The Diagnostic Separation of Transudates and Exudates in Ascitic Fluid and Pleural Fluid

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Abstract

Objectives **: To investigate the utility of fluid and serum values of LDH, cholesterol, protein, albumin and their ratios respectively in differentiating transudate from exudate in ascites and pleural fluids. To compare diagnostic efficacy of these parameters with that of Light's criteria and to identify optimum marker combination for differentiating transudate from exudate.**

Material and Method **: A prospective study of analysis of 100 cases (50 ascites and 50 pleural fluids) was carried out over a period of 6 months. In all these cases, clinical diagnosis was established after clinical examination and appropriate investigations. The fluid and serum levels of protein, albumin, LDH and cholesterol were determined and various ratios were obtained. The statistical analysis was done to find out sensitivity, specificity, accuracy, PPV and NPV of various laboratory parameters. ROC curves were plotted to obtain optimum cut off values for each parameter.**

Results and Conclusion **: The fluid cholesterol (cut off 60 mg/dl) was found to be the best single, cost effective parameter (accuracy 95%) as compared to other parameters including Light's criteria for distinguishing transudates from exudates. The two parameters, fluid cholesterol and fluid/serum cholesterol ratio used in combination had slightly better accuracy than fluid cholesterol alone.**

Introduction

Ascites and pleural effusion are common clinical conditions and pose a diagnostic problem to the clinicians. Pleural effusions and ascitic fluids are classically divided into transudates and exudates. By traditional classification, if fluid protein is more than 3 gm% then it is exudate and fluid protein less than 3 gm% is called transudate.[1] Many discrepancies occur due to this traditional classification. E.g. The 15 - 20% of the cases of ascites due to liver cirrhosis show protein levels more than 3 gm% (i.e. exudative feature). [2] In congestive cardiac failure, total protein level ranges from 1.5 to 5.3 gm% but by definition it should be transudative.[3] Occasionally exudative ascites like malignant ascites have low protein concentration.[1]

The correct diagnosis of fluid as transudate or exudate is important because if fluid is exudative then further diagnostic procedures like cytopathology, pleural biopsy and other invasive procedures can be done on patient for definite diagnosis so that specific therapy can be started. On the other hand, if fluid is transudative then treatment for underlying conditions like CCF, nephrosis, cirrhosis is given.[4]

Many studies have been carried out for differentiating fluids into, transudates

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and exudates. Few showed that Light's criteria are still the best.[5,6,7] Few showed that Fluid albumin gradient (SAAG and SEAG) is the best parameter.[2,5] Few showed that LDH is the best parameter.[8] Few showed that cholesterol is the best parameter.[9,10,11] The present study was undertaken to identify optimum marker combination for differentiating ascitic fluids and pleural fluids into transudates and exudates by using the parameters like fluid LDH, fluid cholesterol, fluid protein, fluid albumin, serum LDH, serum cholesterol, serum protein, serum albumin, and their ratios respectively.

Material and Methods

In this prospective study, total 100 cases (50 ascitic fluids and 50 pleural fluids) were studied over the period of 6 months.

Criteria for Selection of Patients

The patients presenting with ascites and pleural effusion were taken into account. All cases are to be clinically diagnosed and confirmed by laboratory investigations. The diagnosis of patients was made according to the following criteria.

Example :

Cirrhosis : In this group, the patients with signs and symptoms of chronic liver disease, along with characteristic liver function test findings and radiological investigations (USG and OGD scopy findings) suggestive of chronic liver disease.

Tuberculosis : In this group, the patients along with signs and symptoms like evening rise of temperature, loss of weight and appetite, cough with expectoration were supported by raised ESR, sputum for AFB, chest X-ray, biopsy or FNAC of lymph node.

Malignancy : If malignant cells were detected either on cytological examination or in biopsy specimens and or supported by radiological investigations then the patient was categorized in this group.

In the similar way, after confirming the diagnosis, the patients of congestive cardiac failure (CCF), renal failure, nephrotic syndrome, severe anaemia, hypoproteinaemia, parapneumonic effusions and spontaneous bacterial peritonitis were also included in this study.

Biochemical Analysis of Fluid and Serum

10 cc of ascitic fluid or pleural fluid and 5 cc of blood was collected from the patient at the same time in sterile tubes. Samples were processed immediately without any delay. The fluids were centrifuged for 5 min at 1500/rpm. The supernatant fluid and serum were analyzed for protein, albumin, LDH and cholesterol levels by Biuret method, Bromocresol green method, modified IFCC method and enzymatic method respectively.

Laboratory Criteria for Exudates[12]

According to Light's criteria (Light 1972), an exudate meets one or more of following criteria :

Pleural fluid / serum protein ratio > 0.5

Pleural fluid / serum LDH ratio > 0.6

Pleural fluid LDH > 2/3 upper limit of normal serum LDH i.e. > 200 U/L.

The other criteria for exudate are :

Fluid protein > 3 gm/dl

Fluid cholesterol > 60 mg/dl

Fluid / serum cholesterol ratio > 0.3

Serum fluid albumin gradient 1.2 g/dl

Statistical Analysis

Data was analysed and interpreted using SPSS 11.5 software for sensitivity, specificity, accuracy, PPV and NPV of various laboratory parameters. ROC curve (Receiver Operator Characteristic curve) was plotted to find out the optimum cut off value of various biochemical parameters like fluid protein, fluid LDH, fluid cholesterol and serum fluid albumin gradient. This cut off point gives the best accuracy for that particular parameter.

Results

In this study, total 100 fluids were studied out of which 50 were ascitic fluid and 50 were pleural fluid. In the present study, cirrhosis was found to be the most common cause of ascites. The majority patients of ascites were male patients (76%) who were in their 5th decade. Tuberculosis was found to be the most common cause of pleural effusion (56%). Pleural effusions were also seen commonly in the older male patients. Considering the aetiological diagnosis 50 fluids were exudates (43 pleural fluids and 7 ascitic fluids) and 50 fluids were transudates (43 ascitic fluids and 7 pleural fluids) (Table 1). The transudates and exudates of ascitic fluid and pleural fluid were grouped together for proper results evaluation and statistical analysis of biochemical parameters (Table 2). The transudates consist of the cases of liver cirrhosis, nephrotic syndrome, anaemia-hypoproteinaemia and CCF. Exudates consist of the cases of tuberculosis, malignancy, synpneumonic effusion and subacute bacterial peritonitis.

Table 2 : Aetiological classification of 100 cases (50 ascitic fluids and 50 pleural fluids)

Diagnosis	No. of cases (%)
Liver cirrhosis	34 (34%)
Tuberculosis	32 (32%)
Synpneumonia	09 (9 %)
Malignancy	08 (8%)
Nephrotic syndrome	07 (7%)
Anaemia-hypoproteinaemia	07 (7%)
Congestive cardiac failure	02 (7%)
Spontaneous bacterial peritonitis	01 (7%)
Total	100 (100%)

By using cut off value of 3 gm/dl, the parameter fluid total protein level showed sensitivity, specificity and accuracy of 84%, 70% and 77% respectively. By ROC analysis, by using the cut off value of 3.12 gm%, the slightly better sensitivity, specificity of 84 % and72% was obtained respectively

With the cut off value of 1.2 gm/dl, the fluid albumin gradient showed sensitivity of 88%, specificity of 92% and accuracy of 90% respectively. Using the cut off value of 1.12 gm/dl found by ROC analysis, the slightly better sensitivity, specificity of 92% and 88% was obtained respectively.

Table 1 : Categorization of fluids based on diagnosis

Diagnosis	Fluids					
	Ascitis			Pleural effusion		
	Exudate	Transudate	Total	Exudate	Transudate	Total
Liver cirrhosis	-	29	29	-	05	05
CCF	-	02	02	-	00	00
Anaemia-hypoprotein	-	05	05	-	02	02
Nephrotic syndrome	-	07	07	-	00	00
Malignancy	02	-	02	06	-	06
SBP	01	-	01	00	-	00
Synpneumonia	00	-	00	09	-	09
Tuberculosis	04	-	04	28	-	28
Total	07	43	50	43	07	50

(CCF= Congestive cardiac failure , Anaemia-hypoprotein. = Anaemia-hypoproteinaemia , SBP = Spontaneous bacterial peritonitis)

The parameter fluid LDH (cut off value of 200U/L) had sensitivity, specificity and accuracy of 86%, 86% and 86% respectively. With the ROC analysis, by using the newer cut off value of 197.95U/L, the sensitivity and specificity remained same. Light's criteria had sensitivity, specificity and accuracy of 88%, 78% and 81% respectively.

The fluid cholesterol showed highest sensitivity of 96%, specificity of 94%, and accuracy of 95% as a single parameter (cut off value 60 mg %) as compared to other parameters. With the ROC analysis, by using the newer cut off value of 60.06 mg%, the sensitivity and specificity remained same.

The parameter Fluid cholesterol/ serum cholesterol i.e. f/s cholesterol ratio (cut off 0.5) showed sensitivity, specificity and accuracy of 98%, 96% and 97%respectively. Considering both these parameters together i.e. fluid cholesterol level + f/s cholesterol ratio, they had higher sensitivity, specificity and accuracy of 98%, 98% and 98% respectively (Table 3).

Discussion

The aetiological classification of ascites and pleural effusion is quite often a problem especially if the clinical picture is not clear.

Fluid Total Proteins Level

Ascitic or pleural fluid total protein concentration depends upon permeability of pleural mesothelium or peritoneal membrane. During the inflammatory process, alteration of the basement membrane and release of mediators increase the filtration coefficient of pleural or peritoneal capillary membrane leading to accumulation of proteins in fluid.[13] The colloidal osmotic pressure is directly proportional to the protein concentration of the fluid.[13] Also the protein concentration of the fluid is also directly proportional to serum protein concentration and inversely proportional to portal pressure.[2] In transudative fluids due to liver cirrhosis, nephritic syndrome, anaemia-hypoproteinaemia, there is decrease in serum total protein level and decrease in serum albumin and increase in serum globulin as found by the previous workers.[14]

In the present study the parameter fluid total protein (cut off value of 3 gm/dl) had lowest accuracy as compared to other parameters (Table 3). With the ROC analysis, by using the newer cut off value of 3.12 gm%, the sensitivity, specificity of 84% and 72% was obtained respectively but it had never attained the position of the best parameter for differentiation between transudate and exudate.

Table 3 : Diagnostic validity of various biochemical parameters in all 100 cases

Parameter	Cut off value	Sen.	Speci.	Accu.	PPV	NPV
Fluid protein	3 gm%	84%	70%	77%	73.6%	81.4%
Fluid LDH	200U/L	86%	86%	86%	86%	86%
Light's criteria	–	88%	88%	88%	88%	88%
Fluid albumin gradient	1.2gm%	88%	92%	90%	91.6	88.4%
Fluid cholesterol	60mg%	96%	94%	95%	94.1%	95.9%
Cholesterol F/S ratio	0.5	98%	96%	97%	96.0%	97.9%
Fl. chole. + Chole. F/S ratio	–	98%	98%	98%	98%	98%

(Sen. = Sensitivity, Speci.= Specificity, Accu.= Accuracy, PPV= Positive Predictive Value, NPV= Negative Predictive Value, Fl. chole.= Fluid cholesterol, Chole. F/S ratio = Cholesterol Fluid /Serum ratio)

Fluid Albumin Gradient

Serum ascitic albumin gradient (SAAG) and Serum effusion albumin gradient (SEAG)

In contrast to the concept of transudate and exudate, SAAG and SEAG are found to categorize fluids in much better way[2] because it is influenced by only one variable-portal pressure.[3] The poor accuracy of fluid total protein concentration in classifying fluids can be explained by its dependence on multiple factors. SAAG or SEAG = serum albumin concentration fluid albumin concentration. Patients with a gradient of 1.1gm/dl or more have portal hypertension and transudative effusion and vice versa.[15] In the present study, the parameter fluid albumin gradient (cut off value of 1.2 gm/dl) had better accuracy (90%) than fluid total protein parameter (accuracy 77%).

Fluid Lactate Dehydrogenase (LDH) level

LDH levels in fluids are increased in presence of inflammation. Acute inflammation results in increased permeability of vascular supply of pleura or peritoneum and thereby leading to exudation of fluid proteins including LDH along with leucocytes into fluids, or LDH may be derived from fluid leucocytes. It has been shown that alteration of LDH activity in body fluids may occur in absence of actual tissue necrosis. In cases of malignancy, possible mechanism for increased LDH levels is increased glycolytic activity or overproduction of enzyme by tumour cells.[16]

Paramothayan *et al* (cut off value of 130 U/L) [17] and Basran *et al* (cut off value of 163 U/L) [8] have tried different cut off values of fluid LDH which raised the accuracy of fluid LDH. Hence fluid LDH was found to be a better parameter than other parameters. But in the present study, we found that fluid cholesterol (accuracy 95%) is a better parameter than fluid LDH (accuracy 86%).

Light's criteria[4]

Test combination, increases sensitivity, improves accuracy and are the basis for Light's criteria. It includes fluid/serum protein ratio, fluid/serum LDH ratio and fluid LDH level.[12] Burgess *et al*[5] and Romero *et al*[6] showed that Light's criteria are the best criteria to differentiate fluids into transudates and exudates than other parameters including fluid cholesterol. In the present study, we found that Light's criteria had less accuracy (81%) than fluid cholesterol.

Fluid cholesterol level

The possible explanations for rise in cholesterol levels in fluid exudates have been put forward. The cholesterol is synthesized by pleural cells themselves for their own needs (extrahepatic synthesis of cholesterol is now known to be much greater than was once thought) and it depends upon the metabolic needs of cells and is in dynamic equilibrium with cholesterol supply by LDL and cholesterol removal by HDL. The concentration of cholesterol in the pleural cavity is increased by degeneration of leucocytes and erythrocytes which contain large quantity of it. The second possible explanation is that pleural cholesterol derives from plasma; some 70% of plasma cholesterol is bound to LDL and rest to HDL or VLDL and the increased permeability of pleural capillaries in pleural exudates patients would allow plasma cholesterol to enter the pleural cavity.[11] The pathogenesis of high ascitic

cholesterol levels in patients with malignant disease is unknown. It has been suggested that a fraction of the cholesterol could be derived from malignant cell membranes.[15] Another possibility is that cancer cells cause a relative blocking of lymphatic drainage from the peritoneal space and such blocking may lead to sequestration of cholesterol rich macromolecules in the peritoneal cavity.[9,15]

Differences in the serum cholesterol concentration are unlikely to explain high cholesterol level in ascitic fluid because there is no significant difference in serum cholesterol concentration between patients with benign and malignant diseases. Also no correlation found by the previous workers between fluid cholesterol levels and serum cholesterol level. Also no correlation was found by previous workers between cholesterol fluid levels and number of leucocytes / cmm.[11]

In the present study, fluid cholesterol level showed the highest sensitivity, specificity, and accuracy among all the parameters. Different cut off values used by various workers like Hamm *et al*, Valdes *et al*, Costa *et al*, Suay *et al*, Ram *et al*, Prieto *et al*[7] showed the raised sensitivity, specificity and accuracy of the parameter fluid cholesterol. Thus they showed that fluid cholesterol is the best parameter.

Fluid cholesterol/serum cholesterol (f/s cholesterol ratio)

Cut off value of 0.5 for cholesterol f/s ratio was used in the present study to differentiate between transudate and exudates. In this study, it had slightly higher sensitivity and specificity than fluid cholesterol alone.

Considering both these parameters together i.e. fluid cholesterol level + f/s cholesterol ratio, they had highest accuracy than the parameter fluid cholesterol level alone. Similar results were also obtained by Ram *et al.*[10]

Conclusion

As a single best parameter, fluid cholesterol level is a simple and cost effective parameter to differentiate ascitic and pleural fluids into transudates and exudates. The two parameters, fluid cholesterol and f/s cholesterol ratio used in combination had slightly better accuracy than fluid cholesterol alone.

The most commonly used parameter; fluid total protein was found to have lowest accuracy as compared to other parameters like fluid LDH, fluid cholesterol, and fluid albumin gradient.

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MIGRAINE WITH AURA AND THE RISK OF INCREASED MORTALITY

Evidence suggests that people who have migraine **"with aura"** have increased risks of cardiac and cerebrovascular disease.

Once the diagnosis of migraine **"with aura"** is made the next important question is whether the clinician should inform the patient about the increased risk of future vascular disorders and death. Information and treatment of any concurrent risk factors and comorbidities, such as hypertension or overweight, is advised.

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