JOURNAL OF CLINICAL AND BIOMEDICAL SCIENCES

ORIGINAL ARTICLE

OPEN ACCESS

Received: 24-05-2025
Accepted: 24-10-2025
Published: 31-03-2026

Citation: Ranjan A, Zaheer A, Yumkhaibam S, Shashwat V. Biochemical Analysis of Ascitic Fluid in the Differentiation of Transudate vs Exudate. 2026; 16(1):29-33. https://doi.org/10.58739/jcbs/v16i1.25.244

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Funding: None

Competing Interests: None

Published By Sri Devaraj Urs Academy of Higher Education, Kolar, Karnataka

ISSN
Print: 2231-4180
Electronic: 2319-2453

Biochemical Analysis of Ascitic Fluid in the Differentiation of Transudate vs Exudate

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Abstract

Background: Ascites is a common clinical problem resulting from certain abdominal or systemic diseases. The effusion is likely to be exudative or transudative in nature. Biochemical parameters, serological markers and cytology are used in classifying ascites. Combination of the clinical and cytological findings along with the biochemical parameters help in assessing the cause of these effusions. **Materials and Methods**: Two hundred fluid samples from cases presenting with ascites along with their simultaneous serum were collected and analysed for different parameters. The ascitic fluid was further studied for biochemical parameters including protein, albumin, glucose, cholesterol, Alkaline Phosphate, bilirubin, amylase, cell counts total and differential, Gram's stain and, Modified Ziehl-Neelsen stain for AFB based on which they were categorised into different groups. Serum samples were also assayed for protein, albumin, bilirubin, cholesterol and amylase levels. SAAG was used to assess the type of ascites. **Results**: Of these 200 samples, 145 (71.2%) were exudates and 55(28.8%) were transudates. There were 131 males and 69 females, with a M:F ratio of 1.90:1. Tuberculosis followed by peritonitis and malignancy were amongst the common etiologies seen in exudative effusions. Among transudates, alcoholic hepatitis followed by liver cirrhosis and anaemia with hypoproteinaemia were the commonest cause observed.

Keywords: Effusion, SAAG Biochemical, Exudate, Transudate

1 Introduction

Ascites is defined as excessive collection of free fluid in the peritoneal cavity. Peritoneal effusions are a common clinical problem resulting from various abdominal or systemic conditions. Several biochemical, serological and cytological markers are used in classifying and sub typing these effusions[1, 2]. The imbalance in the level of plasma may be as a result of increased capillary permeability, raised venous pressure, reduced protein concentration (oncotic pressure), or increased obstruction of the lymphatics. Ascites may be broadly classified as transudate or exudate[2]. Transudates have a low protein content whereas the protein content in exudates is much higher. The etiology of transudative effusion include mainly congestive cardiac failure, cirrhosis of liver, kidney failure and, anaemia with hypoproteinemia while, for exudative effusion includes malignancy encompassing both primary and secondary types, tuberculosis and, other granulomatous pathologies apart from parasitic or viral infections[3, 4]. Exudative ascites is due to inflammation and tumor studded peritoneal surface so is rich in protein content suggestive of peritonitis or malignant ascites[5].

Cytological evaluation helps in differentiating between the reactive mesothelial cells and the malignant cells. Combination of the clinical observations along with the biochemical findings and cytological findings help in estimating the cause of ascites[6]. SAAG [Serum Ascites Albumin Gradient] has been developed as a new approach, to classify ascites into two categories- High SAAG ≥1.1 g/dl in patients with portal hypertension and Low SAAG ≤1.1 g/dl in patients with ascites, unrelated to portal hypertension. SAAG indicates the oncotic pressure exerted by serum Albumin over ascitic fluid Albumin which equals the high hydrostatic pressure gradient between the portal bed and the ascitic fluid[7, 8].

1.1 Aim & Objectives

The study was undertaken with the aim of analysing the biochemical findings in ascitic fluid samples, paralleled with the serum samples so as to estimate the cause of ascites.

2 Material & Methods

The present study was conducted in the Pathology department of a tertiary care teaching institute of Rajshree Medical Research Institute, Western Uttar Pradesh from July 2023 to December 2024. A total of 200 cases who presented with ascites were included in this study. All the patients enrolled during the research period and who met with the inclusion and exclusion criteria were included in the present study. Patients who had bleeding diatheses, previous abdominal surgery, or bowel distension were excluded out from the study. The tests conducted on the ascites samples included total protein and albumin levels, glucose, LDH, cell counts i.e. total and differential, Adenosine deaminase (ADA) level Gram's stain, culture for bacteria and, Modified Ziehl Neelsen stain for AFB. Serum samples were also simultaneously collected for the estimation of total protein, albumin, glucose and LDH. Modified Ziehl-Neelsen, PCR, culture using LJ media, and peritoneal biopsy were used as ancillary techniques in problematic cases for arriving at the diagnosis of ascites.

The Serum Ascites Albumin Gradient (SAAG) was calculated by subtracting the albumin level in the ascitic fluid from the albumin level detected in the serum.

2.1 Statistical Analysis

Statistical measures were applied. Quantitative data were plotted as mean±1SD. Student t-test was used to calculate the p value. p value equal to or less than 0.05 was considered as statistically significant.

3 Observations & Results

A total of 200 samples of peritoneal fluid paralleled with blood samples from those patients who presented with ascites were studied in the present research project. The pattern of the etiologies in various ages and different sexes is depicted in Table. 1. Out of the 200 patients included, 145(72.5%) cases were exudative and 55(27.5%) were transudative. Amongst the 145 exudates, majority of the patient had tuberculous effusion, followed by 18(22%) cases of peritonitis and malignancy each and, non-specific inflammatory pathology in 15 (Table. 1). Among the parasitic infestations, filariasis and hydatid cyst were the important causes.

Amongst 55 patients with transudative fluid, majority of the ascites was because of alcoholic hepatitis followed closely by liver cirrhosis and anaemia with hypoproteinaemia in 11 cases each (Table. 1).

Of the 145 exudates, 90 were males and 55 were females (Table. 1) with a M:F ration of 1.64:1. As regards the age and gender division of the cases, of the total 145 exudates, majority 49(42.7%) were in the age range of 41-60 years (80.2%) with a male preponderance (Table. 1). Amongst all cases of malignant ascites, which included 11 males and 7 females with majority (16 patients) belonging to the age of more than 61 years with a male:female ratio of 1.57:1. There were 15(17.4%) patients with non-specific exudative fluid. These patients were labeled as non- specific as the diagnosis could not be made in spite of a thorough panel of investigations (Table. 1). Of the 55(28.8%) patients with transudates, the distribution included 41(63.8%) males and 14 (36.2%) females (Table. 1). In the transudates, category, majority of the cases belonged to the age group of 41-60 years. All the peritoneal aspirates were divided into exudative and transudative as per the different criterias. Among the tubercular etiology of effusions, Modified Ziehl-Neelsen stain yielded AFB in 10 (17.9%) patients. The sensitivity of ZN stain in the detection of AFB in effusions with tuberculosis was 17.5%.

Table 1: Showing distribution of patients of Ascites as per the age-group and etiology

Final Diagnosis	Age group in years and sex								Total		Total	
	< 20		21- 40		41- 60		> 61					
	M	F	M	F	M	F	M	F	M	F	n	%
Exudates	7	6	20	16	33	16	30	17	90	55	145	72.5
Tuberculosis	2	2	2	1	19	5	17	6	40	14	54	37.24
Malignant effusion	-	-	-	-	1	1	10	6	11	7	18	12.41
Peritonitis	1	1	3	3	2	4	-	1	6	9	15	10.34
Intestinal obstruction	1	1	4	3	2	2	1	1	8	7	15	10.34
Parasitic infestation	1	1	3	4	2	2	1	1	7	8	15	10.34
Non-specific pathology	2	1	4	2	3	1	-	1	9	5	14	9.655
Ischaemic colitis	-	-	2	2	1	1	1	-	4	3	7	4.828
Pancreatitis	-	-	2	1	3	-	-	1	5	2	7	4.828
Transudates	1	2	6	5	21	4	13	3	41	14	55	27.5
Alcoholic Hepatitis	-	-	2	-	6	-	5	-	13	-	13	8.966
Liver Cirrhosis	-	-	-	-	7	-	4	-	11	-	11	7.586
Anemia with hypoproteinemia	1	2	1	3	1	2	-	1	3	8	11	7.586
Nephrotic Syndrome	-	-	2	2	2	1	1	-	5	3	8	5.517
Portal Hypertension	-	-	1	-	3	1	1	-	5	1	6	4.138
Congestive heart failure	-	-	-	-	1	-	1	2	2	2	4	2.759
Portal vein thrombosis	-	-	-	-	1	-	1	-	2	-	2	1.379
Total	8	8	26	21	54	20	43	20	131	69	200	

4 Discussion

Of the 200 ascitic fluid samples, 145(71.2%) were exudative and 55(28.8%) were transudative. A similar pattern was observed in studies by some of the previous authors[9-11]. In countries such as India tuberculosis constitutes an important cause of exudative effusions[12]. This finding is similar to the observations made in previous studies[1, 10, 11, 13-15]. These findings are different from that of the European countries where the incidence of malignancy is much higher as compared to that of tuberculosis[16].

The present study included 15(7.5%) patients with exudative type of effusions in which in spite of all diagnostic modalities the exact aetiology could not be identified so were labelled as nonspecific pathology. This observation is in consistence with the findings made by some of the previous authors[17-19].

The commonest etiology of transudative type of effusion included alcoholic hepatitis (7.0%) followed by liver cirrhosis and anaemia with hypoproteinaemia in 11(5.5%) each. Congestive cardiac failure accounted for only 2.0% of all transudates. This observation was not in conjunction with the data of the European Countries where heart failure is reported to be the most common etiology of transudates[18, 20, 21].

The gross appearance of the fluid can provide useful diagnostic information. In majority of the patients with cirrhosis the peritoneal fluid appeared clear and straw-colored. Blood in the fluid could be due to a traumatic tap in which case the fluid showed a clot when allowed to stand. Fluids that remained uniformly blood mixed usually indicate towards malignancy, pancreatitis, tuberculosis, or a history of recent abdominal trauma[22-24].

Total protein concentration in the ascitic fluid has been used to determine whether the fluid is transudative or exudative in nature[12, 22]. The observation of our study revealed that the ratio of ascitic fluid protein and serum protein play a vital role in the differentiation of transudatives from exudatives which was statistically significant ($p<0.0001$). The sensitivity and specificity rates were 88.2%, and 54.5% respectively. The misclassification rate calculated was 31.5%. In contrast, Selvaraju *et al.* estimated the protein levels in fluid in 40 patients and observed the sensitivity rate as 80% and specificity rate as 70% with a classification error rate as 25%[12].

Analysis of ascitic fluid helps in differentiating between transudative or exudative categories, as well as in the confirmation of the diagnosis. The biochemical and cytological findings aid in the diagnosis and further help in deciding the further procedure to be followed in the diagnostic work up. If the fluid is transudative in nature, more detailed analysis can be excluded out[25]. It is also possible that with diuretic therapy the concentration of the parameters in the fluid increases, even reaching the exudative range[26-31]. Ascites with high protein content ($\geq$ 25 g/L) indicates exudative nature resulting due to malignancy or infections, whereas fluids with low content of protein (< 25 g/L) suggest transudative aetiology[7]. 15 – 20% of ascites due to liver cirrhosis may show increased protein levels, confirming to be exudates[7]. To identify cirrhosis as the aetiology of fluids SAAG is presently used, where gradient values of greater than or equal to 11 g/L are classified as ascites due to portal hypertension, and values less than 11 g/L as ascites due to non – portal hypertension reasons, including malignancy. Using this method, diagnosis of ascites due to portal hypertension in patients having cirrhosis can be achieved with great accuracy to the tune of 97%[20, 29, 30].

Gupta *et al.* in their report stated that 24% of all cases who had uncomplicated cirrhosis had the total protein concentration in Ascites fluid greater than 25 g/L, whereas Alexandrakis *et al.* stated that nearly one-fifth of malignant ascites had low protein concentration[1, 7]. SAAG has a higher sensitivity and specificity in the differentiation of portal hypertension resulting due to other causes especially peritonitis. The serum pleural fluid gradient for protein and albumin serves as the most ideal method for distinguishing between exudates and transudates especially in patients of congestive cardiac failure on diuretic therapy[32].

SAAG, which was first suggested by Hoefs *et al.* in the year 1981, serves as an important maker for dividing ascites[19]. SAAG is usually low (<1.1 g/dL) in ascites not resulting due to portal hypertension, such as in infection or malignancy. While it is high (>1.1 g/dL) in portal hypertension-related ascites, such as in liver cirrhosis or congestive cardiac failure[16, 19]. SAAG has now been incorporated in the British and American guidelines as an initial testing method in patients of ascites[8, 33].

In a previous study it was observed that 8% of all exudates and 15% of all transudates were wrongly classified as per this criterion[15]. It was also observed that the rate of misclassification was 28.8% in which 65 fluids were mistyped as exudates and 7 as transudates by fluid LDH alone, with a sensitivity rate of 63.4% and a specificity rate of 90.2%. This study highlighted that ascitic fluid LDH accurately diagnosed 64% of exudates including inflammatory pathology. Our results are in concordance with that of the previous workers who reported sensitivity rate of 65% and specificity rate as high as 95%[2]. The LDH levels may be raised in inflammatory ascites. Activated, damaged or dead mesothelial cells and other inflammatory cells that migrated into the peritoneal cavity during inflammation are an important source of peritoneal fluid LDH[2, 8].

Among the misclassified transudates, serum LDH levels were lower as compared to the ascitic fluid LDH levels. The findings are consistent with the data of the previous authors who stated that the LDH concentration in fluids is independent of

the level in serum. The LDH concentration in fluids with low level of serum LDH can lead to a high LDH ratio leading to misclassification of transudates as exudates[8]. Such cases were truly classified by albumin gradient in the serum against that in the fluid.

In our study, the SAAG ratio was observed to be a sensitive (97.7%) criterion of diagnosing exudative fluids. This observation was in concordance with those of the previous other studies. However, specificity rate (41.6%) of SAAG was observed to be less in our study. This distinction of transudative from exudative fluids was observed to be statistically significant (p value=0.0001). Ascitic fluid analysis using Serum Ascitic Albumin Gradient (SAAG) was one of the best methods to diagnose the underlying etiology. High SAAG indicated portal hypertension even with high ascitic fluid protein. It was observed to be superior as compared to the earlier transudate-exudate classification, due to its better diagnostic accuracy rate and also since it gives a better approach to the etiology and pathogenesis of ascitic fluid.

In few cases, ancillary tests such as abdominal and pelvic CT scan, ECG, Thyroid function tests, Upper GI endoscopy and Cytology of peritoneal nodules or a liver biopsy may be required to ascertain the exact underlying cause of ascites. The British Society of Gastroenterology and American Association of the Study of Liver Disease (AASLD) have now included SAAG in their guidelines of investigations for ascites resulting because of cirrhosis[2, 8, 25].

Peritoneocentesis has thus proved to be a safe procedure without any side effect or may carry an occasional mild complication.

5 Conclusion

Diagnosing ascites starts with the patient clinical history, physical examination, and investigating ascitic tap when appropriate. Ascites can be a result or complication of numerous primary diseases and has with it unfavorable prognosis largely depending on the underlying etiology.

Ascitic fluid analysis includes gross examination, biochemical tests (e.g. SAAG, LDH, glucose, amylase, and ADA), and non-biochemical tests (e.g. cell counts, culture for bacterial PCR, and tumor bio-markers assays) providing useful assistance in the differential diagnosis as well as in establishing the final diagnosis.

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