000	1	0	0	0	0	0	0	1	0	1	1	2	0	0	1	0	0	0	0	14,800	3,72,000	11.2	60	3273	57.3	192	4.8	2	2500	1	99	23.4	6.8	3.8	3.2		1
26	Mrs.Bagyalakshmi	70	0	25	9600	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	1	0	0	0	13,600	3,56,000	10.5	112	759	46.5	0.8	2.6	2	8000	10	90	14.2	6.8	3.4	3.4	317	1
27	Mrs.Lakshmi	53	0	24.5	7800	1	0	0	0	0	0	0	0	1	1	0	0	0	0	0	1	0	0	1	14,000	3,73,000	9	114	483	13.3	79	4.7	2	800	52	48	1.6	6.5	3.3	3.6		0
28	Mr.KumaranNair	70	1	23	7800	1	1	30	2	1	600	1	1	0	1	0	0	0	1	1	0	0	0	0	8,800	3,06,000	12.8	46	115	38.2	248	5.4	2	1520	93	7	5	6	3.2	3		2
29	Mr.Chinnasamy	46	1	26	7000	1	1	25	2	0	0	0	0	0	1	1	1	0	1	0	0	0	0	0	9,100	57,000	8.6	65	500	17.2	106	3.5	2	7360	11	85	5.5	6	3.7	2.3		1
30	Mr.Kalisamy	50	1	26	7500	1	1	30	2	1	800	2	1	1	0	0	1	0	1	1	1	1	0	0	17,600	2,26,000	13.9	80	804	21.2	138	3.8	2	5120	40	60	8.2	6.2	3.1	3.1		1
31	Mr.Somasundaram	48	1	28	6000	1	1	20	1	1	800	2	0	0	0	0	0	0	0	1	0	0	0	1	6,000	67,000	10.8	60	642	24.2	85	4.3	0	3800	8	92	4.1	7.1	2.8	4.3		1
32	Mr.Palanisamy	61	1	26.2	7000	1	1	25	1	0	0	0	1	0	1	1	0	1	0	1	0	0	1	0	19,700	4,67,000	12	108	34120	469	105	5.6	0	15960	2	98	35.8	7.1	3.5	3.6		1
33	Mr,Thangavel	67	1	25	7600	1	1	20	2	0	0	0	1	0	1	1	1	0	0	0	0	0	0	1	12,900	2,99,000	11.6	51	2921	24.1	1	3.9	0	1300	10	90	3.1	6.7	2.8	3.9		1
34	Ms.Karthika	21	0	23	0	1	0	0	0	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	20,500	3,25,000	8.7	130	354	12.8	92	4.5	2	5000	13	87	7.7	7.2	3.1	4.1		1
35	Mrs.latha	35	0	24	8000	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	22,800	3,47,000	11.3	90	673	36.9	85	6.7	0	8960	67	33	6	6.8	2.4	3.2		1
36	Mr.Natchimuthu	61	1	25	7800	1	1	20	2	1	600	2	0	0	1	1	1	0	0	1	0	0	0	0	18,400	2,36,000	10.8	102	261	9.5	222	3.7	1	8320	2	98	12	6	2.9	3.1		1
37	Mr.Palanisamy	75	1	27	9000	1	1	20	1	1	500	1	1	0	1	0	1	0	0	0	0	0	0	0	30,000	2,35,000	13.8	11	533	13.1	182	3.7	0	3520	3	97	11.5	5.8	3.4	3.4		1
38	Mr.Bharathan	45	1	27.8	10,000	1	0	0	0	0	0	0	1	0	1	0	1	1	0	0	0	0	0	0	13,700	1,64,000	13.8	30	1054	16.9	6	3.5	2	600	24	76	2.4	6.1	3.7	2.4	573	1
39	Mr.Marimuthu	65	1	24.5	0	1	1	30	1	1	400	1	0	1	0	0	1	0	0	0	0	1	0	1	16,300	3,85,000	8.9	56	814	22.2	105	4.5	2	11,000	10	90	7.3	7.4	2.7	4.6		1
40	Mr.Mariappan	81	1	25.6	5,600	1	0	0	0	0	0	0	1	0	1	0	1	0	0	0	1	0	0	0	11,100	3,46,000	7.9	87	2688	20.8	43	5.5	2	0	0	0	5.6	6.8	3.2	3.4		0

41	Mrs.Poovathal	75	0	25.3	3,500	1	0	0	0	0	0	0	1	0	1	0	0	0	0	0	1	0	0	1	8,000	3,64,000	13.2	35	187	13.7	132	6	2	120	98	2	0.4	6.9	3.2	3.5		0
42	Mr.MaheshPrabhu	21	1	25.7	0	1	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	1	8,800	1,63,000	9.6	92	162	35.2	92	5.3	1	680	80	20	4.1	6.5	3.3	3.8		2
43	Mr.Subramani	63	1	26.7	8,500	1	1	20	0	0	0	0	1	0	1	0	2	0	0	1	1	1	1	0	11,400	2,98,000	7.6	15	249	4.8	210	1.2	0	850	32	68	0.4	6.5	2.8	3.2		3
44	Mr.RangaNaicker	75	1	24.3	8,000	1	1	10	0	0	0	0	1	0	0	1	2	0	0	0	1	1	0	0	7,600	2,62,000	9.6	25	58	2.6	116	1.1	0	180	88	12	0.2	6.2	2.6	3.4		3
45	Mr.Kuppusammy	85	1	26.7	10,000	1	1	10	0	0	0	0	0	0	1	0	2	0	0	0	0	1	0	0	5,800	2,16,000	12.8	41	56	2.8	103	1.5	0	460	98	2	0.4	5.8	3.2	3.3		3
46	Mr.Sivaprakashma	55	1	26.3	7,000	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	1	1	13,600	1,27,000	7.6	51	217	10.1	107	1.6	0	2320	68	32	4.3	4.7	2.6	2.1		3
47	Mrs.RadhaBhai	64	0	27.3	0	1	0	0	0	0	0	0	1	1	0	0	0	0	0	1	0	1	0	0	11,800	2,46,000	12.3	34	61	3.1	240	1.4	0	80	95	5	1	6.8	3.2	3.6		3
48	Mrs.Uthamai	51	0	26.7	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	1	11,700	4,69,000	10.6	69	48	2.1	118	1.1	2	800	77	22	2	7.8	3.2	3.8		3
49	Mr.Karuppusamy	50	1	23.4	6,000	1	1	40	0	0	0	0	1	0	1	0	1	0	1	0	0	0	0	0	20,900	2,16,000	14.8	11	102	6.8	64	4	2	200	70	30	0.5	6.8	3.2	3.6		0
50	Mrs.Devi	67	0	24	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	9,000	4,90,000	10.9	50	1120	18.2	134	4.6	2	1000	77	23	1.1	7	3.8	3.2		0
51	Mr.Rajagopal	75	1	27.2	15,000	1	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	1	9,200	1,70,000	10	35	177	11.4	140	4.4	2	500	78	22	0.7	6.8	3.4	3.3		0
52	Mr.Ghouse	43	1	24.3	4,000	1	1	30	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	300	27,000	7.9	120	1563	81.1	67	5.2	0	7000	10	90	8.3	6.4	2.2	3.4		0
53	Mrs.Chellam	47	0	23.5	0	1	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	8,900	3,12,000	12.8	60	523	18	66	6.3	2	800	90	10	0.4	6.8	3.2	3.6		0
54	Mr.Raja	28	1	24	4,000	1	0	0	0	0	0	0	0	0	1	1	2	0	0	0	0	0	0	1	6,300	3,58,000	10.8	59	1082	57.6	89	4	1	1960	93	7	1.5	7.1	3.5	3.5		0
55	Mr.Bhaskaran	64	0	26.1	10,000	1	1	40	0	0	0	0	1	0	1	0	1	0	1	0	0	0	0	0	13,400	2,50,000	17.3	1	382	25.1	124	6.1	2	3200	50	48	1.9	7.1	3.8	3.3		0
56	Mr.Rangesh	52	1	24	6,000	1	1	30	1	1	300	1	1	0	1	0	1	0	0	1	0	0	0	0	14,600	5,38,000	12.8	90	2722	93	6	4.6	1	3600	3	97	4.8	6.8	3	3.8		2
57	Ms.Aishwarya	18	0	22	0	1	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	5,500	1,85,000	11.7	30	648	68.6	80	5.4	1	2220	70	30	1.8	7.7	3.6	3.3		2
58	Mr.Karuppan	80	1	24	6,000	1	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	0	0	85,000	1,67,000	6	60	478	30	81	6.7	1	2000	99	1	1.52	6.7	3.3	3.4		2
59	Mrs.Vimala	27	0	23	3,500	1	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	7,100	1,87,000	10.7	85	856	54.7	62	5.2	2	3800	98	2	7.72	6.8	3.6	3.7		2
60	Mr.Palanisamy	60	1	26	6,000	1	1	30	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	15,000	5,55,000	12	26	1366	11.9	83	3	2	9600	98	2	0.8	6.8	3.3	3.5	964	0