EVALUATION OF SERUM-PLEURAL FLUID ALBUMIN GRADIENT FOR DIFFERENTIATION OF TRANSUDATE AND EXUDATE

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ABSTRACT

BACKGROUND

The correct diagnostic approach of any Pleural Effusion (PE) is differentiation between Transudates and Exudates. The Light's criteria is used to differentiate between the two, but up to 25% of Transudates are misclassified as Exudates. To overcome this, the gradient between Serum (Sr.) - Pleural Fluid (PF) Albumin should be measured. A gradient of > 1.2 gm/dL has good sensitivity and specificity for confirming transudates.

The aim of this study was to estimate the Sr. - PF Albumin gradient and comparing it with Light's criteria for its efficacy in the identification of Transudates misclassified by Light's criteria as Exudates.

MATERIALS AND METHODS

This is a descriptive study. It was conducted on 50 patients who had only transudative PE with the clinical background of Congestive Cardiac Failure (CCF), Chronic Kidney Disease (CKD) and Hepatic hydrothorax admitted in Medical wards of Govt. Rajaji Hospital, Madurai.

RESULTS

According to PF - Sr. Protein ratio in the Light's criteria, 78% of the cases were detected as Transudative PE. According to Sr. - PF Albumin gradient, 96% of the cases were detected as Transudative PE. According to Sr. - PF Protein gradient, 88% of the cases were detected as Transudative PE.

CONCLUSION

By using Sr. - PF Albumin gradient, our study correctly classified 96% as Transudative PE and by applying Light's criteria only 78% were classified as Transudative PE. So, Light's criteria wrongly classified 22% of Transudative PE as Exudative PE, whereas Sr. - PF Albumin gradient classified only 4% of Transudative PE as Exudative PE. Sr. - PF Protein gradient correctly classified 88% of Transudative PE and wrongly classified 12% of them. From our study, it is conclusive that Sr. - PF Albumin gradient is an effective means of differentiating Exudative and Transudative PE.

KEYWORDS

Pleural Effusion, Congestive Cardiac Failure, Chronic Kidney Disease, Hepatic Hydrothorax, Transudate, Exudate.

BACKGROUND

The Light's criteria[1] is used to differentiate the Transudative PE from Exudative PE with one or more of the following: a) PF Protein/Sr. Protein ratio > 0.5; b) PF Lactic Dehydrogenase (LDH)/Sr. LDH ratio > 0.6; c) PF LDH is more than $2/3^{rd}$ of the upper limit of Sr. LDH. If any one of these critical values is exceeded, the effusion is an exudate.

By applying Light's criteria up to 25% of Transudative PE are misclassified as Exudative PE. Serum-PF Albumin should be measured and if it is > 1.2 gm/dL it has good sensitivity and specificity for confirming as Transudative PE.

This present study is to evaluate the Sr. - PF Albumin gradient in differentiating Transudative PE and Exudative PE. To compare the validation in differentiating a Transudative PE from Exudative PE among 3 parameters such as- 1) Sr.-PF protein ratio, 2) Sr.-PF Protein gradient and 3) Sr.-PF Albumin gradient.

An exudative PE results from disease of the pleural surface itself, while a transudative PE results from alterations in the systemic factors that influence the movement of fluid in and out of the pleural space.[2] The criteria established by Light et al[1] for segregating transudates from exudates have been widely accepted and rely on measurement of protein and Lactate Dehydrogenase (LDH) in serum and PF. In an effort to improve the sensitivity and specificity of the classic criteria of Light et al, Romero et al[3] have recently proposed their modification by the adaptation of new cut-off points for the biochemical analytes, i.e. PF. Protein/Sr. Protein ratio > 0.6, PF LDH/Sr. LDH ratio > 0.9 and PF LDH level > 280 IU.

The hydrostatic pressure in the parietal pleura is approximately ($\approx$) 30 cm of water (H_2O) and the pleural pressure is $\approx$ -5 cm of H_2O. The net hydrostatic pressure is 30 - (-5) = 35 cm of H_2O and this favours the movement of fluid from the capillaries in the parietal pleura to the pleural space.

The normal oncotic pressure of the plasma is $\approx$ 34 cm of H_2O, which is opposing the hydrostatic pressure gradient of the parietal pleura. Normally, the small amount of PF contains a small amount of protein with an oncotic pressure of ($\approx$) 5 cm of H_2O, yielding a net oncotic pressure gradient of 34 - 5 = 29 cm of H_2O, the net pressure gradient i.e. (net hydrostatic pressure- net oncotic pressure) 35 - 29 = 6 cm of H_2O, favouring the movement of fluid from the capillaries in the parietal pleura to the pleural space.

The net gradient for fluid movement across the visceral pleura is probably zero.[4] The pressure in the visceral pleural capillaries is $\approx$ 6 cm of H_2O less than that in the parietal pleural capillaries 6 cm of H_2O. So the visceral pleural capillaries drain into the pulmonary veins and it is the only pressure that differs from those affecting fluid movement across the parietal pleura. The filtration coefficient for the visceral pleura is less than the parietal pleura, because the capillaries in the visceral pleura are much farther from the pleural space than those in the parietal pleura.

The origin of the fluid does not appear to be in the interstitial spaces of the lung, because the protein level in the interstitial spaces is $\approx$ 4.5 g/dL, whereas the protein level in normal PF is $\approx$ 1 to 1.5 g/dL, higher vascular pressures should produce PF with lower protein levels.[4]

The pleural space is in communication with the lymphatic vessels in the parietal pleura by means of stomas in the parietal pleura, which is absent in the visceral pleura. Transcytosis also contributes to the removal of PF protein from the pleural space. Only 29% of the overall removal of albumin occurred through the stoma with small hydrothoraces, while 64% of the removal of albumin occurred through the stoma with large hydrothoraces.

The proteins, cells and all other particulate matters are removed from the pleural space by these lymphatics in the parietal pleura. Increased levels of Nitric Oxide in the pleura will cause these stoma to increase in size. Normal lymphatic drainage in an adult from each pleural space is 20 mL/hr or 500 mL/day. The capacity for lymphatic clearance is 28 times as high as the normal rate of PF formation.

The primary route for the exit of fluid from the pleural space was through the capillaries in the visceral pleura and almost all the PF is removed through the lymphatics in the parietal pleura. Several hundred millilitres (mLs) of water probably traverse the pleural membranes each day, but the net movement is of only a few mLs, because the osmolarity is nearly identical on each side of the membrane.

The most common cause of increased PF formation is due to increased interstitial fluid in the lungs. Whenever the amount of oedema in the lung exceeds 5 gm/gram of dry lung weight, PF accumulates irrespective of whether the oedema is due to high-protein or low-protein fluid and appears to be the predominant mechanism for the accumulation of PE in CCF, Parapneumonic effusions, ARDS and in post lung transplantation status.

With an increase in the gradient between the intravascular pressure and the pleural pressure, there will be an increase in the rate of PF formation through Starling's equation. Increased intravascular pressure can occur with right ventricular failure, left ventricular failure, pericardial effusions or SVC syndrome. The most common situation producing a decrease in the pleural pressure is bronchial obstruction leading to atelectasis of the lower lobe or entire lung, when the visceral pleura becomes coated with a collagenous peel and the lung becomes trapped. Decreased pleural pressures also contribute to PF accumulation due to the elastic recoil of the diseased lung is increased.

The increased levels of Vascular Endothelial Growth Factor (VEGF) increases the permeability of the capillaries and leads to accumulation of PF. VEGF levels are higher in Exudative PE than in Transudative PE. If the pleural surfaces become inflamed the permeability of the capillaries may be increased, which leads to increased PF protein levels occur in pulmonary oedema, haemothorax. This rate of fluid formation is equal to the capacity of the lymphatics to remove PF.

The free fluid in the peritoneal cavity will lead to PF accumulation through the diaphragm and Chyle will accumulate in the pleural space if there is a disruption in the thoracic duct, and blood will accumulate in the pleural space if there is a disruption of a blood vessel in the thorax.

The most common cause of a decrease in PF absorption is obstruction of the lymphatics draining the parietal pleura. Normally, the lymphatic flow from the pleural space is approximately 0.01 mL/kg/hour or 15 mL/day, which is equal to the amount of PF formed. The capacity of the lymphatics is approximately 0.20 mL/kg/hour or 300 mL/day. Lymphatic blockade is an important factor for the development of a malignant pleural effusion.

The causes for Transudative PE are CCF, Cirrhosis, Nephrotic syndrome and Glomerulonephritis, SVC Syndrome, Peritoneal dialysis, Myxoedema and Hypoalbuminaemia.

The causes for Exudative PE are Tuberculous, Bacterial, Fungal, Parasitic and Viral infections, Neoplastic and Metastatic diseases, Mesothelioma, Lymphomas, Pulmonary embolisation, Haemothorax and Chylothorax, Pancreatic diseases, Endoscopic variceal sclerosis, Subphrenic, Intrahepatic and Intrasplenic abscess. Post CABG surgery, Post cardiac injury (Dressler's) syndrome, Pericardial diseases, Pulmonary vein stenosis, Post catheter ablation of atrial fibrillation, Meigs' syndrome, Rheumatoid pleuritis, Systemic lupus erythematosus and Drug-induced pleural disease, e.g. Amiodarone, Methotrexate, Procarbazine, Methysergide and Dantrolene.

When symptoms are related to the effusion they arise from inflammation of the pleura, compromise the pulmonary mechanics, interfere with gas exchange and decrease cardiac output. PE associated with pleuritic chest pain indicates inflammation of the pleura, specifically the parietal pleura, whereas the visceral pleura does not have pain fibres. Some patients with PE experience a dull aching chest pain rather than pleuritic chest pain.

The pleural effusion is probably due to CCF if the patient has cardiomegaly, signs of joint disease or subcutaneous nodules suggest that the PF is due to rheumatoid disease or lupus erythematosus. An enlarged, non-tender nodular liver or the presence of hypertrophic osteoarthropathy suggests metastatic disease, as do breast masses or the absence of a breast. Abdominal tenderness suggests a subdiaphragmatic process, whereas tense ascites suggests cirrhosis and a hepatothorax. Lymphadenopathy suggests lymphoma, metastatic disease or sarcoidosis.

Most transudative PE are clear, straw-coloured, non-viscid and odourless. The PF appears as pinkish tinge if red blood cell (RBC) count is of more than 10,000/mm^3. Approximately, 15% have RBC counts above this level.[5]

Aims and Objectives

To estimate the Sr. - PF Albumin gradient and comparing it with Light's criteria for its efficacy in the identification of transudates misclassified by Light's criteria as exudates.

MATERIALS AND METHODS

This descriptive study was conducted on 50 patients in number who had only Transudative pleural effusion with the clinical background of CCF, CKD and Hepatic hydrothorax admitted in Medical wards of Govt. Rajaji Hospital affiliated to Madurai Medical College, Madurai. Prior written consent was obtained from all the patients included in the study in their own mother tongue. For convenience, sample size of 50 was taken; patients with Transudative PF with the clinical background of CCF, CKD and Hepatic hydrothorax of all age groups and both sexes. Patients with clinical features suggestive of Exudative PE such as Tuberculous PF, Malignant PF and Parapneumonic effusions are to be excluded from the study. Sr. - PF Albumin gradient is a better parameter for identifying Transudative PE compared with Light's criteria. A detailed clinical history, detailed clinical examinations, laboratory estimations of PF Protein, Albumin and Sr. Albumin and Sr. Protein were taken. Patients with CCF, CKD and Hepatic Hydrothorax with Clinical or Radiological evidence of PF are included in the study. Patients whose lab reports favours exudates according to Light's criteria are compared with Sr. - PF Albumin gradient to analyse the validity of Light's criteria in diagnosing transudates; 7 months duration from April 2013 to October 2013. After obtaining the results, the data was compiled in a Microsoft Excel sheet. Statistical analysis was done using IBM Statistical Package for Social Sciences Software version 2.0. Standard deviation and 'p' values, Kappa values were calculated. Chi-square test, Student's 't' test, One Way ANOVA test and p value < 0.05 was taken as significant. All statistical tests were interpreted at 5% level of significance.

RESULTS

This study was conducted on 50 patients who had only Transudative PE with the clinical background of CCF, CKD and Hepatic hydrothorax.

CCF was diagnosed in 11 females and 8 males if the patient had oedematous legs, radiological evidence of cardiomegaly, congested lungs and responded to treatment for CCF.

CKD was diagnosed in 6 females and 12 males with raised Sr. urea and Sr. creatinine levels along with signs and symptoms of volume overload.

Hepatic hydrothorax was diagnosed in 4 females and 9 males if the patient had features of liver cell failure, ascites, splenomegaly and evidence of volume overload status.

| Age Group	Frequency	Percent
41 - 50 years	8	16
51 - 60 years	24	48
61 - 70 years	17	34
> 70 years	1	2
Total	**50**	**100.0**
Table 1. Age Distribution of the Study Population (n = 50)		

In our study 82% (41) patients were in the age group of 51 - 70 years, while 16% (8) patients were in the age group of

41 - 50 years and patient's mean age was 57.5 ± S.D. 6.82, minimum 43 years, maximum 75 years of age.
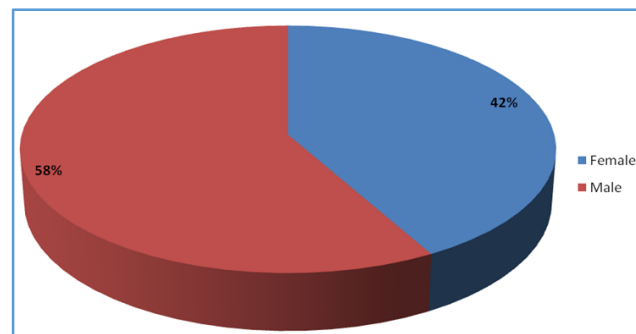
Figure 1. Gender Distribution of the Study Population (n = 50)

Majority of the study subjects were males 58% (29) patients, while remaining 42% (21) patients were females.
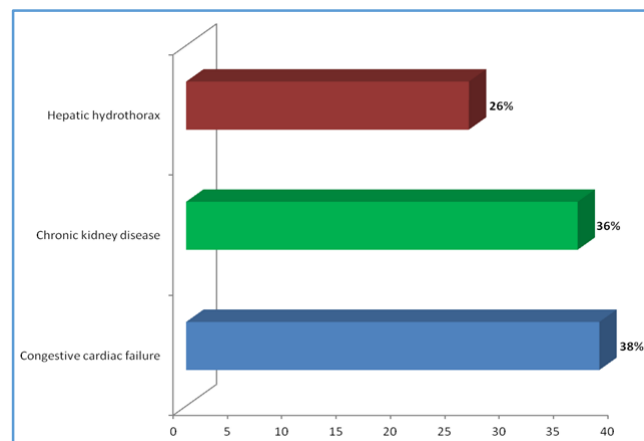
Figure 2. Distribution of the Study Population according to Clinical Diagnosis (n = 50)

About 38% (19) patients had CCF, 36% (18) had CKD and 26% (13) patients had Hepatic hydrothorax.

| Descriptive Statistic	Sr. Protein (gm/dL)	Sr. Albumin (gm/dL)	P.F. Protein (gm/dL)	P.F. Albumin (gm/dL)
Mean	6.26	3.15	2.64	1.32
Standard Deviation	0.2897	0.4427	0.4385	0.2310
Minimum	5.6	2.2	1.8	.9
Maximum	6.8	3.8	3.3	1.8
Table 2. Descriptive Statistics of Sr. and PF Protein and Albumin Levels of the Study Population (n = 50)				

The mean level of protein in Sr. and PF was 6.26 gm/dL and 2.64 gm/dL, respectively. The mean level of Albumin in Sr. and PF was 3.15 gm/dL and 1.32 gm/dL, respectively.

| Descriptive Statistic	(P.F./Sr.) Protein Ratio	(P.F./Sr.) Protein Gradient	(P.F./Sr.) Albumin Gradient
Mean	0.4218	3.622	1.834
Std. Deviation	0.06467	0.4117	0.3414
Minimum	0.31	3.1	1.2
Maximum	0.52	4.5	2.7
Table 3. Descriptive Statistics of Various Parameters for Exudates/Transudate Differentiation (n = 50)			

The mean level of PF Protein to Sr. Protein ratio was 0.42. The mean level of Sr. - PF Protein gradient was 3.62, while Sr. - PF Albumin gradient was 1.8.
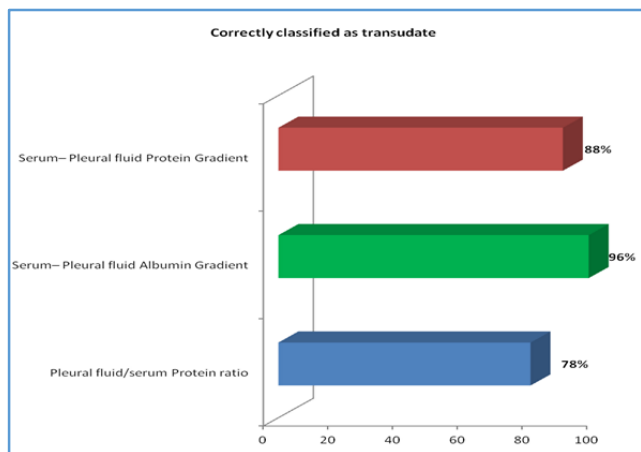
Figure 3. Distribution of Correctly Classified Transudative PF (n = 50)

By applying Light's criteria for PF Protein/Sr. Protein ratio, 78% (39) of the cases were detected as Transudative PE and according to Sr. - PF Albumin gradient, 96% (48) of the cases were detected as Transudative PE. According to Sr. - PF Protein gradient, 88% (44) of the cases were detected as Transudative PE.

The misclassification of subjects as Exudative PE by each criterion does not vary with the type of clinical diagnosis.
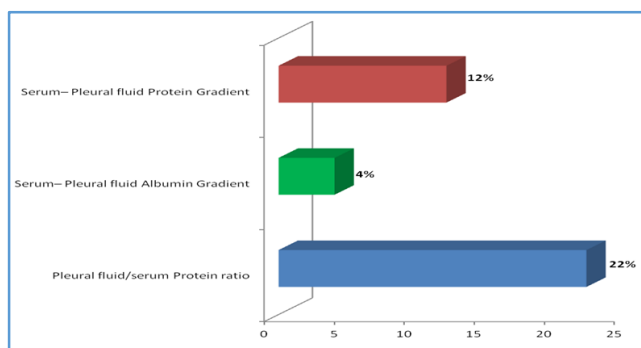
Figure 4. Distribution of Transudates, Wrongly Classified as Exudates

Variables		C.K.D.	C.C.F.	Hepatic Hydro-Thorax	ANOVA Test p value
		Mean	Mean	Mean	
Age		59	58	54	0.165
Sex*	Female	6	11	4	0.20**
	Male	12	8	9	
Sr. Protein (gm/dL)		6.4	6.3	6.0	< 0.001
Sr. Albumin (gm/dL)		3.4	3.4	2.5	< 0.001
P.F. Protein (gm/dL)		2.6	2.7	2.6	0.80
P.F. Albumin (gm/dL)		1.5	1.3	1.1	< 0.001
Table 4. Distribution of Study Population according to Clinical Diagnosis and Baseline Data with Bio-Chemical Parameters (n = 50)					

Criteria		C.K.D.	C.C.F.	Hepatic Hydro-thorax	Chi-Square Test p value
P.F./Sr. Protein Ratio	Transudate < 0.5	15 83.3%	15 78.9%	9 69.2%	0.641
	Exudate > 0.5	3 16.7%	4 21.1%	4 30.8%	
Sr./P.F. Protein Gradient	Transudate > 3.1	17 94.4%	17 89.5%	10 76.9%	0.323
	Exudate < 3.1	1 5.6%	2 10.5%	3 23.1%	
Sr./P.F Albumin Gradient	Transudate > 1.2	18 100.0%	19 100.0%	11 84.6%	0.052
	Exudate < 1.2	0 0.0%	0 0.0%	2 15.4%	
Table 5. Distribution of Type of Pleural Effusion by Various Criteria (n = 50)					

Comments

The misclassification of subjects as exudative PF by each criterion does not vary with the type of clinical diagnosis, i.e. the percentage of misclassification transudate as exudates is similar in all 3 types of clinical diagnosis.

|		Sr. - P.F. Protein Gradient		Total
		Transudate >3.1	Exudate <3.1	
P.F./Sr. Protein Ratio (Light's)	Transudate <0.5	39 (88.6%)	0 (0%)	39 (78%)
	Exudate >0.5	5 (11.4%)	6 (100%)	11 (22%)
Total		44 (100%)	6 (100%)	50 (100%)
Table 6. Agreement between P.F./Sr. Protein Ratio and Sr./P.F. Protein Gradient (n = 50)				

Kappa value: 0.65 (p value: < 0.001)

Comments

There was statistically significant agreement between PE/Sr. protein ratio and Sr. and PF Protein gradient and it was 65%, i.e. about 65% of cases are either correctly classified as transudate or incorrectly classified as exudate by both these criteria.

Graph - 5
Agreement between Pleural fluid/serum protein ratio and Serum– Pleural fluid Albumin Gradient (n=50)
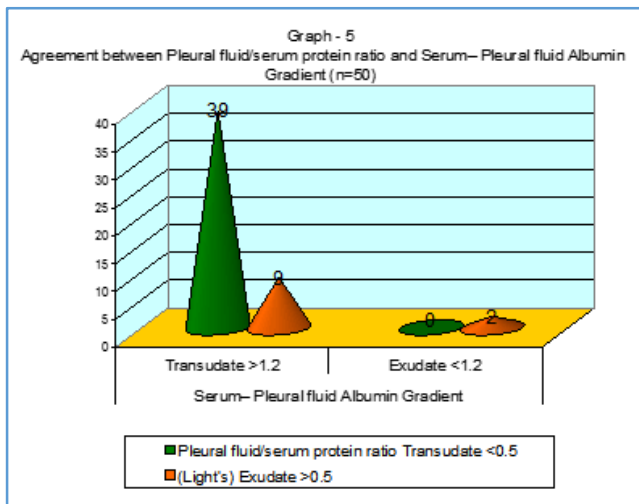
Kappa value: 0.25 (p value: 0.007)

Comments

There was statistically significant agreement between P.E/Sr. protein ratio and Sr. and PF Albumin gradient and it was 25%.

Graph - 6
Agreement between Serum– Pleural fluid protein Gradient and Serum– Pleural fluid Albumin Gradient (n=50)
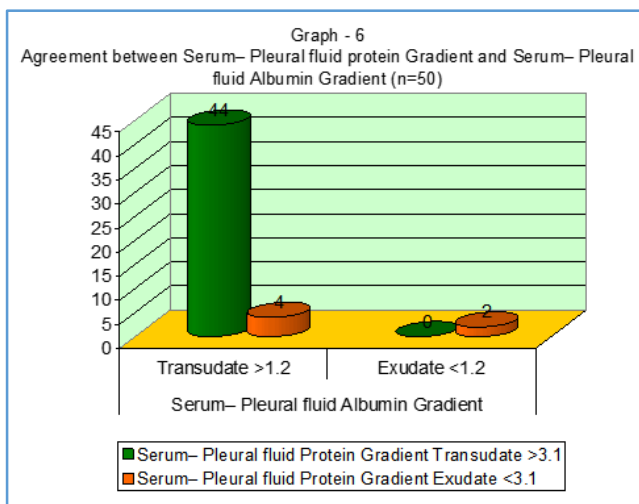
Kappa value: 0.46 (p value: < 0.001)

Comments

There was statistically significant agreement between PF/Sr. protein ratio and Sr. and PF Albumin gradient and it was 46%.

DISCUSSION

In our studies by applying the Light's criteria, about 22% (11) of Transudative PE was wrongly diagnosed as Exudative PE, whereas by applying Sr. - PF Protein gradient the misclassification was only 12% (6) and by applying Sr. - PF Albumin gradient the misclassification was only in 4% (2) cases.

Arijith Kumardas et al[6] evaluated 40 patients of both Transudative and Exudative PE with various parameters and compared to differentiating Transudative PE from Exudative PE. By applying PF to Sr. Protein ratio, 20% of Transudative PE are misclassified as Exudative PE, but Sr. - PF Albumin gradient misclassified only 5%. They have concluded that Sr. - PF Albumin gradient is a very useful parameter between Exudative PE and Transudative PE, especially in cases misclassified by Light's criteria.

Another study by KB Gupta et al,[5] they evaluated a total of 60 patients of PE of varied causes. They measured Sr. - PF Albumin gradient and the results were compared with Light's criteria to distinguish between Transudative PE and Exudative PE. The cut-off value of 1.2 gms/dL was able to differentiate between Transudative PE and Exudative PE with sensitivity of 97.9% and 100%, respectively. They concluded this parameter was found to be better than Light's criteria, especially in respect to misclassified PE.

The study conducted by MC Dhar, S Chaudhuri et al,[7] on 50 patients with PE were evaluated. Sr. - PF Albumin gradient and Light's criteria were compared. Light's criteria misdiagnosed 2 of 5 Transudative, but by using Sr. - PF Albumin gradient all patients were correctly diagnosed. They concluded that Light's criteria was accurate for identifying Exudative PE, but not so much in case of Transudative PE. The Sr. - PF Albumin gradient is accurate equally for Transudative PE and Exudative PE.

A recent study by Silvia Bielsa et al[8] evaluated 364 Cardiac effusions and 102 Hepatic hydrothorax Sr. - PF Albumin ratio and Sr. - PF Albumin gradient were evaluated. Light's criteria misclassified Cardiac effusion and Hepatic hydrothorax as Exudate. Albumin gradient > 1.2 gms/dL correctly identified false Exudative PE and they concluded Albumin gradient is a better indicator in Cardiac effusion.

CONCLUSION

By using Sr. - PF Albumin gradient, our study correctly classified 96% as Transudative PE and by applying Light's criteria in these subjects only 78% of them were classified as Transudative PE. So Light's criteria wrongly classified 22% (11) of Transudative PE as Exudative PE, whereas Sr. - PF Albumin gradient classified only 4% (2) of Transudative PE as Exudative PE. Sr. - PF Protein gradient correctly classified 88% as Transudative PE and wrongly classified 12% of Transudative PE as Exudative PE. The classic criteria of differentiating Exudative PE from Transudative PE by Light's criteria misclassified significant numbers of Transudative PE as Exudative PE.

From our study, it is conclusive that Sr. - PF Albumin gradient is an effective measure of differentiating exudative PE and Transudative PE. This Sr. - PF Protein gradient and Sr. – PF Albumin gradient are especially a good marker for differentiating Transudative PE from Exudative PE in patients with CCF, CKD and Hepatic hydrothorax.

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