Review Article

Ascitic Fluid Analysis in the Differential Diagnosis of Ascites: Focus on Cirrhotic Ascites

Lin-Lin Huang[1], Harry Hua-Xiang Xia[2] and Sen-Lin Zhu[1]

[1]*Department of Gastroenterology, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China;* [2]*Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA*

Abstract

Ascites is the pathologic accumulation of fluid within the peritoneal cavity. Because many diseases can cause ascites, in particular cirrhosis, samples of ascitic fluid are commonly analyzed in order to develop a differential diagnosis. The concept of transudate versus exudate, as determined by total protein measurements, is outdated and the use of serum-ascites albumin gradient as an indicator of portal hypertension is more accurate. Lactate dehydrogenase (LDH), vascular endothelial growth factor (VEGF), and other tumor markers can be helpful in distinguishing between malignant and benign conditions. Glucose and adenosine deaminase levels may support a diagnosis of tuberculous disease, and amylase level may indicate a diagnosis of pancreatitis. Given the specificity and sensitivity of laboratory results, accurate diagnosis should be based on both laboratory data and clinical judgment.

Introduction

Ascites is defined as pathological fluid accumulation within the abdominal cavity.[1] The word ascites is derived from the Greek word '*askos*', which means a bag or sack.[1–3] Clinically, ascites is a consequence or complication of a number of diseases, including hepatic, cardiac, and renal diseases, infection, and malignancy. Ascites usually carries an unfavorable prognosis. For example, the development of ascites in cirrhotic patients is associated with a mortality of 15% and 44% at one-year and five-year follow-up periods, respectively.[4,5] However, the prognosis largely depends on the underlying cause (*i.e.* the primary disease). Combined analysis of laboratory data of ascitic fluid samples and clinical and pathological data is essential for establishing a differential diagnosis. This review aims to assess critically the value of ascitic fluid analysis in the diagnosis of ascites, especially cirrhotic ascites.

Keywords: Ascitic fluid analysis; Differential diagnosis; Ascites; Cirrhosis.
Abbreviations: ADA, adenosine deaminase activity; AFP, α-fetoprotein; BHBT, β-hydroxybutyrate; CA, cancer antigen; CEA, carcinoembryonic antigen; ^{1}H NMR, proton nuclear magnetic resonance; LDH, lactate dehydrogenase; PC, peritoneal carcinomatosis; PCR, polymerase chain reaction; SBP, spontaneous bacterial peritonitis; TBP, tuberculous peritonitis; TP, total protein; SAAG, serum-ascites albumin gradient; VEGF, vascular endothelial growth factor.
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Correspondence to: Sen-Lin Zhu, Department of Gastroenterology, The First Affiliated Hospital, Sun Yat-sen University, 58 Zhongshan 2nd Road, Guangzhou 510080, China. Tel: +86-20-87755766 EXT 8182, E-mail: zhusl@mail.sysu.edu.cn

Types of ascites and their pathogenesis

Under normal circumstances, the amount of peritoneal fluid depends on a balance between plasma flowing into and out of the blood and lymphatic vessels.[6] It is only when this balance has been disrupted does ascites form. The imbalance in the level of plasma may be due to increased capillary permeability, increased venous pressure, decreased protein (oncotic pressure), or increased lymphatic obstruction.[2,7]

Ascites is one of the most frequent complications of cirrhosis and portal hypertension.[1,4,8,9] Up to 50% of cirrhotic patients will develop ascites within a 10 year follow-up period.[10,11] Hepatic cirrhosis accounts for up to 85% of cases of ascites,[12] and malignancies account for approximately 10%.[13–16] The other types of ascites are categorized as cardiogenic, nephrogenic, infectious, and miscellaneous[2,13–16] (Table 1).

Ascitic fluid analysis and clinical implications

Gross appearance

The initial evaluation of the gross appearance of ascitic fluid can offer useful information in the differential diagnosis. Under normal conditions, peritoneal fluid is clear to pale yellow.

Milky ascites, also called chylous ascites, is characterized by the presence of chylomicrons, which are lipoprotein particles that consist of large amounts of triglycerides.[2,17,18] There are many known causes of chylous ascites, including cirrhosis, infections (parasitic and tuberculosis), malignancy, congenital defects, traumatism, inflammatory processes, nephropathies, and cardiopathies.[2,19,20] Abdominal malignancy is a major cause of chylous ascites in adults, whereas congenital lymphatic abnormalities are more likely causes in children.[21] However, it should be noted that pseudochylous ascites or cloudy/turbid ascites is associated with bacterial infection, peritonitis, pancreatitis, or perforated bowel.[22] Therefore, the presence of both chylomicrons and a high concentration of triglycerides is necessary to distinguish chylous ascites from pseudochylous ascites. This is important since the frequency of malignancy is as high as 80% in adults with chylous ascites.[2]

Bloody ascites is a characteristic of benign or malignant tumors, hemorrhagic pancreatitis, or perforated ulcer,[23]

Table 1. Types of ascites and underlying primary diseases

Type of ascites	Primary disease
Hepatic	Cirrhosis Hepatic venous outflow obstruction (Hepatic vein obstruction, Budd-Chiari syndrome, Veno-occlusive disease) Portal vein occlusion Inferior vena cava obstruction Hepatic cancer
Cardiogenic	Congestive cardiac failure Constrictive pericarditis
Nephrogenic	Nephrotic syndrome
Malignant	Ovarian cancer Cervix cancer Endometrial cancer Breast cancer Esophageal cancer Gastric cancer Colorectal cancer Lung cancer Pancreatic cancer Hepatobiliary cancer Primary peritoneal cancer
Infectious ascites	Tuberculous peritonitis Spontaneous bacterial peritonitis Fungal infection Parasite infections Chlamydia infection
Miscellaneous ascites	Chylous ascites Pancreatic ascites Bile ascites Ovarian disease (Meig's syndrome, Struma ovarii, Ovarian hyperstimulation) Systemic lupus erythematosis Whipple's disease Sarcoidosis

whereas clear or straw colored ascites is often associated with cirrhosis.[24] Therefore, the gross appearance of ascites can provide preliminary clues regarding the etiology of the underlying disease.

Biochemical tests

Ascitic fluid total protein and the serum-ascites albumin gradient (SAAG)

For many years, the ascitic total protein concentration has been used to determine whether ascitic fluid was a transudate or exudate.[2] However, this paradigm was flawed and resulted in frequent misclassifications. Currently, it is accepted that the accuracy of the relationship between ascitic protein concentration and etiology of ascites was overestimated.[25] For example, hemodynamic-related cardiac ascites was incorrectly considered to cause low protein concentration.[26,27] The same can be applied to cirrhotic and malignant cases. Gupta *et al*. reported that 24% of patients with uncomplicated cirrhosis had an ascitic total protein concentration greater than 25 g/L,[28] and Alexandrakis *et al.* reported that 20% of malignant ascites cases had a low protein concentration.[27] Thus, the use of ascitic total protein is now considered outmoded and was replaced with SAAG. SAAG is a more sensitive and specific measure for the differentiation of ascites due to portal hypertension from ascites due to other pathophysiological mechanisms (e.g. peritoneal inflammation).

SAAG, which was first proposed by Hoefs *et al.* in 1981, is calculated by subtracting the ascites albumin concentration from the serum albumin concentration. In prospective studies, it was shown to be a better discriminant than the older criterion (transudate versus exudate).[29] SAAG is generally low ($<$1.1 g/dL) in ascites not due to portal hypertension, as in cases of infection or malignancy (not due to portal hypertension). SAAG is high ($\geqslant$1.1 g/dL) in portal hypertension-related ascites, as in cases of liver cirrhosis or congestive heart failure.[30–32] It has been shown that the causal mechanism was identified in 97% of cases with SAAG, whereas only 55% was identified using ascitic total protein concentration.[12] SAAG has been adopted in the British and the American guidelines as an initial testing strategy.[33,34]

Lactate dehydrogenase (LDH)

Early studies found uniformly high levels of LDH in malignant effusions and low levels of LDH in non-malignant effusions.[2,35] Boyer *et al.* observed that the mean ascitic fluid LDH level was much lower in patients with liver disease than in those with malignant ascites (167±9 *vs.* 913±228 SU).[35]

Similar to the classification of pleural fluid proposed by Light *et al.*,[36] the value of combining LDH with total protein analysis has been explored for ascitic fluid. The cut-off values for three parameters in the ascitic fluid for differentiation between hepatic and non-hepatic ascites are, as follows: LDH of 400 SU, fluid/serum LDH ratio of 0.6, and fluid/serum total protein (TP) ratio of 0.5. Ascitic levels higher than the cut-offs for any two out of three parameters indicate a non-hepatic cause of the ascites, whereas values below the cutoffs for all three parameters strongly suggest a hepatic cause of ascites.[2] According to Gokturk *et al*., LDH values were higher in patients with an SAAG of 1.1 g/dL or less than in those with an SAAG greater than 1.1 g/dL.[37] However, Sevinc *et al.* reported that in patients with malignant ascites, ascitic fluid LDH values had high sensitivity but low specificity for the diagnosis of the disease, and a low value of LDH did not necessarily exclude malignancy.[38] Therefore, the value of ascitic LDH levels requires further investigation.

Glucose

Since glucose diffuses readily across membranes, the concentration of glucose in the ascitic fluid, under normal conditions, is similar to that in the serum.[39] However, ascitic glucose concentration decreases due to consumption by bacteria, white blood cells or cancer cells in the fluid in tuberculous peritonitis, spontaneous bacterial peritonitis (SBP), and malignancy.[39,40] According to Mansour-Ghanaei *et al*., ascitic glucose concentration is often significantly lower than normal in tuberculous ascites, which makes it an indicator in differentiating tuberculosis from other diseases, such as cirrhosis.[41] This is consistent with Wilkins *et al.* who recommended that the ascitic/blood glucose ratio is a useful test in the differentiation of tuberculous peritonitis from ascites due to other causes.[42] However, when considering the value of glucose in patients with SAAG greater or less than 1.1 g/dL, there was no significant difference between them.[37] Therefore, due to its low diagnostic sensitivity and specificity, the application of ascitic glucose analysis is limited in routine practice.[43]

Amylase

Amylase-rich ascitic fluid commonly occurs in cases of pancreatic duct damage or obstruction due to pancreatitis or pancreatic trauma.[44] Elevation of amylase levels above the serum reference range in ascitic fluid was found in up to 90% of patients with acute pancreatitis and pancreatic pseudocyst.[2] When pancreatic ascites needs to be distinguished from ascites secondary to alcoholic cirrhosis, it can be accomplished by detecting high amylase levels in the ascitic fluid.[45] During the course of severe acute pancreatitis, the level of ascitic amylase can be 100 times higher than serum. However, increased amylase in ascites can also been found in patients with malignancy,[46] perforated peptic ulcer, upper abdominal surgery, mechanical intestinal obstruction, mesenteric vascular disease, biliary obstruction, and acute cholecystitis. Therefore, hyperamylasemia is not a specific marker for pancreatic damage.[47]

Adenosine deaminase

Ascitic fluid adenosine deaminase activity (ADA) has been reported to be more sensitive and specific for the early diagnosis of tuberculous ascites than for other types of ascites.[48,49] A recent meta-analysis of four studies that included 264 patients confirmed the high sensitivity (100%) and specificity (97%) of using cut-offs of ADA from 36 to 40 IU/L in the diagnosis of tuberculous ascites.[2] Moreover, a recent study reported that ascitic ADA levels in patients with tuberculous peritonitis (TBP) and peritoneal carcinomatosis (PC) were 66.76 ± 32.09 IU/L and 13.89 ± 8.95 IU/L, respectively ($P< 0.01$),[50] indicating that ascitic ADA analysis is valuable in differentiating between TBP and PC. Furthermore, Liao *et al*. found that ADA values of patients with TBP were notably higher than those with cirrhosis, and every patient in the cirrhosis control group had an ascites ADA level lower than the lowest value in the TBP group.[51]

Non-biochemical tests

Cell counts, bacterial culture, and polymerase chain reaction (PCR)

Non-biochemical tests of ascitic fluid, including cell counts, bacterial culture, and PCR, play an important role in diagnosing the cause of ascites, especially in infectious ascites. SBP is defined by the presence of neutrophil cells greater than or equal to 250/μL or a positive bacterial culture in the ascitic fluid without evidence of an abdominal source.[8,52] Cell counts using automatized equipment such as a flow cytometer and culture of ascites fluid should be performed simultaneously.[8] Despite the use of sensitive methods, ascitic fluid cultures are negative in as many as 60% of patients with increased ascites neutrophil counts and clinical manifestations suggestive of SBP.[53–55] Therefore, if SBP is suggested by an elevated ascitic neutrophil cell counts and clinical signs and symptoms, antibiotic treatment must be initiated without waiting for the culture result. In a recent study of 1,041 patients with cirrhosis, Cadranel *et al.* performed total and differential leukocyte counts and bacterial cultures of ascitic fluid and observed that SBP occurred in 11.7% of inpatients and 3.1% of outpatients.[56] Moreover, they reported that the incidence of SBP was 8.3% in symptomatic patients, whereas the rate was 1.2% in asymptomatic patients. Therefore, cell counts and bacterial culture should also be performed in patients with cirrhotic ascites, especially those with symptoms, due to the high incidence of SBP. Moreover, it has been shown that in cirrhotic patients, compared to SBP, tuberculous peritonitis is associated with, in ascites, lower white blood cell counts, a higher proportion of mononuclear leukocytes (lymphocytes and monocytes), a higher protein concentration, and higher ADA.[57] However, the sensitivity of direct microscopic smear detection of acid-fast bacilli in the ascitic fluid (0%–6%) and ascitic fluid mycobacterial culture (20%–35%) is low, and mortality is high in patients with tuberculous peritonitis and other various medical conditions, such as cirrhosis, renal failure, diabetes mellitus, and malignancy. Because of the delay in obtaining the results of mycobacterial cultures of ascitic fluid,[57–59] the value of these tests in the differential diagnosis of ascites is limited. However, in recent years, advances in molecular techniques have provided a new approach to the rapid diagnosis of bacterial infection, including tuberculosis, by PCR in small volumes of ascitic fluid (50 ml).[60] PCR can detect minimal amounts of bacterial DNA and improves the rates and velocity of bacterial identification[61–63] from four to six weeks for microbiological cultures to 24 hours.[64] Soriano*et al.* detected bacterial DNA in ascitic

fluid in 60% of cirrhotic patients with sterile ascites,[61] and this was associated with an increase in inflammatory response[65,66] and a worse prognosis.[67] In diagnosing tuberculous effusions, PCR appears to be an ideal tool, with 94% sensitivity and 88% specificity.[68,69] Therefore, PCR can be a rapid and reliable method for identification of infectious ascites and accelerates the diagnostic decision making process relative to microbiological cultures.

Viscosity

Ascitic fluid viscosity is a newly proposed indicator in differentiating ascites. A recent study by Gokturk *et al.* evaluated the role of ascitic fluid viscosity in discriminating between ascites due to portal hypertension-related and non-portal hypertension-related causes, and compared the results with SAAG.[37] In that study, ascitic fluid viscosity was determined in a programmable rotational viscometer using 0.5 mL ascitic samples from 142 patients with newly diagnosed ascites due to various causes.[37] The mean ascitic fluid viscosities were 0.86±0.12 cP and 1.22±0.25 cP in patients with an SAAG greater than 11 g/L and an SAAG of 11g/L or less, respectively, indicating a close correlation between viscosity and SAAG. Moreover, with a cut-off value of 1.03 cP, ascitic fluid viscosity measurement exhibited high sensitivity (98%), specificity (80%), and positive and negative predictive values (79% and 94%, respectively) for the etiological discrimination of ascites.[37] Although there are only a few studies evaluating the viscosity of ascites,[70,71] the speed, simplicity, inexpensiveness, and necessity of only a small sample volume make it a useful, and likely more popular, diagnostic tool for the differential diagnosis of ascites in clinical research and practice.

Proton nuclear magnetic resonance (^{1}H NMR) spectroscopy

High-resolution ^{1}H NMR spectroscopy of body fluids has emerged as an important tool for differential diagnosis of diseases. In this technique, a few biochemical agents, such as β-hydroxybutyrate (BHBT), lactate, acetone, and acetoacetate, are used. ^{1}H NMR spectroscopy can be used to differentiate benign cirrhotic ascites from malignant ascites. In one study, the ascitic concentrations of BHBT, lactate, acetone, and acetoacetate were significantly higher in patients with malignant ascites than in those with cirrhotic ascites.[39] In contrast, the ascitic concentrations of glutamine, citrate, glucose, tyrosine, and phenylalanine were significantly lower in patients with malignant ascites than in those with cirrhotic ascites.[39] Using a model where BHBT, lactate, citrate, and tyrosine were considered together as markers, ^{1}H NMR spectroscopy differentiated malignant ascites from cirrhotic ascites with 100% sensitivity and 97.9% specificity, whereas the rates were 53.3% and 76.6% for total ascitic protein, and 60% and 87.2% for SAAG, respectively.[39]

Vascular endothelial growth factor (VEGF)

VEGF, initially known as vascular permeability factor, has a recognized role in the accumulation of ascitic fluid.[72–75] Several studies have confirmed, using enzyme immunoassay, the presence of higher VEGF concentrations in malignant ascites than in non-malignant (cirrhotic, tuberculous, inflammatory) ascites.[76–85] Although VEGF concentrations are significantly higher in malignant ascites, the overlap in the concentrations of VEGF between malignant and non-malignant ascites is rather large. For example, relative to non-malignant ascites, when using its VEGF mean levels 119.44 pg/ml (70.90±48.54) as the minimum cut-off limit, the sensitivity and specificity of VEGF to diagnose malignant ascites were 91.3% and 90.9%, respectively.[84] Nascimento *et al*. and Bamias *et al*. used 662 pg/ml[79] and 400 pg/ml[74] as cut-off values to discriminate between malignant ascites and non-malignant ascites, respectively.

Therefore, VEGF, a noninvasive and simple marker available in clinical pathology laboratories, may be useful as a parameter for the differential diagnosis of malignant and non-malignant ascites. However, further investigation is necessary to confirm an optimum cut-off value.

Tumor markers

Tumor markers can be used to determine cancer risk, screen for early cancers, confirm diagnosis, predict prognosis, and monitor metastasis, recurrence, or progression of cancers.[13] Well-established tumor markers, including α-fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen (CA) 19-9, and CA125, have been evaluated for their utility in differentiating malignant ascites from non-malignant ascites. It has been shown that ascitic levels of AFP, CEA, CA19-9, and CA125 are significantly higher in patients with malignancies such as hepatocellular cancer, colorectal cancer, pancreatic cancer, and ovarian cancer than in those with non-malignant etiologies.[2,14,50,86–88] It should be noted, however, that other non-malignant conditions such as gastritis, diverticulitis, cirrhosis, and other cholestatic, pancreatic, and hepatic diseases are known to cause elevations in these tumor markers.[86] For example, increased ascitic CEA and CA 19-9 can be present in cirrhosis,[89–91] and high levels of CA125 in ascitic fluid can occur in patients with tuberculous peritonitis or with cirrhosis.[13,50,92] These findings indicate that elevated tumor marker levels in ascitic fluid must be interpreted with caution when differentiating malignant ascites from other types of ascites. Although these tumor markers are potentially diagnostic, the gold standard for the diagnosis of malignant ascites is detection of tumor cells in the ascitic fluid.[14]

Usefulness of ascitic fluid analysis in patients with cirrhosis

Ascites is one of the most frequent complications of cirrhosis.[1,4,8,9] Up to 60% of patients with compensated cirrhosis will develop ascites within 10 years of the disease course.[10,11,53,93] After the development of ascites, survival rate is only 50% at two to five years.[93] Therefore, differential diagnosis is essential for better management of cirrhosis, and ascitic fluid analysis plays an important role in this purpose. Table 2 outlines the typical characteristics of the ascites in patients with cirrhosis relative to other diseases.

Conclusions

Ascites can be a consequence or complication of many primary diseases and carries an unfavorable prognosis that largely depends on the underlying causes. Cirrhotic ascites accounts for most cases of ascites, and it can be complicated by subsequent infections that also lead to ascites. Ascitic fluid analyses indicating gross appearance, biochemical tests (e.g.

Table 2. Typical characteristics of ascites in patients with cirrhosis compared with other diseases

	Causes of ascites					
Test	Cirrhosis	Congestive cardiac failure	Malignancy	Tuberculosis	SBP	Pancreatitis
Gross appearance	clear straw or milky	clear to pale yellow	milky or bloody	milky or N	cloudy or turbid	milky or cloudy or turbid
TP	< 25 g/L	< 25 g/L	⩾ 25 g/L	⩾ 25 g/L	⩾ 25 g/L	⩾ 25 g/L
SAAG	⩾ 1.1 g/dL	⩾ 1.1 g/dL	< 1.1 g/dL	< 1.1 g/dL	< 1.1 g/dL	< 1.1 g/dL
LDH	↓	↓ or N	↑	↑ or N	↑ or N	↑ or N
Glucose	N	N	↓	↓	↓	↓
Amylase	N		↑ or N			↑
ADA	↓ or N		↓ or N	↑		
Cell counts	⩾ 250/μL or N			⩾ 250/uL or N	⩾ 250/uL	
Bacterial culture	+ or −			+ or −	+	
Viscosity	< 1.03 cP	< 1.03 cP	⩾ 1.03 cP	⩾ 1.03 cP	⩾ 1.03 cP	⩾ 1.03 cP
^{1}H NMR	↑ or ↓	↑ or ↓				
VEGF	↓	N	↑	↓	↓	↓
Tumor markers	↑ or N	N	↑	↑ or N		↑ or N

↑ -increase, ↓- decrease, N -normal, + -positive, − - negative.

SAAG, LDH, glucose, amylase, and ADA), and non-biochemical tests (e.g. cell counts, bacterial culture and PCR, viscosity, ^{1}H NMR spectroscopy, VEGF, and tumor markers) can provide useful clues in the differential diagnosis of ascites and help in establishing a diagnosis. It should be emphasized that physicians should use the ascitic fluid analysis in combination with clinical, pathological, and imaging data, in order to make an accurate diagnosis of the cause of ascites.

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Conflict of interest

None

Author contributions

Writing the article (LLH), organizing the article (HXX), writing and modifing the article (SLZ).

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