PLEURAL FLUID PSEUDOCHOLINESTERASE AND ITS RATIO TO SERUM PSEUDOCHOLINESTERASE: FOR DIFFERENTIATING PLEURAL TRANSUDATES FROM EXUDATES

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CERTIFICATE FROM THE DEAN

This is to certify that this dissertation entitled "**pleural fluid pseudocholinesterase and its ratio to serum pseudocholinesterase -for differentiating pleural transudates from exudates**" is the bonafide work of **DR. ARUN GOVIND**, in partial fulfilment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine, Branch I examination to be held in April 2018.

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This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai in partial fulfilment of the rules and regulations for the award of M.D Degree General Medicine Branch- I examination to be held in April 2018.

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INTRODUCTION

INTRODUCTION

Collection of abnormal quantity of fluid within the pleural space is called pleural effusion . It is a common clinical condition known since the time of Hippocrates (641 – 539 B.C) and still commonly encountered in everyday practice. A correct diagnosis of the underlying disease is essential for the management of pleural effusion. Due to the various etiologies that can cause a pleural effusion, it may often cause a diagnostic dilemma. The initial step in the evaluation of pleural effusion is to differentiate it as either an exudate or a transudate; as this gives an indication of pathophysiological mechanisms, differential diagnosis and the need for further investigation.

Many criteria have been used to distinguish pleural exudates from transudates, but none of them have been found to be satisfactory. Light's criteria is the most commonly used method

According to Light's criteria ,one or more of the following are required to diagnose Exudates.

1. Pleural fluid protein / Serum protein>0.5

2. Pleural fluid LDH/ Serum LDH >0.6

3. Pleural fluid LDH more than 2/3rd of the upper limit of serumLDH

It was found that even Light's criteria misclassified a large number of effusions - 25% of transudates as exudates and 2-3% exudates as transudates (total ~7.8% misclassification rate)

Several alternative parameters have been proposed in segregating the transudates from exudates more reliably than those of Light's criteria [such as pleural fluid(PF)cholesterol level, PF to serum cholesterol ratio, PF to serum bilirubin concentration ratio, alkaline phosphatase value, and serum-pleural effusion albumin gradient]. The pleural fluid pseudocholinesterase level and pleural fluid/serum pseudocholinesterase ratio are newer alternative parameters postulated to be better differentiator of transudates from exudates

Hence, this study is done to evaluate the usefulness of pleural fluid pseudocholinesterase(PChE) level and its ratio with serum pseudocholinesterase in order to differentiate between transudates and exudates.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

PRIMARY AIM

To evaluate the usefulness of pleural fluid pseudocholinesterase (PChE) level and its ratio with serum pseudocholinesterase in order to differentiate between transudates and exudates.

SECONDARY AIM

To compare the diagnostic efficacy of: (1) pleural fluid PChE value and (2) pleural fluid PChE to serum PChE ratio; with the efficacy of Light's criteria

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Even though the pleural space is a very thin space between the visceral and parietal pleura, it plays a very important role in the normal breathing mechanism. It acts as a lubricating area that allows for the normal lung movements. The membrane that covers the chest wall cavity is the parietal pleura while the membrane covering the lung surface and dips into the fissures between the lobes is the visceral pleura. Normally there is 15-20 ml of pleural fluid between these membranes, which prevents the friction during inspiration and expiration. In normal individuals, these two layers are in contact with each other. These two layers are continuous with each other around and below the root of hilum. The mediastinum separates the right and the left pleural space.

PARIETAL PLEURA

The parietal pleura is the one that lines the chest wall, covers the domes of the diaphragm and is reflected medially over the structures of the mediastinum. Depending on the location, different parts of the pleura have different names:

- Costal pleura – lines the inner surface of the ribs and intercostal muscles
- Diaphragmatic pleura – lines the convexities of the diaphragm
- Cupula of the pleura (cervical pleura) – lines the summit of the lungs and is seen at the neck level

- Mediastinal pleura – the one that is reflected into the mediastinal structures

  Mean thickness of parietal pleura is 20-25 μm

VISCERAL PLEURA

It is attached directly to the lungs and lines the adjoining structures ie., the blood vessels, bronchi and nerves. It is tightly attached to the lungs and cannot be stripped off. It contributes to the elastic recoil of the lung and lung deflation. Mean thickness of visceral pleura is 25-83 μm.

PULMONARY LIGAMENT

It is an extension of the pleura and is seen at the root of the lungs where it forms a mesenteric fold called pulmonary ligament. It extends from the lower part of the mediastinal surface of the lungs to the pericardium and ends in a free falciform ligament at the level of the diaphragm. Its main function is to retain the lower part of the lung in position.

PLEURAL FLUID

Normally it is around 5-10 ml and is formed by hydrostatic and osmotic pressures between the capillaries. It is normally absorbed into the capillaries of the visceral pleura. Any condition that increases the production or decreases the absorption of pleural fluid leads to its abnormal accumulation in the pleural space, which is known as pleural effusion. The presence of 300 ml of fluid in

the costodiaphragmatic space can obliterate it and can lead to clinical detection in an adult.

The normal volume of pleural fluid is 8.4 +/- 4.3 mL.or 0.26 +/- 0.1 mL/Kg

Cell count:

- WBC: 1716x103 cells/ml.
- RBC: 700x103 cells/ml.
- Macrophages: 75%.
- Lymphocytes: 23%
- Mesothelial cells, neutrophils and eosinophils: 2%.

Functions of pleural fluid:

It acts as a lubricant.

It helps in the respiratory movements and helps in the sliding of the visceral pleura over the parietal pleura.

Blood supply

The blood supply of the parietal pleura is from systemic circulation namely, the intercostal artery, superior phrenic, pericardio-phrenic artery, and musculo-phrenic artery and the venous drainage by phrenic and intercostal veins.

The thin pleura of visceral pleura is supplied by the pulmonary circulation while the thick pleura by the bronchial arteries. The venous drainage is through the pulmonary veins.

Lymphatic supply

The lymphatics of parietal pleura drains into the intercostal, phrenic, tracheobronchial, parasternal and mediastinal nodes. The lymphatics communicate with the pleura through the stomas, which ranges from 2 to 6 microns and helps in the removal of particulate matters.

In the visceral pleura, the lymphatics drain into bronchial circulation.

NERVE SUPPLY OF THE PLEURA

The parietal pleura is sensitive to pain, temperature, touch and pressure. It is supplied by the phrenic nerve and intercostal nerves. The visceral pleura is insensitive to pain but is sensitive to touch and receives nerve supply from autonomic nervous system via pulmonary plexus.

HISTOLOGY OF PLEURA

It is lined by mesothelial cells overlying vascularized connective tissue.

The mesothelial cells are keratin positive and consist of monolayer of flat or low cuboidal cells with bland and uniform nuclei, fine delicate chromatin, inconspicuous nucleoli.On electron microscopy, they contain apical tight

junctions, desmosomes, surface microvilli, cytoplasmic tonofilaments in bundles.

Connective tissue cells resemble fibroblast and stain positive for vimentin. Connective tissue layer helps in the elastic recoil of lung and restricts the volume of the lung thereby protecting it.

The mesothelial cells help in the transport of particulate matter and leucocytes across pleura, synthesis of cytokines and various growth factors . It also helps in antigen presentation and has the potential to change into myofibroblasts.

PHYSIOLOGY OF PLEURA

Negative pressure generated between the visceral and parietal pleura by the opposing elastic forces of the chest wall and lung at FRC is the pleural pressure.

It represents the balance between the outward pull of the thoracic cavity and the inward pull of the lung. The actual pleural pressure in humans is approximately – 5 cm H2O at FRC and –30 cm H2O at TLC

Pleural pressure is not uniform. The gradient between the superior (lowest, most negative) and inferior (highest, least negative) portions of the lung is 0.3 cm H20/ cm vertical distance. In the upright position, gradient of pleural pressure between the apex and the base is approximately 8 cm H20. The pleural

Pressure gradient is determined by gravity, mismatching of the shapes of the lung and chest wall, and the weight of the lung and other intra thoracic structures.

Starling's Law of Trans capillary Exchange

$Qf = Lp \times A[(Pcap-Ppl) - \sigma d(\pi cap-\pi pl)]$

Qf = liquid movement

Lp = filtration coefficient /unit area of the membrane

A = surface area of the membrane

σd = solute reflection coefficient for protein (membranes ability to restrict passage of large molecules)

P = hydrostatic pressures

π = oncotic pressure

A gradient for fluid formation is normally present in the parietal pleura.

- Hydrostatic pressure: 30cm H20
- Pleural Pressure: -5 cm H20.
- Oncotic pressure in plasma: 34 cm H20
- Oncotic pressure in the pleural fluid: 5 cm H20
- Net pressure gradient: 6 cm H20.

The presence of pulmonary effusion is more closely correlated with the pulmonary venous pressure than with the systemic venous pressure.

High permeability pulmonary edema: Pleural fluid accumulates only after pulmonary edema develops.

In general: pleural effusion develops when the extravascular lung water has reached a critical level in a certain amount of time., 5-8 g of fluid/ gram of dry lung.

PLEURAL FLUID FORMATION

Much of what we know about normal pleural liquid turnover is derived from studies in sheep, which have a pleural anatomy similar to that in humans. Studies of normal liquid turnover have been hampered by the narrowness of the pleural space and its sensitivity to inflammation. Most experiments, therefore, have relied on noninvasive studies of liquid formation, with the assumption that, in a steady-state condition, liquid absorption and formation will occur at the same rate.

The current consensus of pleural liquid formation is that the liquid originates from the systemic vessels of the pleural membranes, not from the pulmonary vessels. In other words, pleural liquid is interstitial fluid of the systemic pleural microvessels. There are three major considerations that support this hypothesis:

- The systemic vessels (of both parietal and visceral pleural membranes) are adjacent to the pleural space and are much closer to the pleural space than are the pulmonary vessels.
- The low pleural liquid protein concentration (1 g/dL) and ratio to the plasma protein concentration (0.15 g/dL) are consistent with a filtrate from high-pressure systemic vessels. If liquid and protein are filtered at high pressure and high flow across a semipermeable membrane, large particles will be sieved and relatively restrained compared to the liquid. Thus, plasma proteins, being large, will be retarded much more than the liquid in their movement across a membrane, and the protein concentration of the resultant filtrate will be low. On the other hand, if liquid and protein are filtered at low pressure and low flow, proteins are retarded less, and the protein concentration of the resultant filtrate is higher. Filtrates from low-pressure pulmonary vessels, eg, lung lymph, have a high protein concentration (4.5 g/dL) and ratio (0.7) compared to filtrates from systemic vessels and to pleural liquid.

Of note in this argument, pleural liquid formation is described as high flow, whereas its measured rate is relatively slow (0.01 mL/kg per h). However, it is the filtration at the systemic microvessels that is described as high, or at least higher than filtration across pulmonary microvessels. Some of that filtrate is reabsorbed into the low-pressure postcapillary venules, and some is removed

by bulk flow via the local lymphatic vessels. It is only the remainder that then moves into the low-pressure pleural space.

- In situations where systemic pressure varies, the pleural liquid protein concentration varies in concert. For example, systemic hypertensive rats have a lower pleural liquid protein-to-plasma protein concentration ratio than do normotensive rats (0.42 versus 0.55), even though their pulmonary pressures are the same . During development from the fetus to the adult, systemic blood pressure generally rises and pulmonary pressure falls. In a study in sheep, the pleural protein ratio decreased with development, as would be expected if the pleural liquid originated from the high-pressure systemic vessels.

Of the two pleural membranes, the parietal is thought to be more important than the visceral for normal pleural liquid formation. The arguments in favor of this view are as follows:

- The parietal pleural microvessels are closer to the pleural space (10 to 12 μm) than are those of the visceral pleura (20 to 50 μm).
- The parietal pleural microvessels probably have a higher filtration pressure than do the visceral bronchial microvessels, which are known to empty into the low-pressure pulmonary veins.

- The parietal membrane has a consistent anatomy and thickness over its extent in the body and among different species; the visceral membrane varies greatly.
- Pleural liquid formation rates are similar among species, even when the species have significantly different visceral pleural structures and circulations. Sheep, with a thick pleura and systemic visceral circulation, have similar pleural liquid formation rates as do dogs and rabbits, which have similar parietal pleural anatomy as sheep, but have very different visceral pleural anatomy. If the bronchial circulation of the thick visceral pleura in sheep did contribute, one would expect the liquid formation rate of sheep to be higher than that of the other two species.

The formation of pleural liquid is dependent upon a balance of hydrostatic pressures (microvascular minus pleural) opposed by the counterbalancing osmotic pressures (microvascular minus pleural). These pressures can be quantified by application of Starling's equation. A balance of pressures has been proposed that estimates an average 14 cmH2O driving pressure for movement of liquid into the pleural space from the parietal pleura versus 9 cmH2O from the visceral pleura.

Alterations of the balance that could increase pleural liquid formation include: an elevation of systemic microvascular pressure (eg, from systemic venous hypertension), a decrease in pleural pressure (eg, in atelectasis), or a decrease in systemic protein concentration (eg, with hypoproteinemia). (The fourth possibility, an increase in pleural liquid protein concentration, is not relevant clinically). The alteration in balance would presumably be transient and followed by a new balance at a different combination of hydrostatic and countering osmotic pressures.

PLEURAL LIQUID ABSORPTION — Because the normal situation is a steady state, the absorption rate of pleural liquid should equal the formation rate. If excess liquid is introduced into the pleural space, however, the rate of absorption increases several-fold, from the baseline rate of 0.01 to 0.02 mL/kg per hour to 0.22 to 0.28 mL/kg per hour.

The route of exit of the pleural liquid has been debated, in part because of the difficulty studying the pleural space. Various proposals have included reabsorption by the mesothelial cells themselves, and passive flow of pleural liquid into the "low" pressure interstitial tissues of the lung. Nonetheless, current evidence supports the conclusion that the liquid exits the pleural space via the lymphatic stomata of the parietal pleura. This conclusion is based upon knowledge of the physical forces operating at the pleural tissue and the evidence for bulk flow as opposed to diffusion.

Physical forces — Our current understanding of the physical forces operating at the pleural spaces do **not** support an important role for active transport or uptake by capillaries in the absorption of pleural liquid.

- The intrapleural pressure is lower than the interstitial pressure of either of the pleural tissues. With this pressure difference, a gradient of pressure directs liquid movement into but not out of the pleural space.
- The pleural membranes are leaky, offering little resistance to the movement of liquid and protein, as has been shown for peritoneal mesothelium. Such a condition favors the passive movement of liquid, proteins, and other molecules. This is the underlying characteristic that allows for successful dialysis across the peritoneal membranes.
- Mesothelial cells have not been shown to generate an electric potential difference, which would be expected if mesothelial cells moved ions by active transport. Although pleural liquid has been reported to be alkaline with a higher bicarbonate concentration than plasma, there is no evidence yet for mesothelial participation in generating a bicarbonate gradient. Furthermore, it is difficult to explain how the mesothelium could maintain a transport gradient since it is a leaky membrane. Another explanation for ionic differences across a semipermeable membrane is by the passive distribution of ions in

response to a difference in protein concentration (a "Donnan equilibrium").

Evidence for bulk flow — The majority of liquid appears to exit the pleural space by bulk flow, not by diffusion. At least four findings underlie this assertion.

- Pleural liquid protein concentration does not change as a hydrothorax is absorbed. With bulk flow, liquid and protein are removed together, and the protein concentration of the liquid remaining in the pleural space does not change. With diffusion, however, proteins would diffuse at a slower rate than the liquid, resulting in a progressive increase in protein concentration.
- The absorption rates of pleural liquid are constant despite differences in protein concentration. If diffusion were predominant, the presence of protein would be expected to slow the removal of the pleural liquid because the higher protein osmotic pressure would reduce the pressure gradient for flow out of the pleural space.
- Absorption rates are constant despite changes in pleural liquid volume, at least once the liquid volume rises above some threshold. If diffusion were the predominant mechanism of absorption, the absorption rate would be expected to change with pleural liquid volume, as the pleural liquid pressure gradient changed.

- Erythrocytes are absorbed intact from the pleural space and at nearly the same rate as the liquid and protein. This relatively free exit of erythrocytes from the pleural space indicates that the major route of exit is via holes large enough to accommodate erythrocytes (6 to 8 µm for the sheep erythrocytes used in the study). The only possible route then is via the parietal pleural stomata (2 to 10 µm) and the lymphatics.

LYMPHATIC FLOW — Lymphatic flow is influenced both by intrinsic contractility of the lymph vessels and by extrinsic respiratory movements. Intrinsic contractility could potentially be altered by hormones, cytokines, or adrenergic stimulation. Respiratory movements may assist lymphatic flow by applying an alternating pressure on the subpleural lymphatics or by expanding and contracting the openings of the lymphatic stomata. Respiratory movements also promote a continuous intrapleural circulation of pleural liquid, which may favor delivery of pleural liquid to the stomata.

Pathogenesis of Pleural Effusions

The following mechanisms may play a role in the formation of pleural effusion:

- Altered permeability of the pleural membranes (eg, inflammation, malignancy, pulmonary embolism)
- Reduction in intravascular oncotic pressure (eg, hypoalbuminemia due to nephrotic syndrome or cirrhosis)

- Increased capillary permeability or vascular disruption (eg, trauma, malignancy, inflammation, infection, pulmonary infarction, drug hypersensitivity, uremia, pancreatitis)
- Increased capillary hydrostatic pressure in the systemic and/or pulmonary circulation (egcongestive heart failure, superior vena cava syndrome)
- Reduction of pressure in the pleural space (ie, due to an inability of the lung to fully expand during inspiration); this is known as "trapped lung" (eg, extensive atelectasis due to an obstructed bronchus or contraction from fibrosis leading to restrictive pulmonary physiology)
- Decreased lymphatic drainage or complete lymphatic vessel blockage, including thoracic duct obstruction or rupture (eg, malignancy, trauma)
- Increased peritoneal fluid with microperforated extravasation across the diaphragm via lymphatics or microstructural diaphragmatic defects (eg, hepatic hydrothorax, cirrhosis, peritoneal dialysis)
- Movement of fluid from pulmonary edema across the visceral pleura
- Persistent increase in pleural fluid oncotic pressure from an existing pleural effusion, causing further fluid accumulation

CLINICAL MANIFESTATIONS OF PLEURAL EFFUSION

History

A detailed medical history should be obtained from all patients presenting with a pleural effusion, as this may help to establish the etiology. For example, a history of chronic hepatitis or alcoholism with cirrhosis suggests hepatic hydrothorax or alcohol-induced pancreatitis with effusion. Recent trauma or surgery to the thoracic spine raises the possibility of a CSF leak. The patient should be asked about a history of cancer, even remote, as malignant pleural effusions can develop many years after initial diagnosis.

An occupational history should also be obtained, including potential asbestose, which could predispose the patient to mesothelioma or benign asbestos-related pleural effusion. The patient should also be asked about medications they are taking.

The clinical manifestations of pleural effusion are variable and often are related to the underlying disease process. The most commonly associated symptoms are progressive dyspnea, cough, and pleuritic chest pain.

Dyspnea

Dyspnea is the most common symptom associated with pleural effusion and is related more to distortion of the diaphragm and chest wall during

respiration than to hypoxemia. In many patients, drainage of pleural fluid alleviates dyspnea despite limited alterations in gas exchange. Drainage of pleural fluid may also allow the underlying disease to be more easily recognized on repeat chest radiographs. Note that dyspnea may be caused by the condition producing the pleural effusion, such as underlying intrinsic lung or heart disease or obstructing endobronchial lesions rather than by the effusion itself.

Cough

Cough in patients with pleural effusion is often mild and nonproductive. More severe cough or the production of purulent or bloody sputum suggests an underlying pneumonia or endobronchial lesion.

Chest pain

The presence of chest pain, which results from pleural irritation, raises the likelihood of an exudative etiology, such as pleural infection, mesothelioma, or pulmonary infarction.

Pain may be mild or severe. It is typically described as sharp or stabbing and is exacerbated with deep inspiration. Pain may be localized to the chest wall or referred to the ipsilateral shoulder or upper abdomen because of diaphragmatic irritation. Pain may diminish in intensity as the pleural effusion increases in size and the inflamed pleural surfaces are no longer in contact with each other.

Extrapulmonary symptoms

Other symptoms in association with pleural effusions may suggest the underlying disease process. Increasing lower extremity edema, orthopnea, and paroxysmal nocturnal dyspnea may all occur with congestive heart failure.

Night sweats, fever, hemoptysis, and weight loss should suggest TB. Hemoptysis also raises the possibility of malignancy, other endotracheal or endobronchial pathology, or pulmonary infarction. An acute febrile episode, purulent sputum production, and pleuritic chest pain may occur in patients with an effusion associated with pneumonia.

Physical Examination

Physical findings in pleural effusion are variable and depend on the volume of the effusion. Typically, there are no clinical findings for effusions less than 300 mL. With effusions greater than 300 mL, chest wall/pulmonary findings may include the following:

- Dullness to percussion, decreased tactile fremitus, and asymmetrical chest expansion, with diminished or delayed expansion on the side of the effusion: These are the most reliable physical findings of pleural effusion.
- Mediastinal shift away from the effusion: This finding is observed with effusions greater than 1000 mL. Displacement of the trachea and mediastinum toward the side of the effusion is an important clue to

obstruction of a lobar bronchus by an endobronchial lesion, which can be due to malignancy or, less commonly, to a nonmalignant cause, such as a foreign body obstruction.

- Diminished or inaudible breath sounds
- Egophony (known as "E-to-A" changes) at the most superior aspect of the pleural effusion
- Pleural friction rub

Other physical and extrapulmonary findings may suggest the underlying cause of the pleural effusion.

Peripheral edema, distended neck veins, and S_3 gallop suggest congestive heart failure. Edema may also be a manifestation of nephrotic syndrome, pericardial disease, or, when combined with yellow nailbeds, the yellow nail syndrome.

Cutaneous changes and ascites suggest liver disease.

Lymphadenopathy or a palpable mass suggests malignancy

DIFFERENTIAL DIAGNOSIS OF PLEURAL EFFUSION

Pleural effusions are generally classified as transudates or exudates, based on the mechanism of fluid formation and pleural fluid chemistry. Transudates result from an imbalance of oncotic and hydrostatic pressures, whereas exudates

are the result of inflammatory processes of the pleura and/or decreased lymphatic drainage. In some cases, it is not rare for pleural fluid to exhibit mixed characteristics of transudate and exudate

1. **Transudative pleural effusions**

Transudates result from an imbalance in oncotic and hydrostatic pressures. Transudative effusions are usually ultrafiltrates of plasma squeezed out of the pleura as a result of an imbalance in hydrostatic and oncotic forces in the chest. However, other mechanisms of injury may include upward movement of fluid from the peritoneal cavity or, in iatrogenic cases, direct infusion into the pleural space from misplaced (or even migrated) central venous catheters or nasogastric feeding tubes.

- Transudates are caused by a small, defined group of etiologies, including the following:
- Congestive heart failure
- Cirrhosis (hepatic hydrothorax)
- Atelectasis (may be due to occult malignancy or pulmonary embolism)
- Hypoalbuminemia
- Nephrotic syndrome
- Peritoneal dialysis
- Myxedema

- Constrictive pericarditis
- Urinothorax (usually due to obstructive uropathy)
- Cerebrospinal fluid (CSF) leaks to the pleura (in the setting of ventriculopleural shunting or of trauma/surgery to the thoracic spine)
- Duropleural fistula (rare, but may be a complication of spinal cord surgery)
- Extravascular migration of central venous catheter]
- Glycinothorax (rare complication of bladder irrigation with 1.5% glycine solution following urologic surgery)

2. Exudative pleural effusions

Produced by a variety of inflammatory conditions (and often requiring a more extensive evaluation and treatment strategy than transudates), exudative effusions develop from inflammation of the pleura or from decreased lymphatic drainage at pleural edges.

Mechanisms of exudative formation include pleural or parenchymal inflammation, impaired lymphatic drainage of the pleural space, transdiaphragmatic cephalad movement of inflammatory fluid from the peritoneal space, altered permeability of pleural membranes, and/or increased capillary wall permeability or vascular disruption. Pleural membranes are involved in the pathogenesis of the fluid formation. Of note, the permeability of

pleural capillaries to proteins is increased in disease states with elevated protein content.

The more common causes of exudates include the following:

- Parapneumonic
- Malignancy (most commonly lung or breast cancer, lymphoma, and leukemia; less commonly ovarian carcinoma, stomach cancer, sarcomas, melanoma)
- Pulmonary embolism
- Collagen-vascular conditions (rheumatoid arthritis, systemic lupus erythematosus)
- Tuberculosis (TB)
- Pancreatitis
- Trauma
- Postcardiac injury syndrome
- Esophageal perforation
- Radiation pleuritis
- Sarcoidosis
- Fungal infection
- Pancreatic pseudocyst
- Intra-abdominal abscess
- Status post coronary artery bypass graft (CABG) surgery

- Pericardial disease
- Meigs syndrome (benign pelvic neoplasm with associated ascites and pleural effusion)
- Ovarian hyperstimulation syndrome
- Drug-induced pleural disease
- Asbestos-related pleural disease
- Yellow nail syndrome (yellow nails, lymphedema, pleural effusions)
- Uremia
- Trapped lung (localized pleural scarring with the formation of a fibrin peel prevents incomplete lung expansion, at times leading to pleural effusion)
- Chylothorax (acute illness with elevated triglycerides in pleural fluid)
- Pseudochylothorax (chronic condition with elevated cholesterol in pleural fluid)
- Fistula (ventriculopleural, biliopleural, gastropleural)

GENERAL TESTS TO DIFFERENTIATE THE CAUSES OF EXUDATIVE PLEURAL EFFUSION

Appearance of the fluid

Most pleural effusions are clear, straw colored, nonviscid and odourless. Presence of red blood cells in the pleural fluid can be due to hemothorax or a traumatic tap. To differentiate between the two, a haematocrit should be done. In case of hemothorax, the haematocrit of pleural fluid will be 50% more than the blood haematocrit. Or if the macrophages contains Hb, it indicates the presence of blood even before thoracocentesis and not a traumatic tap. When the pleural fluid is blood tinged the RBC count is 5000 to 10000 / mm^3.

Turbidity of the pleural fluid can be due to lipid content or cellular debris. To differentiate between the two, centrifuge the sample and see the colour of the supernatant. If turbidity persists it is due to lipid content. Amebiasis with a hepato-pleural fistula – chocolate sauce or anchovy sauce pus is seen. The mixture of blood, cytolysed and normal liver tissue make this appearance.

Distinguishing Transudates From Exudates

The initial diagnostic consideration is distinguishing transudates from exudates. Although a number of chemical tests have been proposed to

differentiate pleural fluid transudates from exudates, the tests first proposed by Light et al have become the criterion standards.

The fluid is considered an exudate if any of the following are found:

- Ratio of pleural fluid to serum protein greater than 0.5
- Ratio of pleural fluid to serum LDH greater than 0.6
- Pleural fluid LDH greater than two thirds of the upper limits of normal serum value

The fluid is considered a transudate if all of the above are absent.

These criteria require simultaneous measurement of pleural fluid and serum protein and LDH. However, a meta-analysis of 1448 patients suggested that the following combined pleural fluid measurements might have sensitivity and specificity comparable to the criteria from Light et al for distinguishing transudates from exudates

- Pleural fluid LDH value greater than 0.45 of the upper limit of normal serum values
- Pleural fluid cholesterol level greater than 45 mg/dL
- Pleural fluid protein level greater than 2.9 g/dL

Clinical judgment is required when pleural fluid test results fall near the cutoff points.

The criteria from Light et al and these alternative criteria identify nearly all exudates correctly, but they misclassify approximately 20-25% of transudates as exudates, usually in patients on long-term diuretic therapy for congestive heart failure (because of the concentrating effect of diuresis on protein and LDH levels within the pleural space).

Using the criterion of serum minus pleural protein concentration level of less than 3.1 g/dL, rather than a serum/pleural fluid ratio of greater than 0.5, more correctly identifies exudates in these patients.

Serum-effusion albumin gradient (SAG)

In general Light's criteria occasionally misidentify a transudative effusion as an exudative effusion as in cardiac failure with diuretic therapy . Clinically if a patient should have a transudative effusion, but meets Light's criteria for an exudative effusion, measure serum - pleural fluid albumin gradient,or measure the serum-pleural protein gradient. Serum- effusion albumin gradient of more than 1.2 g/dl and Serum-effusion protein gradient more than 3.1g/dl is seen in transudates.

SPECIFIC GRAVITY

Used in past to separate transudative from exudative. A specific gravity of 1.015 corresponds to protien contents of 3 g /dl, and this value was used to separate exudates from transudates .

NT PRO BNP

The level of NT pro BNP in the pleural fluid is used to establish the diagnosis of CHF(>1500pg/ml). level of NT pro BNP in making diagnosis of heart failure is superior to that of the BNP .

GLUCOSE MEASURMENT

Low pleural glucose level (<60mg/dl)indicates-parapneumonic effusion, malignant disease, rheumatoid disease, tuberculus pleuritis. presence of low glucose level is poor prognostic sign in parapneumonic effusion

AMYLASE DETERMINATION

Pleural fluid amylase level above upper normal limit (200iu/ml)for serum indicates the patient has one of three problems-

1. pancreatic disease

2. malignant tumor

3. esophageal rupture

Amylase in malignant pleural effusion and esophageal rupture is of salivary type.

LDH MEASUREMENT

LDH is reliable indicator of the degree of pleural inflammation.Higher the LDH ,more inflamed the pleural surface .

Most of the patient who meet the criteria of exudative pleural effusion with LDH but not with protein level have either parapneumonic effusion or malignant pleural disease. The indication for LDH isoenzyme determination is in only one situation- when there is bloody pleural effusion in a patient who is clinically thought to have transudative pleural effusion. In such a patient, if LDH is in exudative range, and the protein is in transudative range ,the demonstration of LDH1 as the major isoenzyme indicates that the increase in the LDH is due to blood .

PH

If the pleural fluid pH is less than 7.2 it means that the patient has 1 of 10 conditions

1. Complicated parapneumonic effusion

2. Esophageal rupture

3. Rheumatoid pleuritis

4. Tuberculous pleuritis

5. Malignant pleural disease

6. Hemothorax

7. Systemic acidosis

8. Paragonimiasis

9. Lupus pleuritis

10. Urinothorax

In general pleural fluid with low pH also have a low glucose and high LDH level. If the laboratory report a low pH with normal glucose and low LDH level ,the pH measurement is probably a laboratory error .

Total and Differential Cell Counts

Predominance of neutrophils in the fluid >50% indicates that an acute process is affecting the pleura. IL8 is primary chemotaxins for neutrophil in the pleural space. Common causes include - parapneumonic effusions ,effusions secondary to pulmonary embolus ,and those secondary to pancreatitis. Mononuclear cells like small lymphocytes >50% indicates a chronic process

like - cancer or tuberculous pleuritis, effusions after coronary-artery bypass surgery.

Pleural-fluid eosinophilia >10% : Mediated by IL5(CD4 CELLS) and eotaxin 3. In about two thirds of cases caused `by blood or air in the pleural space. Uncommon in cancer or tuberculosis, unless the patient has undergone repeated thoracentesis . Other causes are reactions to drugs (dantrolene, bromocriptine, or nitrofurantoin), exposure to asbestos, paragonimiasis, and the Churg–Strauss syndrome.

Basophil-count more than 10% are common with leukaemic pleural involvement

Markers of Tuberculosis

ADA MEASUREMENT

ADA is enzyme that catalyze the conversion of adenosine to inosine. cutoff level is 40u/l. Two main diseases that cause an elevated ADA in addition to tuberculosis are rheumatoid pleuritis and empyema. If the diagnostic criteria for tuberculous pleuritis patient also include a pleural fluid lymphocyte to neutrophil ratio greater than 0.75 the specificity of the test is increased. ADA has 2 isoenzymes ADA1 and ADA2. ADA1 is produced by lymphocyte, neutrophil , monocyte and macrophage. ADA 2 exist only in monocyte and macrophages. The increase in ADA activity in tuberculous pleuritis is mainly

due to ADA2 .(origin of pleural fluid ADA is probably pleural tissue).ADA1 to ADA2 ratio of less than 0.42 increased the accuracy. Sensitivity and specifity for ADA is 93%

INTERFERON-GAMMA

It is produced by CD4 lymphocytes . levels above 140pg/ml are very suggestive of TB.It is elevated irrespective of the immune status of the patient..but it is more expensive than ADA. The Sensitivity and specificity for interferon-gamma is 96%.

C REACTIVE PROTIEN

Patient with tuberculous pleuritis tend to have higher pleural fluid level of C reactive protein than do patient with other lymphocytic pleural effusion. Levels >50 mg/dl has high specificity for tuberculosis, but it doesn't appear to be as accurate as ADA level

Lysozyme

The level of lysozyme in pleural fluid tend to be higher in pleura fluid from patient with tuberculous pleuritis than in other types of exudate.

Procalcitonin

Higher mean levels of procalcitonin are seen with empyema followed by parapneumonic effusion and then tuberculous pleurisy and malignant pleural effusion. If eosinophils are found in pleural fluid in significant number(>10 %),one can virtually exclude the diagnosis of tuberculous pleuritis unless the patient has pneumothorax or had a previous thoracentesis. Pleural fluid from patient with TB rarely contains more than 5% mesothelial cells. It has been suggested that HIV infected patients with TB have significant number of mesothelial cells.

PCR FOR DIAGNOSIS OF TUBERCULOUS PLEURITIS

With PCR one can identify the presence of DNA from M. tuberculosis in the pleural fluid. PCR was not superior to an ADA level >45. In general PCR in pleural fluid has been less sensitive than PCR of other material. Sensitivity and specificity of PCR for diagnosis of tuberculous pleuritis is 81% and 100% respectively.

PLEURAL BIOPSY IN TUBERCULOUS PLEURITIS

Demonstration of granuloma in the parietal pleura suggests tuberculous pleuritis; caseous necrosis and AFB need not be demonstrated in TB effusion. More than 95 per of patient with granulomatous pleuritis have TB. ADA is as sensitive in diagnosing tuberculous pleuritis as needle biopsy of the pleura, thus

resulted in decrease use of the needle biopsy of pleura. Indication of needle biopsy of pleura

- Tuberculous pleuritis
- malignancy

Smears and Cultures

For nonimmunosuppressed patients, routine smears of the pleural fluid for mycobacteria are not indicated because they are usually negative, unless the patient has tuberculous empyema. Pleural fluid from patients with undiagnosed exudative pleural effusion should be cultured for bacteria, mycobacteria and fungi. Fluid should be inoculated directly into blood culture media at bedside because the number positive culture will increase with this methods. For mycobacteria culture use of BACTEC system with bedside inoculation provides higher yields and faster result. The sensitivities of pleural fluid culture and AFB smear were 42% and 1%, respectively

RADIOGRAPHIC EXAMINATION

The fluid first gravitates at the base of hemithorax and come to rest between inferior surface of the lung and diaphragm, particularly posteriorly where the pleural sinus is most posteriorly.

Subpulmonic or infrapulmonary effusion. At times for unknown reason substantial amount of pleural fluid (>1000ml) can be present may remain in an infrapulmonary location without spilling into costophrenic sulci or extending up the chest wall. such pleural fluid accumulation are called subpulmonic or infrapulmonic effusion. The following radiologic characteristics are common to subpulmonic effusion and presence of one or more of these characteristics serve as an indication of decubitus examination

a)apparent elevation of one or both diaphragm

b)apex of apparent diaphragm is more lateral than usual

c)slope of apparent diaphragm is more sharply towards the costophrenic angle

d)normally the top of the left diaphragm on the PA view is less than 2 cm above stomach air bubble.A separation greater than 2 cm suggests subpulmonic effusion

e) lower lobe vessels may not be seen below the apparent diaphragmatic border

- 75 mL-subpulmonic space without spill over, can obliterate the posterior costophrenic sulcus,

- 175 mL is necessary to obscure the lateral costophrenic sulcus on an upright chest radiograph
- 500 mL will obscure the diaphragmatic contour on an upright chest radiograph;
- 1000 ml of effusion reaches the level of the fourth anterior rib,
- On decubitus radiographs and CT scans, less than 10 mL.

Based on the decubitus films

- small effusions are thinner than 1.5 cm,
- moderate effusions are 1.5 to 4.5 cm thick, and
- large effusions exceed 4.5 cm.

• Effusions thicker than one cm are usually large enough for sampling by thoracentesis, since at least 200 mL of liquid are already present

ROLE OF USG-

1. Determining whether pleural fluid is present
2. Identification of appropriate location for an attempted thoracentesis ,pleural biopsy or chest tube placement
3. Identification of pleural fluid loculations
4. Distinction of pleural fluid from pleural thickening
5. Quantitation of amount of pleural fluid

6. Differentiation of pyopneumothorax from lung abscess

7. Assessment as to whether a pleurodesis is present

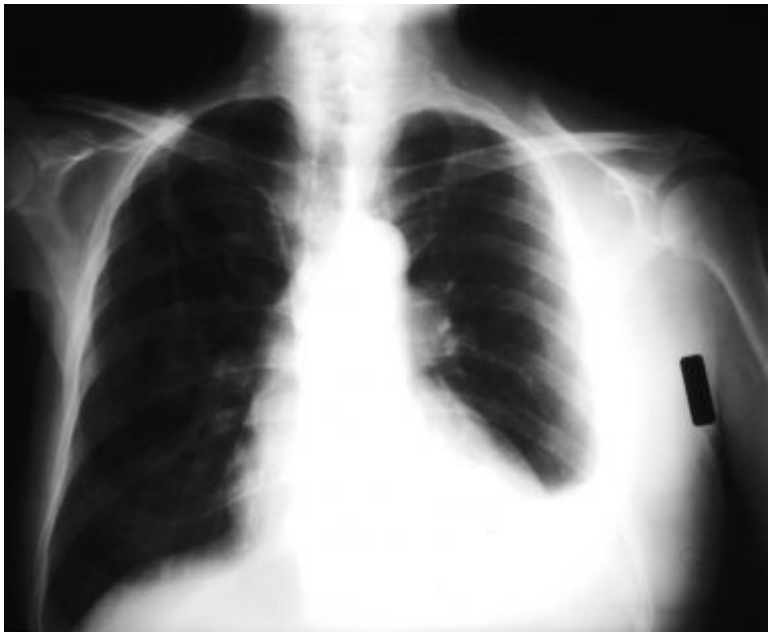
8. Evaluation of trauma patient for the presence of a Hemothorax or pneumothorax

Role of CT scan

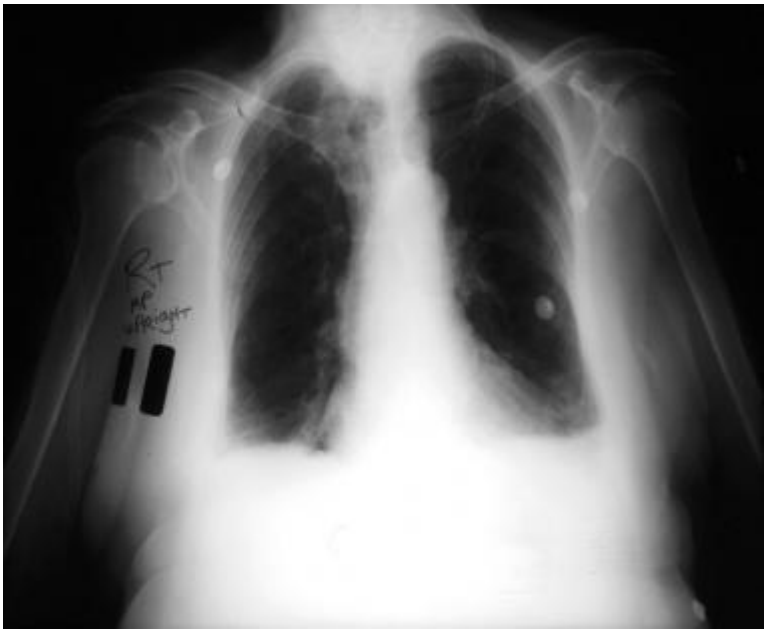
It is used for visualization of underlying lung parenchymal processes that are obscured on chest radiographs by large pleural effusions. It helps in distinguishing empyema from lung abscess and also in distinguishing benign from malignant pleural effusion-pleural nodularity, mediastinal pleura involvement, pleural thickening greater than 1 cm.

Loculated pleural effusion

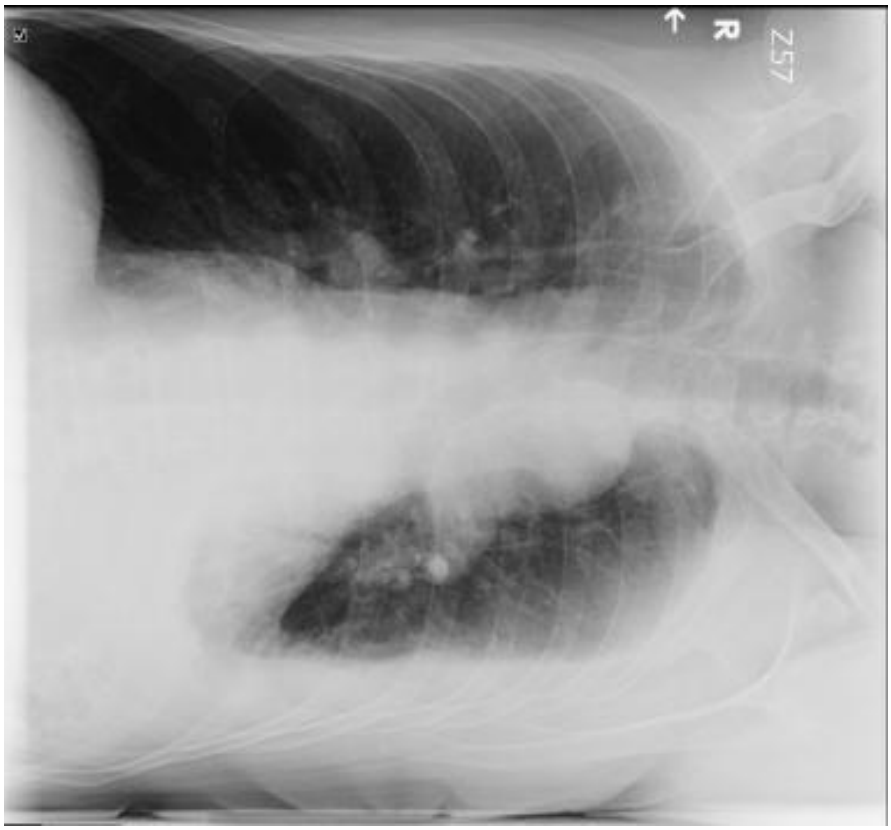
The effusion is encapsulated by adhesion anywhere between parietal and visceral pleura or in the interlobar fissure. It occurs most commonly with intense pleural inflammation such as empyema hemothorax,or tuberculous pleuritis. A definitive diagnosis of loculated pleural effusion is best established by ultrasound. Loculated effusion in fissure may simulate a mass in PA radiograph. It is most frequently seen in patient with CHF, and because the fluid absorb spontaneously when the CHF is treated these fluid collection have been termed vanishing tumor or pseudotumor.. The most common location of these tumor is right horizontal fissure.



Isolated, left-sided pleural effusion with visualized loss of left, lateral costophrenic sulcus.



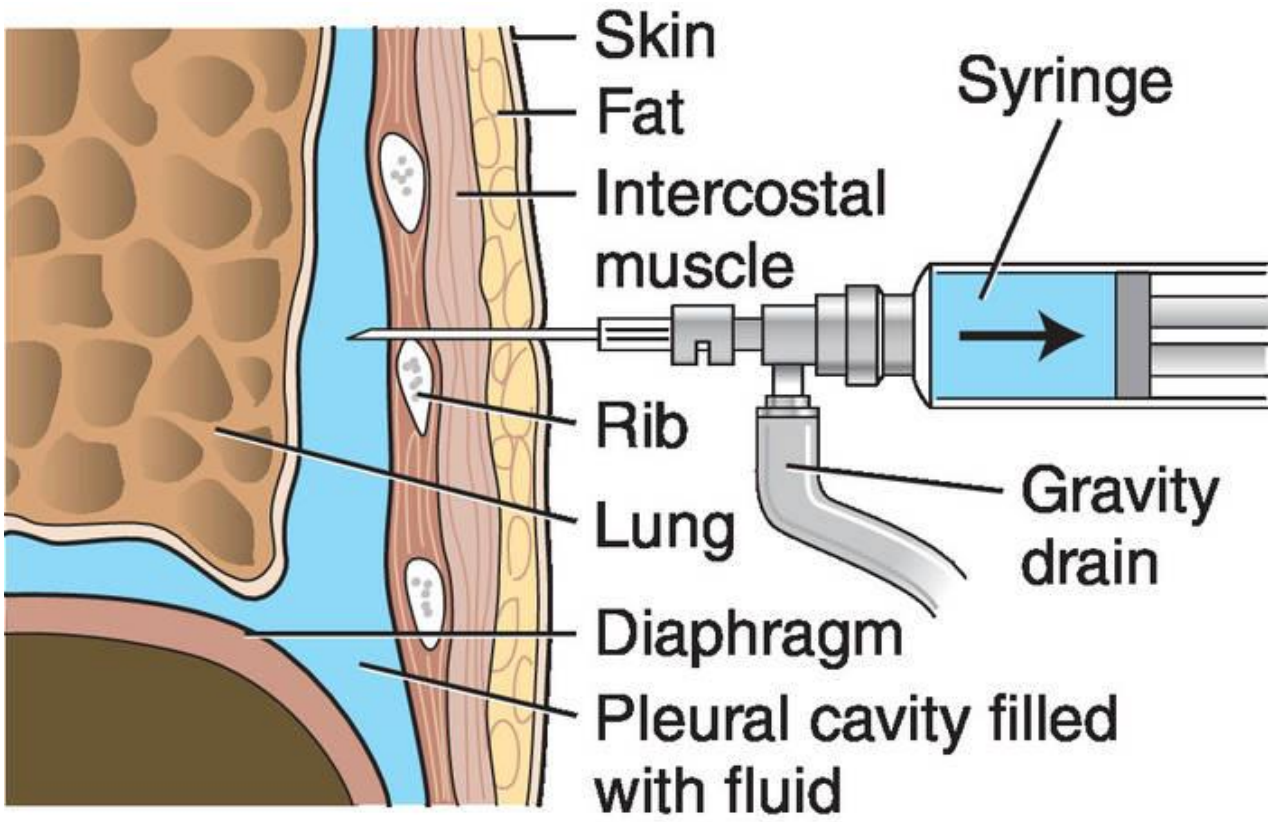
Bilateral pleural effusions with loss of bilateral costophrenic sulci (meniscus sign).



Left lateral decubitus film displaying freely layering left-sided pleural effusion.

Diagnostic Thoracentesis

A diagnostic thoracentesis should be performed if the etiology of the effusion is unclear or if the presumed cause of the effusion does not respond to therapy as expected.



Contraindications

Relative contraindications to diagnostic thoracentesis include a small volume of fluid (< 1 cm thickness on a lateral decubitus film), bleeding diathesis or systemic anticoagulation, mechanical ventilation, and cutaneous disease over the proposed puncture site.

Complications

Complications of diagnostic thoracentesis include pain at the puncture site, cutaneous or internal bleeding from laceration of an intercostal artery or spleen/liver puncture, pneumothorax, empyema, reexpansion pulmonary edema, malignant seeding of the thoracentesis tract, and adverse reactions to anesthetics used in the procedure.

The following procedures are done for patients whose cause cannot be found out with extensive investigations.

- ✓ Bronchoscopy – in a patient has parenchymal abnormalities or hemoptysis
- ✓ Surgical approaches to the diagnosis of pleural effusions - Includes video-assisted thoracoscopy (pleuroscopy) and open thoracotomy, allows direct visualization and biopsy of the pleura for diagnosis of exudative effusions, which reveals an etiology in 92% of effusions that remain undiagnosed after a medical evaluation.
- ✓ Medical thoracoscopy - Where available, may be diagnostic and therapeutic; complete drainage of the effusion and talc sclerosis can be performed at the time of the procedure.

Indication of thoracoscopy

- ✓ • Undiagnosed pleural effusion
- ✓ • Malignant pleural effusion
- ✓ • Parapneumonic pleural effusion
- ✓ • Pneumothorax
- ✓ • Postpnemonectomy empyema
- ✓ • Chylothorax
- ✓ • Hepatic hydrothorax

Indication of neeedle biopsy of pleura

- ✓ • Tuberculous pleuritis
- ✓ • malignancy

Lipids

Chylothorax –Accumulation of chyle in the pleural space due to disruption of the thoracic duct. In these situations the triglyceride levels are increased.

Chyliform pleural effusions – This is characterised by high levels of lecithin globulin levels.

Pseudo chylous effusions – There is increased levels of cholesterols crystals. Triglyceride levels more than 110 mg / dL – Chylothorax is confirmed.

But if the levels are less than 50 mg / dL then the patient does not have chylothorax.

If triglyceride level is between 50 to 110 mg / dL then a lipoprotein analysis should be done. Presence of chylomicrons in the lipoprotein analysis of pleural fluid is diagnostic of Chylothorax.

TREATMENT

MANAGEMENT OF PARAPNEUMONIC EFFUSION

Antibiotic selection-

1. For CAP that are not severe- fluoroquinoles or beta-lactam

2. For severe community acquired pneumonia in whom pseudomonas infection is not issue-beta lactam plus macrolide or fluoroquinolone

3. If pseudomonas infection is suspected an antipseudomonal antibiotic should be added-piperacillin- tazobactam, imipenem, meropenem, cefepime

4. Because anaerobic bacteria causes a sizable percentage of parapneumonic effusion anaerobic coverage recommended-clindamycin or metronidazole

5. Health care associated pleural infection coverage should be provided for gram negative bacteria and MRSA- carbapenem plus vancomycin

Management of pleural fluid

1. Therapeutic thoracentesis

2. Tube thoracostomy-complicated parapneumonic effusion

3. Tube thoracostomy and fibrinolytics-loculated effusion,

4. Video assisted thoracoscopy –incompletely drained parapneumonic effusion.it is effective in loculated parapneumonic effusion

5. Decortication-with decortication all the fibrous tissue is removed from the visceral and parietal pleura,and all pus is evacuated from the pleural space. decorication can be performed with VATS

TREATMENT OF MALIGNANT PLEURAL EFFUSION

1. Observation without invasive interventions may be appropriate for some patients with malignant pleural effusions.

2. Therapeutic thoracentesis may improve patient comfort and relieve dyspnea. The rapid removal of more than 1 L of pleural fluid may rarely result in re-expansion pulmonary edema.

3. When frequent or repeated thoracentesis is required for effusions that reaccumulate, early consideration should be given to tube drainage with pleurodesis or placement of a chronic indwelling pleural catheter.

4. Before pleurodesis medaistinal shifting should be identified.if the mediastinum is shifted towards the side of the effusion ,a bronchoscopy should be done before plurodesis is attempted because it is likely that patient has an obstructed bronchus.the presence of an obstructed bronchus is a contraindication to pleurodesis

5. Choice of sclerosing agents-talc,tetracycline derivative,bleomycin mitoxantrone ,silver nitrate,iodopovidone

6. Chemotherapy and mediastinal radiotheapy 7. Pleurectomy and pleural abrasion.

TREATMENT OF TUBERCULOUS PLEURAL EFFUSION

Tuberculous pleuritis is typically self-limited. Since 65% of patients with primary tuberculous pleuritis have reactivation of their disease within five years, empiric anti-TB treatment is usually begun pending culture results when sufficient clinical suspicion is present, such as an unexplained exudative or lymphocytic effusion in a patient with a positive PPD finding. In patient with loculated tuberculous pleural effusion , intrapleural administration of fibrinolytic is used.

INDICATION OF THERAPEUTIC THORACOCENTESIS

- To remove pleural effusion in patients with parapneumonic effusion or empyema
- To remove symptom of dyspnea secondary to pleural effusion
- To remove pleural effusion so that underlying pleural effusion can be evaluated

• Serial thoracentesis can be performed in patient who are dyspniec from malignant pleural effusion

Indication of chest tube

• Empyema

• Complicated parapneumonic effusion

• Hemothorax

• Malignant effusion- chest tube +/- pleurodesis (sclerosants

PSEUDOCHOLINESTERASE

Acetyl cholinesterase and cholinesterase (also called pseudocholinesterase or PChE) are two different enzymes, produced by different tissues, that are able to cleave acetyl choline, one of the body's major neurotransmitters. True cholinesterase has acetyl choline as it's primary natural substrate. It is found in high activity in CNS,RBC.

The normal function of the enzyme found in serum, PChE(also called acylcholine acyl hydrolase)is not known, but it is important in the cleavage of succinylcholine and mivacurium, muscle relaxants used during surgery. Pseudocholinesterase production occurs primarily in the liver. while both enzymes hydrolyse acetyl choline, only pseudocholinesterase can hydrolyse butyryl choline. This property of pseudocholinesterase is used in its quantification.

Cabrer *et al* estimated ChE activity in pleural effusions of diverse etiologies and concluded that there exists differences in the activity of ChE and it was possible to differentiate transudate and exudate. In 1996, Eduardo *et al* concluded that pleural fluid to serum cholinesterase ratio was the most accurate criterion for separating pleural fluid transudate and exudates and suggested that it should be used as the first step in the diagnosis of pleural effusions, if further studies confirmed their results.

In 1996, Garcia-Pachon *et al* conducted a study on 153 patients with pleural effusion and applied Light's criteria, the pleural fluid cholesterol level, the pleural fluid to serum cholesterol ratio, the pleural fluid cholinesterase level, and the pleural fluid to serum cholinesterase ratio to each case. The percentage of effusions misclassified by each parameter was as follows:

- Light's criteria -7.8%
- Pleural fluid cholesterol - 7.8%
- Pleural fluid to serum cholesterol ratio - 6.5%
- Pleural fluid cholinesterase - 8.5%
- Pleural fluid to serum cholinesterase ratio - 1.3%

The present study is being done to evaluate the diagnostic efficacy of pseudocholinesterase levels in pleural fluids and pleural fluid to serum pseudocholinesterase ratio and compare it with Light's criteria.

A cholinesterase or choline esterase is an enzyme that lyses choline based esters, several of which serve as neurotransmitters.

The two types of cholinesterases are acetyl cholinesterase and butyrylcholinesterase. The difference between the two types has to do with their respective preferences for substrates.The former hydrolyses acetylcholine more quickly; the latter hydrolyses butyrylcholine more quickly

Acetylcholinesterase also known as true cholinesterase, choline esterase I, or erythrocyte cholinesterase, is found primarily in the blood on red blood cell membranes, in neuromuscular junctions, and in other neural synapses. Acetylcholinesterase exists in multiple molecular forms.

Butyrylcholinesterase also known as **pseudocholinesterase**, cholinesterase, choline esterase II, plasma cholinesterase (PChE), serum cholinesterase (SChE), butylcholinesterase, or acylcholine acylhydrolase, is produced in the liver and found primarily in blood plasma..

The half-life of pseudocholinesterase is approximately 10 to 14 days. Its levels may be reduced in patients with advanced liver disease

SUMMARY OF PRIOR PUBLICATIONS

1)Evaluation of Cholinesterase to Differentiate Pleural Exudates and Transudates

Conclusions : The estimation of PChE and P/SChE ratio had better discriminatory capacity than Light's criteria. It is cost effective and more specific, therefore its routine estimation is recommended

2)evaluation of pleural fluid to serum cholinesterase ratio for differentiating pleural transudates from exudates

Conclusion: The number of misclassifications are more with the Light's criteria than the PF/S cholinesterase ratio.

Hence, the pleural fluid to serum cholinesterase ratio and pleural fluid cholinesterase level are the reliable method in separating pleural transudates from exudates

3) Comparison of Diagnostic Efficacy of Cholinesterase Levels to Differentiate Pleural Exudates and Transudates that of Lights Criteria

Conclusion: the pleural fluid cholinesterase level is one of the reliable parameter in separating pleural transudates from exudates.

4) Transüda-Eksüda Ayrımında levral Sıvı Psödokolinesteraz üzeyinin Tanısal Değeri-(Diagnostic Efficiency of Pseudocholinesterase Level in Discrimination of Transudates-Exudates)

Tüberküloz ve Toraks Dergisi 2003; 51(4): 398-404

Conclusion: pleural pseudocholinesterase level and pleural fluid/serum pseudocholinesterase ratio can be used as a parameter with high diagnostic efficiency in discrimination of pleural effusions as exudates and transudates.

5) pleural fluid to serum psuedocholinesterase ratio and its validation with light's criteria

Conclusion: Light's criteria has a good sensitivity and specificity, but pleural fluid to serum psuedocholinesterase ratio was the most efficient parameter in differentiating between transudates and exudates with a sensitivity of 100% and specificity of 96.7%.

6) **Pleural Fluid to Serum Cholinesterase Ratio for the Separation of Transudates and Exudates**

Conclusion: The pleural fluid to serum cholinesterase ratio is the most accurate criterion for separating pleural transudates and exudates. If further studies confirm our results, the cholinesterase ratio could be used as the first step in the diagnosis of pleural effusions.

MATERIALS AND METHODS

MATERIALS AND METHODS

STUDY POPULATION

- Patients with pleural effusion (evaluated cases with a proven etiology) from the dept. of general medicine, dept of thoracic medicine, dept of medical oncology, dept of nephrology and dept of cardiology in GRH.
- 60 patients with pleural effusion resulting from a single disease (CCF, nephrotic syndrome, malignancy, tuberculosis, pneumonia)were selected for the study

Inclusion criteria

- ✓ Patients with **malignant effusion**
- ✓ Patients with **Tubercular effusion**
- ✓ Patients with **parapneumonic effusion**
- ✓ Patients with pleural effusion due to **congestive cardiac failure**
- ✓ Patients with pleural effusion due to **nephrotic syndrome**

Exclusion criteria

- ✓ Effusions of undetermined origin
- ✓ Pts having pleural effusion with > 1 possible etiology
- ✓ Pts with liver disease

- ✓ Pts on – OCPs, anti-cancer drugs, MAO inhibitors, neostigmine, chlorpromazine
- ✓ Pregnant pts
- ✓ Pts with h/o exposure to OPC.
- ✓ Pts with uremia.
- ✓ Maliganant effusions who are already started on chemotherapy and those with superior vena caval obstruction..

ANTICIPATED OUTCOME:

- The pleural fluid pseudocholinesterase level and pleural/serum pseudocholinesterase ratio are reliable parameters in separating pleural transudates from exudates and have better discriminatory capacity than Light's criteria in distinguishing transudates from exudates.

DATA COLLECTION

A Brief history with detailed clinical examination and the following investigations were done , so that the study population meets the inclusion and exclusion criteria.

- ➢ RFT, LFT
- ➢ Urine routine
- ➢ CHG/PS

- CXR
- Echocardiography
- USG abdomen
- Sputum AFB/GenXpert
- TFT
- Pleural fluid malignant cytology
- Pleural fluid genexpert*
- Pleural fluid ADA*
- CT chest*
- 24 hr urine protein*
- ANA*, RF*

* in selected cases only

- Thus The study population was selected and classified as exudates and transudates based on the etiology
- Pleural fluid pseudocholinesterase, Serum pseudocholinesterase, Pleural fluid total protein, Serum total protein, Pleural & Serum LDH were estimated in all selected patients.

STUDY PROTOCOL

- Patients with pleural effusion with a proven etiology were selected for the study.
- Then a detailed clinical examination with brief history and a battery of investigations were done on these patients so that they meet the inclusion and exclusion criteria specified for the study
- Thus the study population was selected and they were further classified as exudates and transudates , based on the etiology of pleural effusion
- In all patients Pleural fluid pseudocholinesterase & Serum pseudocholinesterase , Pleural fluid total protein, Serum total protein , Pleural & Serum LDH were estimated.
- Then the patients are classified in to exudates and transudates on the basis of Light's criteria"
- Now the classification of exudates and transudates done on the basis of Pleural fluid pseudocholinesterase & Serum pseudocholinesterase is compared with results of the classification of exudates and transudates done on the basis of Light's criteria."
- Sensitivity, specificity , Positive predictive value , negative predictive value of each tests are calculated.

DESIGN OF STUDY

Cross sectional analytical study

PERIOD OF STUDY

April 2017 TO October 2017

COLLABORATING DEPARTMENTS:

Department of Medicine, Thoracic medicine , medical oncology,cardiology,nephrology,Biohemistry,pathology,radiodiagnosis

CONSENT*:* Individual written and informed consent.

ANALYSIS*:* Statistical analysis

CONFLICT OF INTEREST*:* Nil

Method of study

This study was conducted in Govt. Rajaji Hospital, Madurai which is affiliated to Madurai Medical College. The study subjects were selected from the patients admitted in Department of Medicine, Department of medical oncology, Department of cardiology and department of nephrology , Govt. Rajaji Hospital.

The study was conducted in 60 patients; the patients had pleural effusion with clinical background of: Tuberculosis, parapneumonic effusions, malignancy, congestive cardiac failure and nephrotic syndrome.

The patients are examined clinically with the following parameters and only 60 patients are taken for study.

Clinical criteria to classify patients as exudates and transudates

Effusions secondary to tuberculosis, malignancy and pneumonia were grouped as exudative and effusions secondary to congestive cardiac failure, and nephrotic syndrome were grouped as transudative

"If the patient had oedema legs, ascites, cardiac enlargement, radiological evidence of congested lungs and echocardiographic evidence of cardiac failure and responded to treatment for congestive cardiac failure , then the diagnosis of transudative effusion due to congestive cardiac failure was made".

If the patient had pedal edema/anasarca with proteinuria of > 3 gm/ 24 hrs, hypoalbuminemia and hypercholesterolemia then the diagnosis of transudative effusion due to nephrotic syndrome was made.

The diagnosis of tuberculous effusion was made if the pleural fluid AFB/GeneXpert was positive OR pleural fluid ADA >70 OR TB was proven by pleural biopsy.

The diagnosis of parapneumonic effusion was made if there is clinical and imaging evidence of effusion with bacteria in pleural fluid/sputum.

The diagnosis of malignant pleural effusion was made if Pleural fluid malignant cytology was positive and demonstration of primary sites with or without biopsy. Only treatment naïve patients without signs of SVC obstruction were enrolled.

Statistical analysis

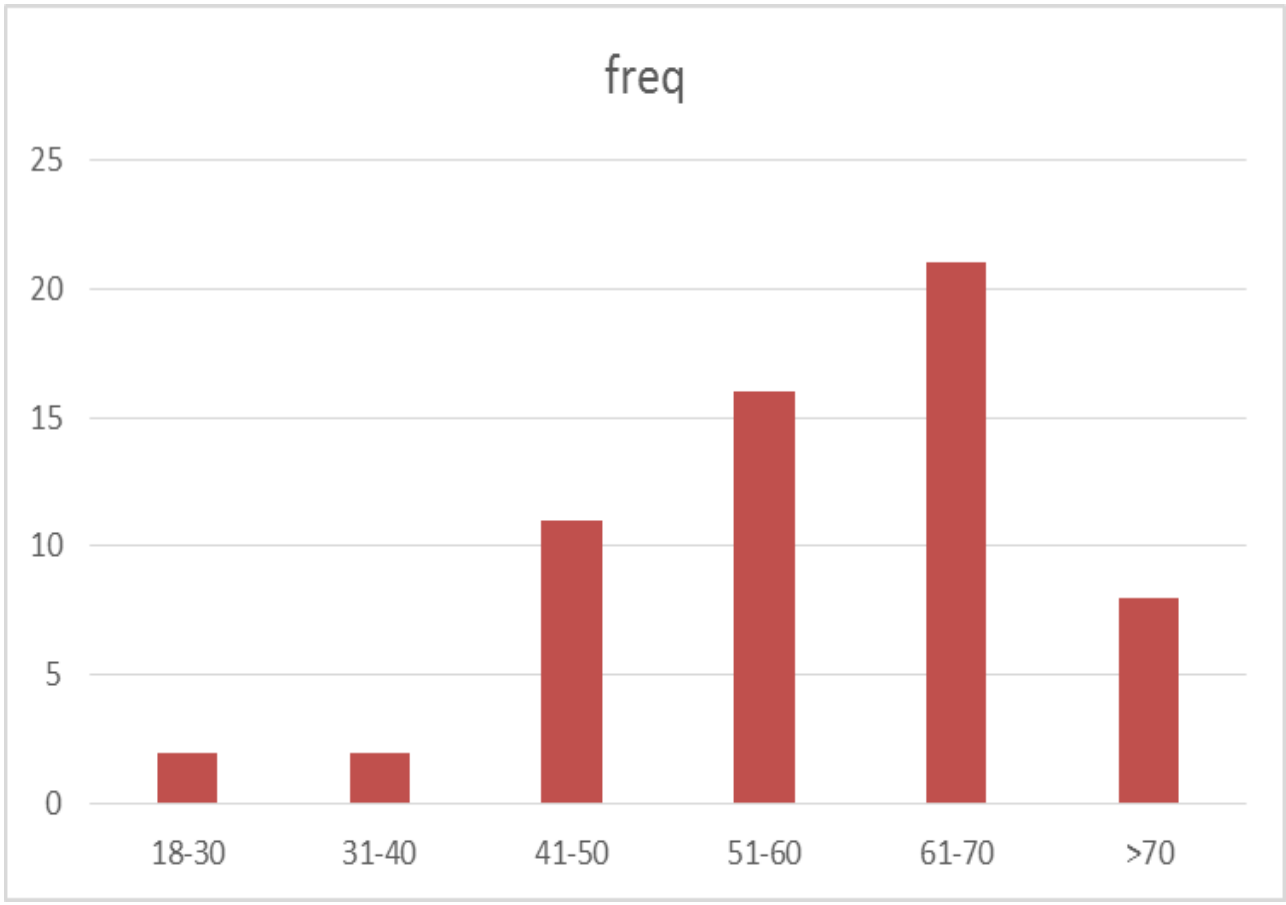
ROC analysis was done for pleural fluid PChE and pleural fluid to serum PChE ratio.Youden index was calculated for each of the plotted values and the value with the maximum youden index was taken as the cut off point with optimum sensitivity and specificity

Unpaired t test was applied for for pleural fluid PChE and pleural fluid to serum PChE ratio of transudates and exudates

RESULTS AND INTERPRETATION

RESULTS AND INTERPRETATION

AGE DISTRIBUTION



age	freq	%
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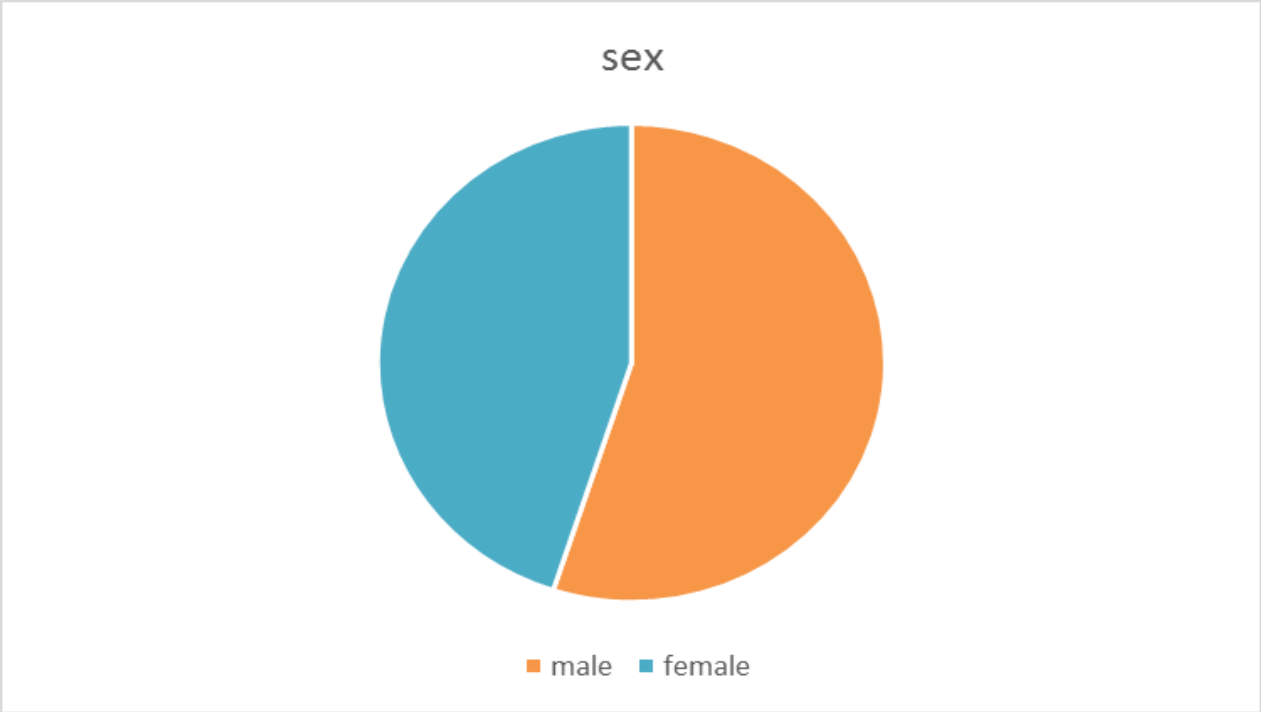
31-40	2	3.33
41-50	11	18.33
51-60	16	26.67
61-70	21	35
>70	8	13.33

35% of the study subjects were in the age group of 56-70yrs, 26.67% were in the age group of 51-60yrs, 18.33% were in the age group of 41-50 yrs.

13.33% patients were more than 70 yrs. 3.33% were 21- 30 yrs. 3.33% were 18-20 yrs

SEX DISTRIBUTION

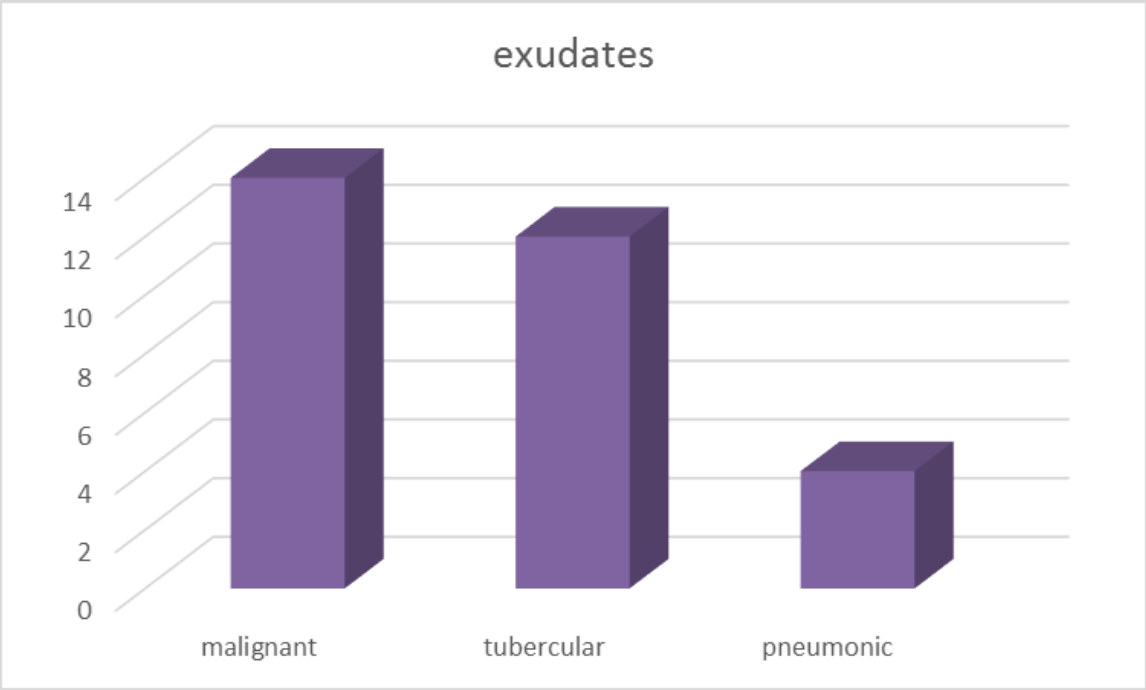


Sex	freq	percent
Male	33	55%
female	27	45%

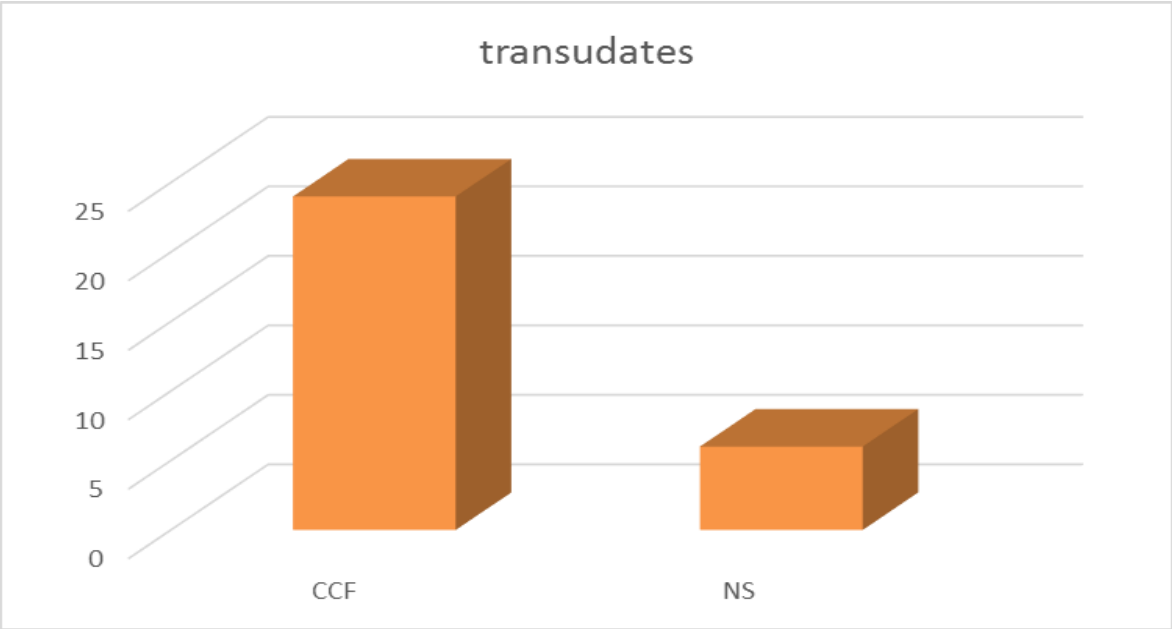
Majority of the study subjects were males 55% while remaining 45% were females.

ETIOLOGICAL CLASSIFICATION

Exudates and transudates distribution in our study is as follows:



etiology	freq (total-30)	percent
malignant	14	46.67%
tubercular	12	40%
pneumonic	4	13.33%



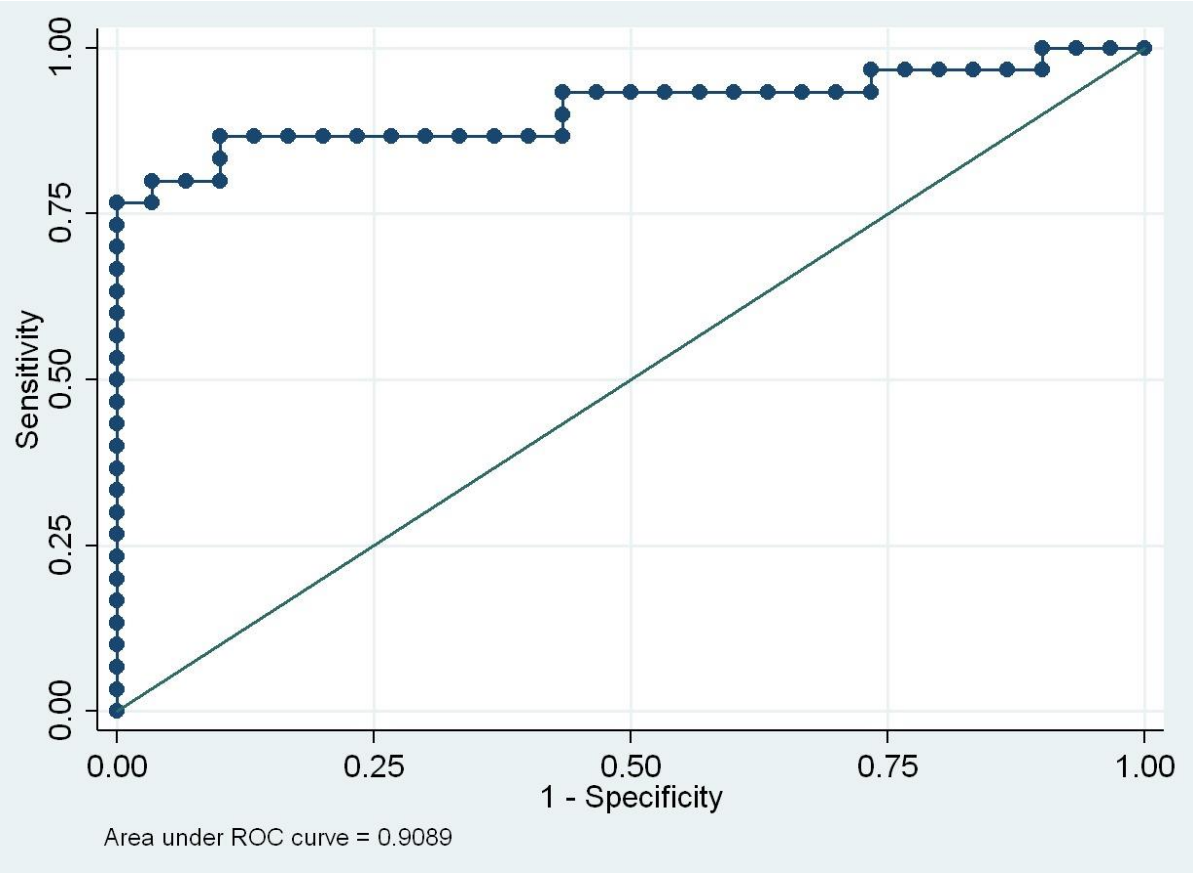
etiology	frequency (total-30)	percent
CCF	24	80
NS	6	20

In our study about 55% of the study subjects were exudates while 45% were transudates.

Among the exudates, about 40 % of study groups have tuberculosis, 46.67% have malignancy and 13.33 % have parapneumonic effusions.

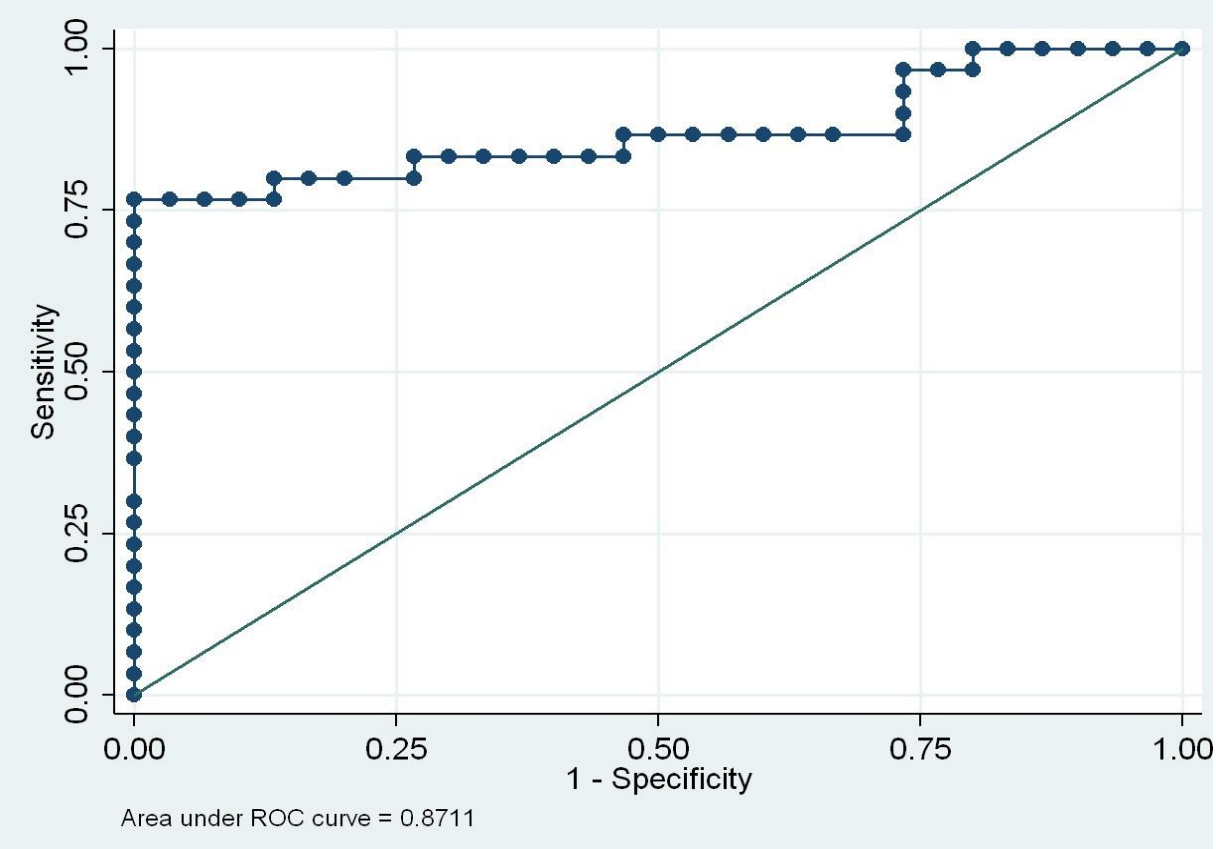
Among the transudates, 80% were due to congestive cardiac failure and 20% due to nephrotic syndrome.

ROC Pleural fluid PChE level



After ROC analysis, the cutoff point of pleural fluid PChE level with optimum sensitivity and specificity was calculated as 589 U/L.

ROC Pleural fluid to Serum PChE ratio



Aftter ROC analysis, the cutoff point of pleural fluid to serum PChE ratio with optimum sensitivity and specificity was calculated as 0.26.

	transudates misclassified as exudates (total-30)	**exudates misclassified as transudates(n-30)**
lights criteria	8(26%)	2(6%)
PF PChE	2(6%)	2(6%)
P/S PChE	2(6%)	0

Lights criteria misclassified 8 transudative effusions and 2 exudates. Pleural fluid PChE misclassified 2 transudates and 2 exudates.

Pleural fluid to serum PChE ratio misclassified 2 transudates whereas no exudates were misclassified in the study population.

Mean values

	exudates	**transudates**
Pf PChE(mean+/-2SD)	1071+/- 448	447+/-121
P/S PChE ratio(mean+/-2SD)	0.508+/-0.257	0.176+/-0.069

The mean pleural fluid PChE was 1071U/L in exudates and 447U/L in tansudates.

The mean value of P/S PChE ratio was 0.508 in exudates and 0.176 in transudates.

Unpaired T test done on pleural fluid PChE and pleural fluid to serum PChE ratio showed statistically significant difference between exudates and transudates with p value <0.001 in both groups.

The sensitivity, specificity, PPV and NPV for light's criteria in our study are 93.3%, 77.7%,83.3% and 95.6% respectively while for pleural fluid PChE, these are 96.2%, 85.36%,89.6% and 97.6% respectively. P/S PChE had maximum sensitivity and specificity of 97.14% and 91.6% with PPV and NPV of 94.2% and 98.3% respectively.

parameter	**sensitivity(%)**	**specificity(%)**	**PPV(%)**	**NPV(%)**
lights criteria	93.3	77.7	83.3	95.6
PF PChE	96.2	85.36	89.6	97.6
P/S PChE	97.14	91.6	94.2	98.3

DISCUSSION

DISCUSSION

Earlier, exudates were separated from transudates by means of specific gravity, cell count and presence or absence of clotting of fluid. Later in 1972, ,lights criteria was developed to differentiate between exudates and transudates. But lights criteria misclassified a significant number of effusions. Thus dawned the need for newer parameters. Our study focused on pleural fluid pseudocholinersterase and its ratio with serum pseudocholinesterase for differentiating transudates and exudates.

In a study done by Manju Sharma et al found that, using a cutoff of 0.24 for P/S PChE ratio they classified 98.1% of effusions correctly with PPV 98.75% and NPV 96.67%. In another study done by Prakash Kikkeri Gowdaiah et al, the sensitivity and specificity were 100% and 96.7%, PPV was 96.7% and NPV was 100%. In our study, sensitivity and specificity are 97.14 and 91.6%, PPV is 94.2% and NPV is 98.3% which is comparable to the other studies.

Similarly, the sensitivity and specificity of Light's criteria according to Prakash et al was 93% and 96% respectively while in the present study, it is 93.3% &77.7% respectively. These results are also comparable.

Comparison of Light's Criteria in various studies

	Present study	Prakash et al	Manju Sharma et al
Sensitivity (%)	93.3	93	91.25
Specificity (%)	77.7	96	90
PPV (%)	83.3	96	96.05
NPV (%)	95.6	93	79.42

Comparison of pleural fluid PChE in various studies

	Present study	Manju Sharma et al
Sensitivity (%)	96.2	97.5
Specificity (%)	85.36	90.0
PPV (%)	89.6	96.29
NPV (%)	97.6	93.11

Comparison of P/S PChE in various studies

	Present study	Prakash etal	Manju Sharma et al
Sensitivity (%)	97.14	100	98.7
Specificity (%)	91.6	96.7	96.67
PPV (%)	94.2	96.7	98.7
NPV (%)	98.3	100	96.6

In our study, the mean pleural fluid PChE was 1071 U/L in exudates and 447 U/L in tansudates. The mean value of P/S PChE ratio was 0.508 in exudates and 0.176 in transudates. Students t test was applied to these values and it was found that this difference was statistically significant (p value < 0.001)

MEAN VALUES

	EXUDATES	TRANSUDATES
Pleural fluid PChE	1071	447
P/S PChE ratio	0.508	0.176

In a study by Prakash et al, the mean PChE levels in exudates was 2074 +/- 660 U/L and in case of transudates, it was 385 +/- 142 U/L. and was found to be statistically significant. In the study by Manju Sharma et al, the mean PChE ans P/S PChE were significantly higher in the exudates compared to transudates ($P < 0.0001$).

Aftter ROC analysis, the cutoff point of pleural fluid to serum PChE ratio with optimum sensitivity and specificity was calculated as 0.26.and the cutoff value for pleural fluid PChE was 589.

In our study, it was found that the sensitivity and specificity of pleural fluid PChE and P/S PChE was found to be higher than Light's criteria. Both pleural fluid PChE and its ratio misclassified lesser number of cases than Light's criteria and had a better discriminatory capacity. These results were also comparable to the previous studies.

CONCLUSION

CONCLUSION

Both pleural fluid PChE and P/S PChE ratio are relliable parameters in differentiating transudates and exudates

PChE and P/S PChE ratio are more efficient than lights criteria in differentiating transudates and exudates

P/S PChE ratio is the most sensitive and specific parameter among the parameters studied

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LIMITATIONS OF THE STUDY

LIMITATIONS OF THE STUDY

The study was conducted in a relatively small group. So more studies with larger study population are needed for establishing the usefulness of the studied parameters and also for defining the cutoff levels of the parameters in differentiating exudates and transudates in the general population.

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BIBLIOGRAPHY

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PROFORMA

PROFORMA

Name:

Age / Sex:

Occupation:

Presenting complaints:

Past History:

H/o DM, HT, CKD, CVD, DRUG INTAKE, CAD, LIVER DISEASE,OPC exposure

Clinical Examination:

General Examination:

Consciousness,

Pallor,

Jaundice,

Clubbing,

Lymphadenopathy,

Hydration status

Vitals:

PR

BP

RR

SpO2

Systemic examination:

CVS:

RS:

ABDOMEN:

CNS:

Laboratory investigations:

chest X-ray PA view

echocardiogram

complete hemogram including ESR and peripheral smear

Urine albumin, sugar

RBS

Blood urea/ creatinine

Liver function tests

Serum lactate dehydrogenase

Serum pseudocholinesterase

Pleural fluid cytology including malignant cells

Pleural fluid proteins, sugar

Pleural fluid Lactic dehydrogenase

Pleural fluid pseudoCholinesterase

ABBREVIATIONS

ABBREVIATIONS

PChE	-	pseudocholinesterase
P/S PChE ratio	-	pleural fluid to serum pseudocholinesterase ratio
PF	-	pleural fluid
ADA	-	adenosine deaminase
LDH	-	lactate dehydrogenase
NPV	-	negative predictive value
PPV	-	positive predictive value
ROC curve	-	receiver operating characteristic curve

MASTER CHART

MASTER CHART

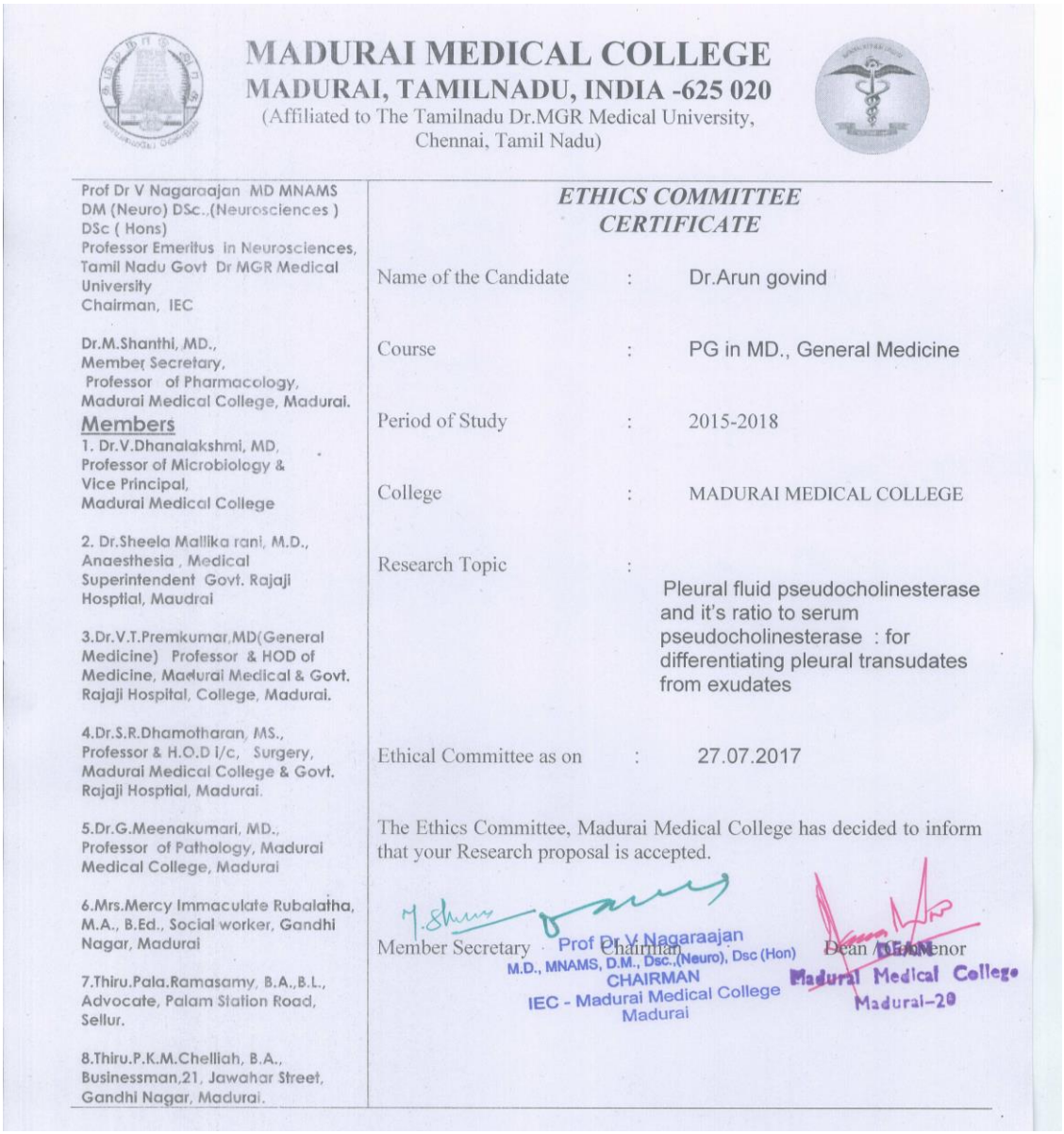
Sl. No	Age	Sex	Group (E/T)	Etiology	P/S protein	PF LDH	P/S LDH	PF PChE	P/S PChE
1	67	Male	E	M	0.56	198	0.69	1727	0.909
2	62	Male	E	M	0.63	191	0.72	375	0.995
3	50	Female	E	M	0.62	204	0.89	1438	0.476
4	67	Male	E	M	0.74	293	1.12	1860	0.368
5	61	Male	E	M	0.55	288	0.98	1072	0.811
6	23	Female	E	M	0.7	161	0.68	1563	0.345
7	53	Female	E	M	0.81	256	0.84	610	0.402
8	63	Male	E	M	0.58	199	0.66	1434	0.628
9	55	Female	E	M	0.65	261	0.92	1094	0.788
10	50	Female	E	M	0.69	214	0.84	625	0.625
11	52	Female	E	M	0.68	285	1.04	1339	0.545
12	64	Male	E	M	0.72	302	1.2	771	0.966
13	55	Female	E	M	0.46	156	0.52	1534	0.756
14	69	Male	E	M	0.64	212	0.81	1208	0.628
15	43	Female	E	T	0.58	193	0.73	967	0.325
16	60	Female	E	T	0.69	200	0.65	604	0.297
17	46	Male	E	T	0.47	149	0.58	589	0.302
18	39	Male	E	T	0.58	265	0.97	482	0.272
19	54	Female	E	T	0.65	291	1	1643	0.661
20	33	Male	E	T	0.59	201	0.78	1301	0.602

21	58	Male	E	T	0.66	264	0.86	1594	0.334
22	41	Male	E	T	0.74	286	0.93	1363	0.298
23	61	Male	E	T	0.57	191	0.84	683	0.456
24	41	Female	E	T	0.69	294	1.1	974	0.341
25	55	Male	E	T	0.72	261	0.96	596	0.641
26	64	Female	E	T	0.61	211	0.72	646	0.422
27	75	Male	E	P	0.75	190	0.65	939	0.47
28	70	Female	E	P	0.68	205	0.88	826	0.706
29	60	Male	E	P	0.61	241	0.98	1390	0.276
30	64	Female	E	P	0.71	302	1.14	1381	0.57
31	46	Female	T	C	0.48	120	0.42	500	0.098
32	71	Female	T	C	0.54	90	0.34	448	0.254
33	70	Female	T	C	0.47	84	0.43	523	0.138
34	53	Male	T	C	0.35	93	0.5	566	0.237
35	60	Male	T	C	0.26	102	0.63	442	0.111
36	56	Male	T	C	0.36	96	0.51	540	0.197
37	46	Female	T	C	0.42	105	0.52	417	0.071
38	56	Female	T	C	0.37	191	0.59	205	0.148
39	72	Male	T	C	0.53	53	0.28	290	0.279
40	78	Male	T	C	0.25	133	0.58	454	0.254
41	73	Female	T	C	0.48	54	0.37	472	0.108
42	70	Male	T	C	0.39	34	0.22	529	0.243
43	67	Male	T	C	0.25	37	0.16	584	0.278
44	67	Female	T	C	0.3	88	0.4	605	0.094

45	70	Female	T	C	0.31	99	0.31	441	0.204
46	64	Male	T	C	0.57	47	0.28	472	0.123
47	78	Male	T	C	0.42	49	0.17	402	0.09
48	54	Female	T	C	0.28	143	0.54	548	0.257
49	78	Male	T	C	0.32	63	0.21	209	0.144
50	66	Male	T	C	0.35	189	0.57	520	0.103
51	64	Male	T	C	0.4	44	0.24	307	0.124
52	73	Male	T	C	0.22	143	0.65	343	0.167
53	62	Female	T	C	0.29	52	0.28	200	0.224
54	61	Male	T	C	0.35	68	0.29	366	0.165
55	60	Female	T	N	0.42	66	0.21	606	0.243
56	53	Male	T	N	0.19	70	0.36	579	0.16
57	24	Male	T	N	0.26	54	0.31	534	0.22
58	46	Male	T	N	0.25	189	0.58	448	0.138
59	44	Female	T	N	0.3	57	0.26	301	0.156
60	42	Female	T	N	0.17	45	0.27	489	0.208

ETHICAL COMMITTEE APPROVAL LETTER

ETHICAL COMMITTEE APPROVAL LETTER



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ETHICS COMMITTEE CERTIFICATE

Name of the Candidate : Dr.Arun govind

Course : PG in MD., General Medicine

Period of Study : 2015-2018

College : MADURAI MEDICAL COLLEGE

Research Topic :
Pleural fluid pseudocholinesterase and it's ratio to serum pseudocholinesterase : for differentiating pleural transudates from exudates

Ethical Committee as on : 27.07.2017

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

Member Secretary Chairman Dean / Convenor

Prof Dr V Nagaraajan
M.D., MNAMS, D.M., Dsc.,(Neuro), Dsc (Hon)
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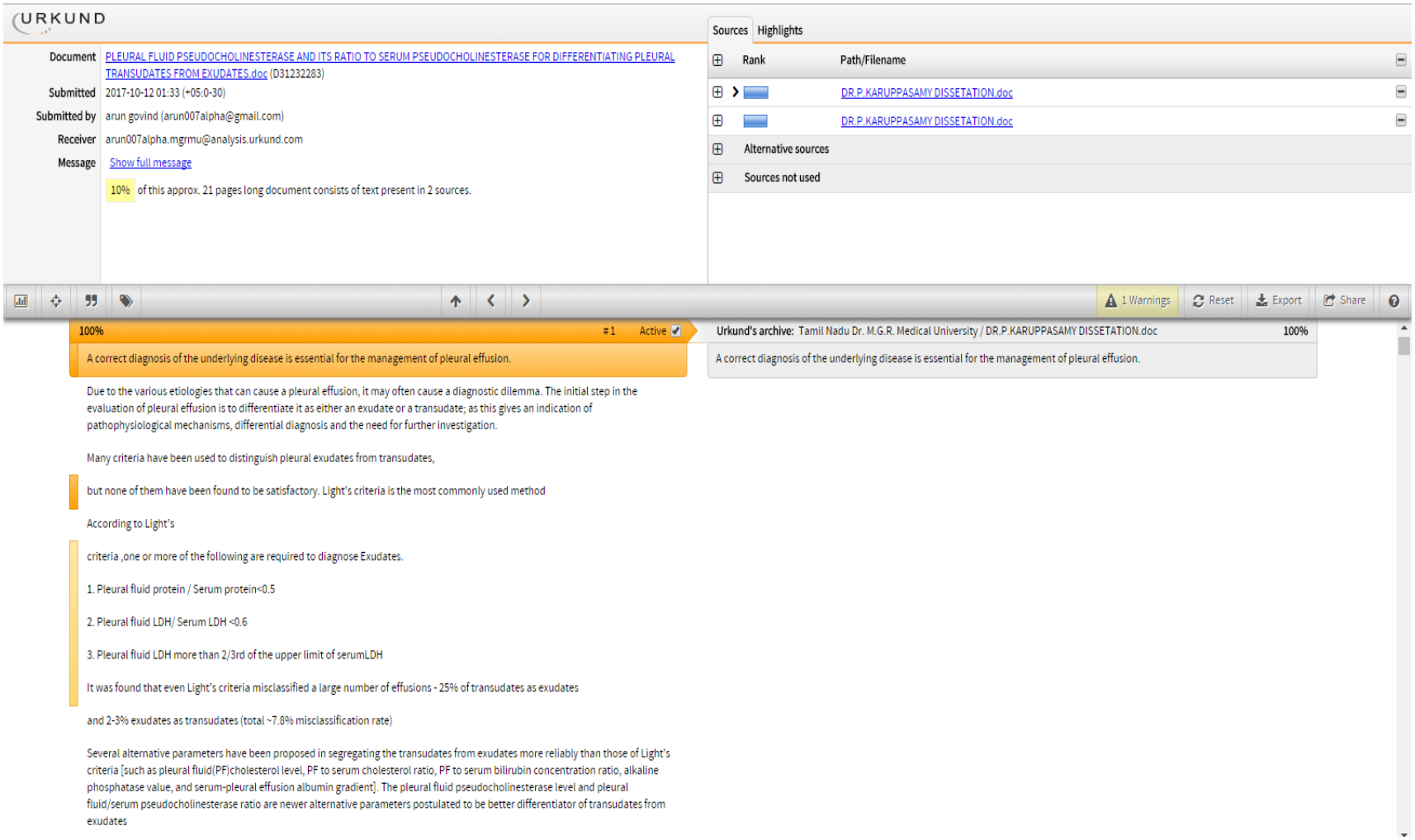
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A correct diagnosis of the underlying disease is essential for the management of pleural effusion.
Due to the various etiologies that can cause a pleural effusion, it may often cause a diagnostic dilemma. The initial step in the evaluation of pleural effusion is to differentiate it as either an exudate or a transudate; as this gives an indication of pathophysiological mechanisms, differential diagnosis and the need for further investigation.
Many criteria have been used to distinguish pleural exudates from transudates,
but none of them have been found to be satisfactory. Light's criteria is the most commonly used method
According to Light's
criteria ,one or more of the following are required to diagnose Exudates.
1. Pleural fluid protein / Serum protein<0.5
2. Pleural fluid LDH/ Serum LDH <0.6
3. Pleural fluid LDH more than 2/3rd of the upper limit of serumLDH
It was found that even Light's criteria misclassified a large number of effusions - 25% of transudates as exudates
and 2-3% exudates as transudates (total ~7.8% misclassification rate)
Several alternative parameters have been proposed in segregating the transudates from exudates more reliably than those of Light's criteria [such as pleural fluid(PF)cholesterol level, PF to serum cholesterol ratio, PF to serum bilirubin concentration ratio, alkaline phosphatase value, and serum-pleural effusion albumin gradient]. The pleural fluid pseudocholinesterase level and pleural fluid/serum pseudocholinesterase ratio are newer alternative parameters postulated to be better differentiator of transudates from exudates

CERTIFICATE

This is to certify that this dissertation titled "**PLEURAL FLUID PSEUDOCHOLINESTERASE AND ITS RATIO TO SERUM PSEUDOCHOLINESTERASE -FOR DIFFERENTIATING PLEURAL TRANSUDATES FROM EXUDATES**" of the candidate **DR. ARUN GOVIND** with registration number **201511104** for the award of **M.D degree in the branch of GENERAL MEDICINE**. I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows 10 **Percentage** of plagiarism in the dissertation.

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