Journal of Clinical Gastroenterology and Hepatology
ISSN: 2575-7733

Open access Research Article

Importance of Cholesterol Determination in Ascitic Fluid to Identify the Etiology of Ascites

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ABSTRACT

Background: Abdominal paracentesis with appropriate fluid analysis is considered the most rapid and cost-effective method of diagnosis the etiology of ascites.

Objective: The aim of this study is to examine the diagnostic value of ascites fluid cholesterol levels for differentiating between various etiologies of ascites.

Materials and methods: An analytic descriptive study was conducted in adult patients with a diagnosis of ascites. They are selected from gastroenterology department, Tishreen University Hospital between April 2021 and April 2022.

Results: A total of 142 patients, 84 males (59.2%) and 58 females (40.8%) were included in the study. Portal hypertension related ascites represented the most frequent pathophysiology of ascites (47.8%), followed by non-portal hypertension (43.7%) and mixed ascites (8.4%). There were significant differences between various etiologies of ascites regarding cholesterol levels in which high levels were observed in tumors (72.68 ± 32.7), followed by non-related portal hypertension (50.80 ± 7.8), and mixed ascites (43.41 ± 32.12), p:0.0001. Additionally, levels of SAAG were different significantly according to the etiology of ascites, in which high levels were found in portal hypertension related ascites (2.06 ± 0.4), followed by heart failure (1.95 ± 0.4), and cirrhosis (1.66 ± 0.5), p:0.0001. The mean value of serum ascites cholesterol gradient was higher in cirrhosis (92.57 ± 24.5) versus (63.78 ± 38.9) in tumors, p:0.0001. Serum ascites cholesterol gradient was significantly higher in portal hypertension (89.73 ± 24.9) versus (58.64 ± 41.2) in non-portal hypertension, p:0.001. In portal hypertension related ascites, sensitivity and specificity of cholesterol were 85.19% and 77.41% respectively, whereas sensitivity and specificity of SAAG were 91.17% and 69.35% respectively. Using of combination cut off for: Cholesterol <45 mg/dL and SAAG ≥ 1.1 led to specificity 91.93%. In non-portal hypertension related ascites, sensitivity of cholesterol was 77.41%, whereas specificity of SAAG was 91.17%. Combination of Cholesterol <45 mg/dL with SAAG ≥ 1.1 led to specificity 100%.

Conclusion: The current study demonstrated that cholesterol (cutoff 45 mg/dL) has suitable diagnostic value in distinguishing between portal from non-portal hypertension etiologies for ascites and also help in addition to atypical cells analysis in distinguishing between malignant from non-malignant ascites (cutoff 75 mg/dL). So we should routinely determine this simple and cost-effective measure in all new-onset ascites and in all patients with portal hyper tension ascites who do not respond to treatment because these patients maybe have mixed ascites.

Keywords: Ascites; Cholesterol; Fluid analysis

Received:	01-June-2022	**Manuscript No:**	IPJCGH-22-13809
Editor assigned:	03-June-2022	**PreQC No:**	IPJCGH-22-13809 (PQ)
Reviewed:	17-June-2022	**QC No:**	IPJCGH-22-13809
Revised:	22-June-2022	**Manuscript No:**	IPJCGH-22-13809 (R)
Published:	29-June-2022	**DOI:**	10.36648/2575-7733.6.6.29

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Citation Alkharfan O, Zaizafoun H, Daghman D (2022) Importance of Cholesterol Determination in Ascitic Fluid to Identify the Etiology of Ascites. J Clin Gastroenterol Hepatol. 6:29

INTRODUCTION

Ascites is defined as the pathologic accumulation of fluid inside the peritoneal cavity [1]. There are numerous etiologies of ascites, but the most common cause is parenchymal liver disease, followed by malignancy related ascites and ascites due to heart failure [2]. Approximately 5% of patients have more than on cause, usually cirrhosis with peritoneal carcinoma or tuberculosis peritonitis [3].

Ascites is divided traditionally into two groups based on levels of total protein: transudates (<2.5 mg/dL) due to increased leakage of fluid secondary to high intravascular pressure, and exudate which represents protein rich fluid (protein>2.5 mg/dL) secondary to infection, hemorrhage, inflammation, or neoplasia [4]. Serum Ascites Albumin Gradient (SAAG) had replaced the traditional method of classification, and the level of SAAG ≥ 1.1 is associated with increased portal pressure [5].

Abdominal distension represents the common clinical manifestation of ascites that may be painless or associated with abdominal discomfort. The time for development of distension is dependent on the etiology of ascites, which may develop over days or months [6]. Other patients, complaints regarding ascites include weight gain, shortness of breath, early satiety and dyspnea. Patients may develop spontaneous bacterial peritonitis with additional manifestations that include fever, abdominal tenderness, and altered mental status. In addition to that, there are lots of symptoms related to the potential disease [7].

Diagnosis of ascites depends on combination of physical examination and imaging tests of abdomen. After that abdominal paracentesis is considered an essential step to determine the etiology of ascites through routine tests that performed on samples obtained from ascitic fluid [8]. These tests include: appearance, SAAG, cell count, total protein. Other tests may be performed to confirm the etiological diagnosis such as: glucose, lactate dehydrogenase, amylase, triglyceride, bilirubin, and cytology [9]. Successful management of ascites depends on accurate determination of the etiology. Some studies have proved the diagnostic value of cholesterol in differentiating various causes of ascites, with conflicting results in identical studies. Therefore, the aims of this study were:

1. To investigate the diagnostic value of cholesterol level of ascitic fluid in determining the etiology of ascites.
2. To determine the diagnostic accuracy of cholesterol cut-off 45 mg/dL compared to SAAG.
3. To identify the most frequent etiology for ascites.

PATIENTS AND METHODS

It was a prospective, cross-sectional study conducted in three university teaching hospitals in Yaounde for a period of 12 months from November 1st 2013 to October 31st 2014. All patients underwent a detailed clinical evaluation at inclusion. Patients with evidence of hepatocellular carcinoma and/or portal vein thrombosis on ultrasonography or computer tomography, previous or current treatment with beta blockers, nitrates and diuretics were excluded from the study including those who had received endoscopic treatment for portal hypertension.

Study Population

After approval by local research ethics committee, an analytic descriptive study was conducted in adult's patients admitted at Gastroenterology and Hepatology department at Tishreen University Hospital over a period of one year from April 2021 to April 2022.

Inclusion criteria were as follows: Patients who underwent to diagnostic abdominal paracentesis.

Exclusion criteria: Patients with renal failure who underwent dialysis, bloody ascites due to trauma, and incomplete medical data of patients. Complete history, review of systems, physical examination, and laboratory and radiology investigations were performed to determine the etiology of ascites. Ascitic samples were obtained and sent for analysis. Levels of cholesterol, SAAG and SACG were determined in all samples. SACG was calculated by measuring the cholesterol concentration of serum and ascitic fluid specimens and simply subtracting the ascitic fluid value from the serum value.

Statistical Analysis

Statistical analysis was performed by using IBM SPSS version 20. Basic Descriptive statistics included means, standard deviations (SD), median, Frequency and percentages. To examine the relationships and comparisons between the two groups, chi-square test or Fisher's test was used. Independent t student test was used to compare 2 independent groups. One way analysis of variance (ANOVA) was used to determine whether there are any statistically significant differences between the means of more two independent groups. All the tests were considered significant at a 5% type I error rate ($p<0.05$), β:20%, and power of the study:80%.

RESULTS

A total of 142 cases of ascites in adults were studied during study period. Ages range from 18 years to 85 years (mean 57.14 ± 11.4 years). The maximum cases in the study were males constituting 84(59.2%) and females were 58(40.8%). Patients were classified according to the underlying pathophysiology of ascites into three groups: portal hypertension in 68 cases (47.8%), non-portal hypertension in 62 cases (43.7%), and mixed in 12 cases (8.4%). The etiologies of ascites resulting from portal hypertension were classified into five groups: liver cirrhosis in 56 cases (39.4%), heart failure in 7 cases (4.9%), Budd Chiari syndrome in 3 cases (2.1%), portal vein thrombosis in 1 case (0.7%), and sub-acute liver cirrhosis in 1 case (0.7%). Ascites resulting from non-portal etiologies included the main four categories; tumors (40.2%), pancreatitis (2.1%), visceral perforation (0.7%), and nephrotic syndrome (0.7%). The most common causes of cirrhosis were as follow: idiopathic in 18 cases (12.7%), alcoholic fatty liver disease in 14 cases (9.9%), hepatitis C in 11 cases (7.7%), hepatitis B in 8 cases (5.6%), autoimmune hepatitis in 3 cases (2.1%), and non-alcoholic fatty liver disease in 2 cases (1.4%) whears the most common causes of malignant related ascites were colorectal cancer then ovarian and gastritic tumors. Among patients with mixed ascites, all patients have SAAG value ≥ 1.1 mg/dL and only 5 patients (1 pancreatitis, 1 peritoneum carcinoma, 1 nephrotic syndrome, 1 pancreatic tumor, 1 prostate carcinoma without peritoneum

metastasis) have cholesterol level <45 mg/dL (Tables 1 and 2).

Table 1: Distribution of the study population according to demographic characteristics and etiologies

Variable	Result
Age (years)	57.14 ± 11.4(18-85)
Gender	
Male	84(59.2%)
Feamle	58(40.8%)
Etiology of ascites	
Portal hypertension	68(47.8%)
Liver cirrhosis	56(39.4%)
Heart failure	7(4.9%)
Budd Chiari syndrome	3(2.1%)
Portal vein thrombosis	1(0.7%)
Sub-acute liver cirrhosis	1(0.7%)
Non-portal hypertension	62(43.7%)
Tumors	57(40.2%)
Pancreatitis	3(2.1%)
Visceral perforation	1(0.7%)
Nephrotic syndrome	1(0.7%)
Mixed ascites	12(8.4%)

Table 2: Causes of mixed ascites mixed ascitesa

Mixes ascites (12 patients)								
Buddchiari syndrome	**HCV cirrhosis**	**Auto-immune cirrhosis**	**HBV cirrhosis**	**Alcholic cirrhosis**	**Alcholic cirrhosis**	**Heart failure**	**Heart failure**	**Portal hyper tension causes**
Pancreatic tumor	Nephrotic syndrome	Nephrotic syndrome	Prostate Cancer	Lung cancer	Alcoholic pancreatitis	Alcoholic pancreatitis	*malignant causes	Non-portal hyper tension causes
1	1	1	1	1	1	1	5	12

Statistically, there was a significant difference between ascetic fluid cholesterol levels according to the etiologies, in which high levels were found with malignancy related ascites (72.68 ± 32.7) followed by benign miscellaneous non-portal hypertension (50.80 ± 7.8) and mixed etiologies (43.41 ± 32.12). Lower cholesterol levels were found in heart failure (31 ± 16.46), cirrhosis (24.53 ± 15.5), cirrhosis with Spontaneous Brimary Pertonitis (24.12 ± 14.5), and miscellaneous portal hypertension (19.20 ± 15.6), p: 0.0001. There was a significant difference between ascetic fluid SAAG levels according to the etiologies, in which high levels were found with miscellaneous portal hypertension (2.06 ± 0.4), followed by heart failure (1.95 ± 0.4), and cirrhosis (1.66 ± 0.5). Lower SAAG levels were found in mixed ascites (1.64 ± 0.2), followed by cirrhosis with SBP (1.58 ± 0.8), tumors (0.84 ± 0.3), miscellaneous non-portal hypertension (0.64 ± 0.1), p: 0.0001 (Table 3).

Table 3: Chemical parameters according to the etiology of ascites

Variable Etiology of ascites	Cholesterol	SAAG
Cirrhosis	24.53 ± 15.5(6-60)	1.66 ± 0.5(0.60-2.70)
Cirrhosis with SBP	24.12 ± 14.5(5-57	1.58 ± 0.8(0.56-2.62)
Heart failure	31 ± 16.46(17-56)	1.95 ± 0.4(1.50-2.70)
Buddchiari-syndrome, portal vein, thrombosis, sub-acute liver failure.	19.20 ± 15.6(8-46)	2.06 ± 0.4(1.70-2.80)
Mixed		
Tumors	43.41 ± 32.12(6-105)	1.64 ± 0.2(1.30-1.90)
Non-portal hypertension	72.68 ± 32.7(0-125)	0.84 ± 0.3(0.30-1.50)
Nephrotic syndromr, visceral perforation, sub-acute liver failure	50.80 ± 7.8(41-59)	0.64 ± 0.1(0.40-0.80)
P value	0.0001	0.0001

Serum ascites cholesterol gradient was higher in portal hypertension related ascites (89.73 ± 24.9) compared to non-portal hypertension (58.64 ± 41.2), p: 0.001. In addition to that, there was a significant difference regarding serum ascites cholesterol gradient between tumors and cirrhosis (63.78 ± 38.9 vs 92.57 ± 24.5), p:0.0001 (Table 4).

Table 4: Serum-ascites cholesterol gradient according to various etiologies of ascites

Variable	Serum-ascites cholesterol gradient	P-value
Portal hypertension	89.73 ± 24.9 (33-195)	0.001
Non-portal hypertension	58.64 ± 41.2 (0-155)	
Tumors	63.78 ± 38.9 (0-155)	0.0001
Cirrhosi	63.78 ± 38.9 (0-155)	

In our study there were 3 cirrhosis patients who develop HCC and the mean ascitc cholesterol value still like cirrhosis patients without HCC 24.12 ± 17.5. Of the 68 patients with portal hypertension, 58 patients had cholesterol <45 mg/dL, and 62 patients had SAAG ≥ 1.1. The sensitivity of cholesterol was 85.19% and specificity was 77.41%, whereas sensitivity of

SAAG was 91.17% and specificity was 69.35%. Using a combined cut off; <45 mg/dL for cholesterol and ≥ 1.1 for SAAG led to sensitivity 69.11% and specificity 91.93%. Of the 62 patients with non-portal hypertension, 48 patients had cholesterol <45 mg/dL, and 43 patients had SAAG ≥ 1.1. The sensitivity of cholesterol was 77.41% and specificity was 85.29%, whereas sensitivity of SAAG was 69.35% and specificity was 91.7%. Using a combined cut off; <45 mg/dL for cholesterol and ≥ 1.1 for SAAG led to sensitivity 73% and specificity 100%. We notice that, in our study cholesterol value ≥ 75 mg/dL has a sensitivity 52.63% and specificity 100% in determination malignant related ascites (**Tables 5 and 6**).

Table 5: Sensitivity and specificity of chemical parameters in predicting portal from non-portal hypertension

Parameter	Portal hypertension (68)	Non-portal hypertension (62)
	Ascites cholesterol	
<45	58	48
45 ≤	10	14
	SAAG	
≥ 1.1	62	43
1.1>	6	19
	Cholesterol	
Sensitivity	85.19%	77.41%
Specificity	77.41%	85.29%
	SAAG	
Sensitivity	91.17%	69.35%
Specificity	69.35%	91.70%
Cholesterol & SAAG	**Cholesterol<45& SAAG≥1.1**	**Cholesterol≥45& SAAG<1.1**
Specificity	91.93%	100%

Table 6: Sensitivity and specificity of 75 mg/dl ascites cholesterol value to malignant related ascies

Malignant-related ascites 57 group patients	Non-Malignant-related ascites 75 group patients
30 patients have cholesterol level ≥ 75 mg/dl	0 patients have cholesterol level ≥ 75 mg/dl

DISCUSSION

Ascites is not per se a disease; however, it is a sequel of an illness. Identification of the nature of ascetic fluid can guide for the correct diagnosis of etiology and initiation the appropriate treatment. The result of the current study revealed that ascites was more frequent in males than females and portal hypertension related ascites represented the most common cause of ascites. Cirrhosis represented the most common etiology in portal hypertension related ascites, whereas tumors were more frequent in non-portal hypertension. There were significant differences in cholesterol levels between various etiologies of ascites in which high levels were found in tumors compared to cirrhosis, p<0.05 and the cutoff 75 mg/dL cholesterol ascetic level has a specificity 100% to malignant related ascites. Serum ascites cholesterol gradient was significantly higher in portal hypertension than non-portal hypertension etiologies, which might be explained by the inflammatory mechanism that occurred in non-portal hypertension which increases vascular permeability to cholesterol from blood toward ascites fluid. SAAG was more sensitive than cholesterol in predicting presence of portal hypertension p=0.435, and combination of the two markers led to specificity 91.1%, whereas cholesterol was more sensitive than SAAG in predicting absence of portal hypertension p=0.458 and combination of the two markers led to specificity 100%. The results of current study are consistent with the previous studies. And in mixed ascites cholesterol level ≥ 45 mg/dL simply reflects to mixed ascies and does not have any specificity for peritoneum lesion, we do not agree this result with results in previous studies.

Gupta et al (1995) demonstrated in a study conducted in 76 patients with a diagnosis of ascites presence of significant differences in cholesterol levels between various etiologies, in which high levels were found in tuberculosis 77.1 ± 19 versus 75 ± 6.5 in tumors and 28.3 ± 16 in cirrhosis. Serum ascites cholesterol gradient was significantly higher in cirrhosis 118.3 ± 1.9 versus 83.6 ± 31.6 in tumors and 56.5 ± 21.6 in tuberculosis [10].

Du et al (2018) showed in a study conducted in 629 patients with ascites that portal hypertension related ascites was the most frequent etiology, and cirrhosis represented the most frequent etiology, whereas tumors were the most common etiology in non-portal hypertension. Cholesterol levels were significantly higher in tumors (87 ± 35.96) versus (20.88 ± 12.37) in cirrhosis. SAAG was more sensitive in predicting presence of portal hypertension, whereas cholesterol was more sensitive than SAAG in predicting absence of portal hypertension, also ascitic cholesterol level Showed excellent performance in identifying peritoneal lesions in patients with mixed ascites [11].

Lawso E demonstrated in a study included 61 patients with ascites presence of significant difference in the cholesterol levels between various etiologies of ascites; 80.07 ± 28.81 in tumors versus 24.69 ± 9.28 in cirrhosis. SAAG levels were higher in cirrhosis compared to tumors. Specificity of cholesterol in differentiating tumors from cirrhosis reached to 94.7% for cut-off value 72.7 [12].

CONCLUSION

In conclusion, cholesterol has an important value in differentiating various etiologies of ascites, so we emphasis the importance of measuring cholesterol along with SAAG to obtain best diagnostic accuracy in distinguishing portal from non-portal hypertension ascites.

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