Review

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Differential diagnosis of ascites: etiologies, ascitic fluid analysis, diagnostic algorithm

https://doi.org/10.1515/cclm-2023-1112
Received October 6, 2023; accepted December 7, 2023;
published online December 20, 2023

Abstract: Ascites is the pathological accumulation of fluid within the peritoneal cavity. It often occurs as results of liver cirrhosis, malignant neoplasia, tuberculous infection, cardiac insufficiency, renal diseases, etc. Determining the etiology is an essential step in the management of patients with new-onset ascites. Abdominal paracentesis with appropriate ascitic fluid analysis is probably the most cost-effective method of determining the cause of ascites. We performed a literature search of PubMed and identified articles published in the field of ascites, to evaluate diagnostic values of various parameters in defining the etiologies of ascites and then provides diagnostic algorithm for patients with new-onset ascites. In patients with ascites, the constituent ratio of underlying etiology varies between developed and developing countries. It is a challenge to define the etiologies of ascites in developing countries. Routine ascitic fluid analysis should include the serum ascites albumin gradient (SAAG), total protein concentration, cell count and differential. Optional ascitic fluid analysis includes cholesterol, fluid culture, cytology, tumor markers, lactate dehydrogenase, adenosine deaminase (ADA), triglyceride, amylase, glucose, brain natriuretic peptide (BNP), etc. Our review evaluated diagnostic values of the above parameters in defining the etiologies of ascites. Diagnostic algorithm established in this review would provide a practical and convenient diagnostic strategy for clinicians in diagnosing patients with new-onset ascites.

Keywords: ascites; ascitic fluid analysis; etiology; diagnosis algorithm

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Introduction

Ascites refers to the buildup of excess fluid in the abdominal cavity. Generally, ascites is divided into portal hypertensive ascites, non-portal hypertensive ascites and mixed ascites [1]. Ascites formation is a complex and multifactorial process, an imbalance between fluid secretion and absorption by peritoneum contributes to abnormal accumulation of fluid within peritoneal cavity. The pathophysiology of ascites varies depending on its etiology. Pathogenetic events of portal hypertensive ascites are renal sodium retention, arterial underfilling, and portal hypertension [2–4]. Recent studies have demonstrated systemic inflammation secondary to bacterial translocation and gut dysbiosis contributed to the formation of portal hypertensive ascites [5, 6]. Vascular permeability, inflammatory cytokines, and the obstruction of lymphatic drainage contribute to the formation of non-portal hypertensive ascites (malignant ascites and infected ascites) [7, 8]. Additionally, our recent study demonstrated that interferon-γ secreted by recruited Th1 cells in peritoneal cavity inhibited the formation of malignant ascites [9].

Determining the etiology is an essential step in the management of patients with new-onset ascites. Abdominal paracentesis with appropriate ascitic fluid analysis is probably the most rapid and cost-effective method of defining the cause of ascites [3, 10, 11]. Potential complications of abdominal paracentesis include hematoma of the abdominal wall, leakage at the puncture site, and intestinal perforation [12]. Severe hemorrhage occurs in 0.2–2.2 % of punctures, and death is rare. In one study, the death rate was 0.02 % among 4,729 procedures [13]. A large number of tests on ascites specimens have been performed in ascitic fluid analysis. In clinical practice, it is difficult to define the etiologies of ascites caused by miscellaneous portal hypertension, non-portal hypertension and mixed ascites. Therefore, this review aims to evaluate diagnostic values of different parameters in ascitic fluid analysis, and then establish diagnostic approach to new-onset ascites.

Different etiologic constituent ratio between developed and developing countries

Ascites is divided into portal hypertensive ascites, non-portal hypertensive ascites and mixed ascites according to its underlying etiology [1, 10, 14]. Portal hypertensive ascites includes liver cirrhosis, cardiac ascites, hepatic failure, hepatic sinusoidal obstruction syndrome, Budd-Chiari syndrome and portal vein occlusion, etc. Non-portal hypertensive ascites includes malignant ascites, tuberculous peritonitis, pancreatic ascites, secondary bacterial peritonitis, connective tissue disease, eosinophilic gastroenteritis, nephrotic syndrome, dialysis-related ascites and fungal/candida peritonitis. Mixed ascites is diagnosed when portal hypertension accompanied another etiology of non-portal hypertension. The details of the etiologies are described in Figure 1 [1, 10, 14], and diagnosis criteria referred to different causes of ascites were described in Supplementary Table S1.

In patients with ascites, the constituent ratio of underlying etiology varies in different countries. In USA, the causes of ascites included liver cirrhosis (84.1 %), cardiac insufficiency (2.7 %), malignant neoplasia (2.4 %), miscellaneous portal hypertension (3.9 %), and mixed ascites (4.6 %), miscellaneous non-portal hypertension (2.1 %) [14]. While, in China, the etiologies of ascites contained liver cirrhosis (30.3 %), malignant neoplasia (24.2 %), tuberculous peritonitis (6.7 %), cardiac insufficiency (4.0 %), miscellaneous portal hypertension (10.3 %), and mixed ascites (15.3 %), etc. in our study [1]. The etiologies of ascitic in USA and China were presented in Table 1. As described above, the percentage of miscellaneous portal hypertensive ascites, non-portal hypertensive ascites and mixed ascites in developing countries (China) [1] was greater than that in developed countries (United States) [14]. Thus, it is a challenge to define the etiologies of ascites in developing countries. More importantly, the constituent ratio of underlying etiology probably results in the difference in the value of ascitic fluid analysis.

Initial evaluation of patients with ascites

The initial evaluation of ascites should include medical history, physical examination, abdominal doppler ultrasound, blood tests and a diagnostic paracentesis for analysis of the ascitic fluid [3, 10]. Medical history includes chronic liver disease, heart disease, malignancy, tuberculous, autoimmune disorder, pancreatitis, travel history, etc. A careful physical examination should be performed in patients with ascites. A full, bulging abdomen, shifting abdominal dullness, umbilical/inguinal hernias reveal the presence of ascites. Additionally, physical examination should contain stigmata of chronic liver disease (splenomegaly, spider angioma, palmar erythema, or abdominal

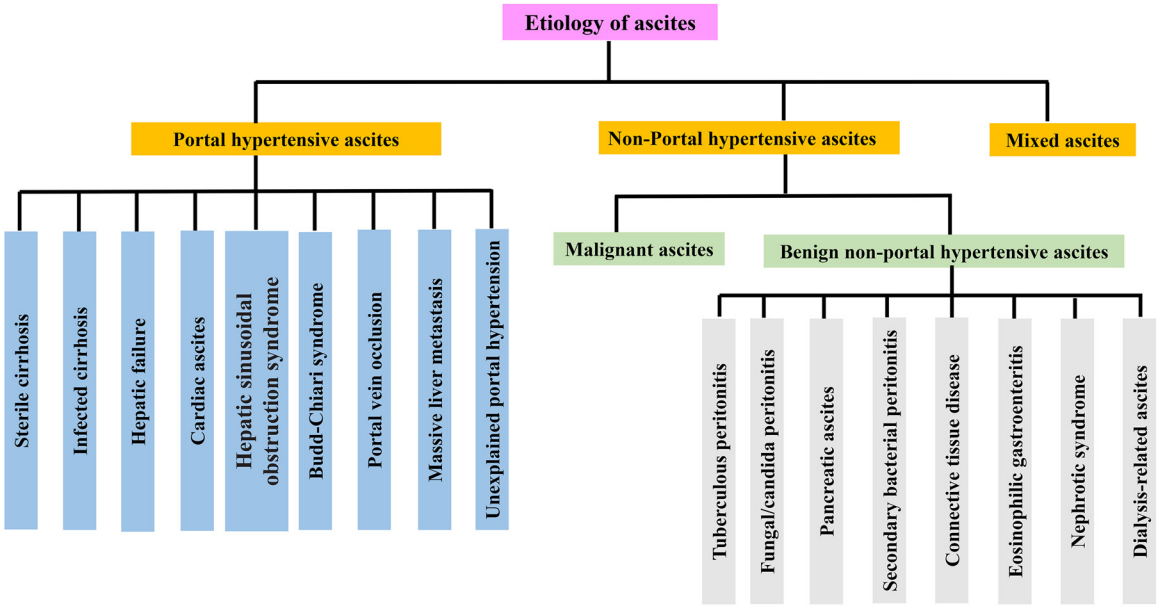

Figure 1: Etiologies of peritoneal effusion.

Table 1: Different etiological distributions of ascites in developed and developing countries.

Etiologies	USA, %	China, %
Portal hypertension	90.7	44.7
Cirrhosis	84.1	30.3
Cardiac ascites	2.7	4.0
Miscellaneous portal hypertensive	3.9	10.3
Fulminant hepatic failure	0.7	1.7
Acute hepatitis superimposed on cirrhosis	1.2	3.5
Hepatic sinusoidal obstruction syndrome	0	4.6
Budd-Chiari syndrome	0	0.2
Portal vein occlusion	0	0
Chylous cirrhotic ascites	1.1	0.2
Unexplained portal hypertension	0	0.2
Non-portal hypertension	4.5	40.1
Malignant ascites	2.4	24.2
Miscellaneous non-portal hypertensive	2.1	15.9
Tuberculous peritonitis	0.7	6.7
Pancreatic ascites	0.4	3.2
Secondary bacterial peritonitis	0.3	1.7
Chylous malignant ascites	0.1	0.3
Connective tissue disease	0	1.3
Eosinophilic gastroenteritis	0	1.1
Nephrotic syndrome	0.2	0.6
Dialysis-related ascites	0	0.3
Mixed ascites	4.6	15.3

wall collaterals), signs of heart failure or constrictive pericarditis (jugular venous distension, pulmonary congestion, pericardial rub), signs of malignancy or infection (lymphadenopathy). It is recommended to assess complete blood count, liver function test (prothrombin time, serum total bilirubin, serum albumin), renal function tests (serum creatinine, urea), serum and urine electrolytes (Na, K), etc. Paracentesis is generally a safe procedure. Abdominal paracentesis with appropriate ascitic fluid analysis is probably the most rapid and cost-effective method of diagnosing the cause of ascites [10, 15]. The initial ascitic fluid analysis should include total protein concentration, the serum ascites albumin gradient (SAAG), cell count and differential. Ascites fluid analysis for cholesterol, cytology, tumor markers, lactate dehydrogenase (LDH), amylase, brain natriuretic peptide (BNP) and adenosine deaminase (ADA) should be considered based on pretest probability of specific diagnosis.

Initial ascitic fluid analysis

Gross appearance of ascites

The initial evaluation of the gross appearance of ascitic fluid provide useful diagnostic information. Uncomplicated cirrhotic ascites is usually clear and light yellow. Cloudy/turbid ascites is associated with bacterial infection, pancreatitis, or gastrointestinal perforation [16, 17]. Bloody fluid indicates malignancy, hemorrhagic pancreatitis, intestinal infarction, heterotopic pregnancy and rupture of corpus luteum [17, 18]. “Milk-like” chylous ascites is generally due to the presence of a large amount of triglyceride, observed in liver cirrhosis, malignancy, infections (parasitic and tuberculosis), congenital defects, traumatism, inflammatory processes, and cardiopathies [19, 20]. Dark brown ascites indicates the rupture of gallbladder or bile duct injuries [21]. Thus, sometimes, the gross appearance of ascites provides preliminary clue for differential diagnosis of ascites.

Serum-ascites albumin gradient (SAAG)

Serum-ascites albumin gradient (SAAG) which was first proposed by Hoefs et al. in 1981, is calculated by subtracting ascitic albumin concentration from serum albumin concentration [22]. Rector et al. revealed superiority of SAAG over ascitic total protein concentration in separation of “transudative” and “exudative” ascites based on a small number of enrolled patients [23]. Then, a multicenter, prospective research demonstrated the SAAG in portal and non-portal hypertension concept was superior to the exudates-transudates concept in the differential diagnosis of ascites [14]. If the SAAG is ≥11 g/L, the patient has portal hypertension, with approximately 97 % accuracy [14] (Figure 2). Underlying etiologies of ascites with a high SAAG (≥11 g/L) or a low SAAG (<11 g/L) are described in Tables 2 and 5. Therefore, SAAG has been recognized as a reliable marker in the differentiation of portal hypertension from non-portal hypertension, and recommended as an initial ascitic fluid analysis according to clinical practice guidelines [3, 5, 11–13, 24] (Table 6). Additionally, patients with mixed ascites also have a SAAG ≥11 g/L [1, 14] (Figure 2 and 3).

Runyon and we demonstrated a high SAAG (SAAG ≥11 g/L) possessed high sensitivity in detecting portal hypertensive ascites [1, 14]. However, diagnostic accuracy of SAAG in our study was inferior to that in previous studies, and the difference was attributed to the constituent ratio of underlying causes [1]. Additionally, low SAAG (SAAG<11 g/L) was also found in patients with cirrhotic ascites. Hashim et al. reported that a SAAG<11 g/L in patients with liver cirrhosis had low yield. In their study, of the 76 patients with cirrhosis and a low SAAG, only 29 (38 %) had an identifiable cause such as peritoneal carcinomatosis. Interestingly, a repeat paracentesis changed 73 % cases with a SAAG<11 g/L into a high SAAG (SAAG≥11 g/L) [25]. Thus, a repeat paracentesis is recommended as part of the workup in patients with liver

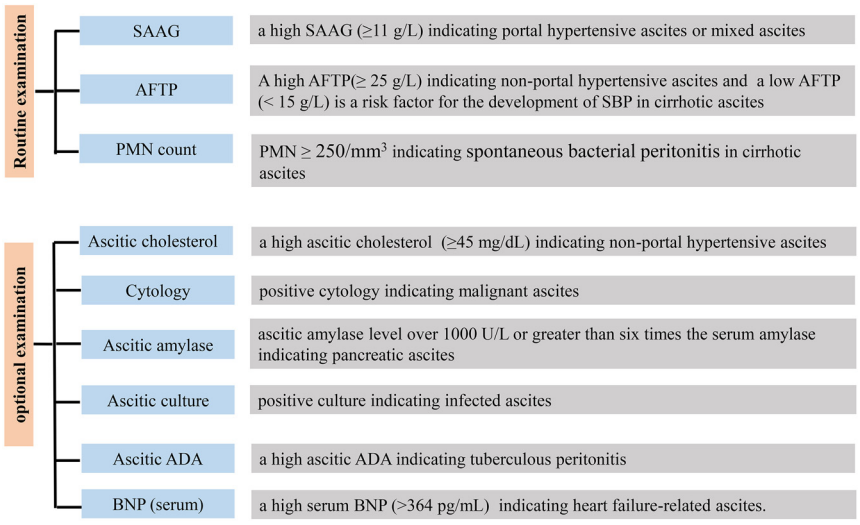

Figure 2: Diagnostic values of the parameters in ascitic fluid analysis. SAAG, serum-ascites albumin gradient; AFTP, ascitic fluid total protein; PMN, polymorphonuclear; ADA, adenosine deaminase activity; BNP, B-type natriuretic peptide; SBP, spontaneous bacterial peritonitis.

Table 2: SAAG in discriminating the causes of ascites.

SAAG≥11 g/L	SAAG<11 g/L
Cirrhotic ascites	Peritoneal carcinomatosis
Cardiac ascites	Tuberculous peritonitis
Massive liver metastasis	Nephrotic syndrome
Liver failure	Pancreatic ascites
Hepatic sinusoidal obstruction syndrome	Secondary bacterial peritonitis
Budd-Chiari syndrome	Connective tissue diseases
Portal vein thrombosis	Eosinophilic gastroenteritis
Mixed ascites	Dialysis-related ascites
	Fungal/candida peritonitis

cirrhosis and a SAAG<11 g/L. Diuretic therapy, albumin administration, and the time of sample collection might give rise to the error in SAAG.

Ascitic fluid total protein (AFTP)

Traditionally, ascites is classified into broad categories of transudates or exudates according to ascitic fluid total protein concentration. A qualitative protein assay (Rivalta test) and quantitative analysis of AFTP concentration have been

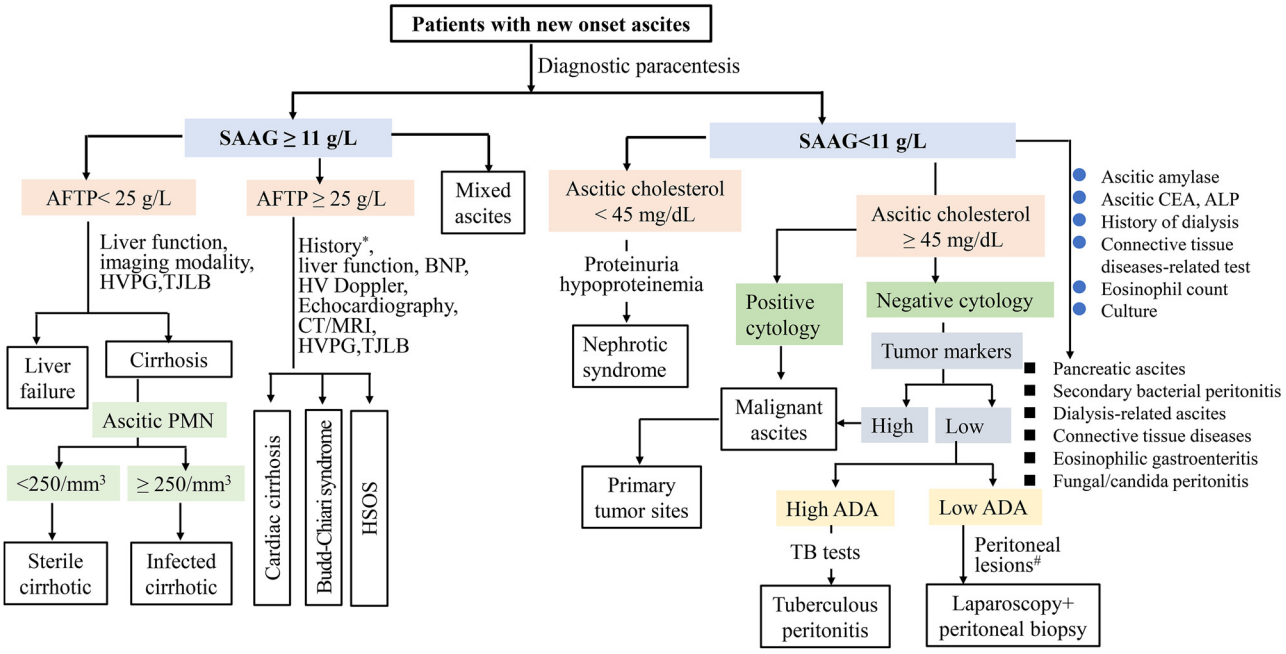

Figure 3: Diagnostic algorithm for patients with new onset ascites. #Peritoneal lesions are defined when thickening, adhesion, nodular changes or abnormal metabolism of peritoneum based on image results (CT, MRI, PET-CT); high ascitic cholesterol (≥45 mg/dL) probably had peritoneal lesions. *Ingestion of pyrrolizidine alkaloids, cytoreductive therapy prior to hematopoietic stem cell transplantation, use of tacrolimus in liver transplantation. SAAG, serum-ascites albumin gradient; AFTP, ascitic fluid total protein; HVPG, hepatic venous pressure gradient; TJHB, transjugular hepatic biopsy; BNP, B-type natriuretic peptide; HV, hepatic vein; PMN, polymorphonuclear; HSOS, hepatic sinusoidal obstruction syndrome; ADA, adenosine deaminase activity; TB, tuberculosis; CEA, carcinoembryonic antigen; ALP, alkaline phosphatase.

performed for the classification of transudates or exudates [17, 26, 27]. Rivalta test, a qualitative protein assay, was widely used for the differentiation between exudates and transudates in human body cavity [26]. In quantitative analysis, ascites is classified as exudates if AFTP≥25 g/L and as transudates if AFTP<25 g/L [18]. Our recent study demonstrated diagnostic performance of Rivalta test was inferior to AFTP in both exudates-transudates concept and portal hypertension- non portal hypertension concept [28]. Thus, Rivalta's test is not recommended in identifying etiologies of ascites. Importantly, previous study and our research showed infected cirrhotic ascites with low AFTP (<25 g/L) and cardiac ascites with high AFTP (≥25 g/L) [14, 28]. Thus, the transudate-exudate classification based on AFTP concentration is now considered outmoded and flawed. Interestingly, we found AFTP, at the predetermined cut-off value of 25 g/L, was more useful in the differentiation of non-portal hypertensive ascites from portal hypertensive ascites compared with the exudate–transudate classification [28]. AFTP had a sensitivity of 90.14 %, specificity of 84.52 % and accuracy of 87.21 % in diagnosing non-portal hypertensive ascites; while SAAG showed sensitivity of 80.43 %, specificity of 96.13 % and accuracy of 88.74 % in the same cohort [28]. Thus, AFTP displayed better diagnostic value for non-portal hypertensive ascites, while SAAG showed better diagnostic performance for portal hypertensive ascites. Underlying etiologies of ascites with a high AFTP (≥25 g/L) or a low AFTP (<25 g/L) are described in Tables 3 and 5.

AFTP concentration is a risk factor for the development of spontaneous bacterial peritonitis in patients with cirrhotic ascites [29, 30]. Thus, AFTP is strongly recommended to predict the occurrence of spontaneous bacterial peritonitis [3, 5, 11, 13]. However, a previous study of 274 cirrhotic patients with ascites demonstrated low ascitic fluid total protein levels were not associated with the development of spontaneous bacterial peritonitis [31]. In addition, ascitic fluid total protein didn't change during the infection or after anti-infectious treatment [32]. Further researches should be performed to determine whether AFTP<15 g/L protein level is a risk factor for the development of spontaneous bacterial peritonitis.

Table 3: Ascitic fluid total protein in discriminating the causes of ascites.

AFTP≥25 g/L	AFTP<25 g/L
Peritoneal carcinomatosis	Sterile cirrhosis[a]
Tuberculous peritonitis	Infected cirrhosis[b]
Cardiac ascites	Liver failure
Pancreatic ascites	Nephrotic syndrome
Secondary bacterial peritonitis	Portal vein thrombosis
Connective tissue diseases	
Eosinophilic gastroenteritis	
Budd-Chiari syndrome	
Hepatic sinusoidal obstruction syndrome	
Dialysis-related ascites	

[a]Cirrhotic ascites without spontaneous bacterial peritonitis, [b]cirrhotic ascites with spontaneous bacterial peritonitis.

Cell count and differential

Polymorphonuclear (PMN) cell count and bacterial culture have been used in the diagnosis of infected ascites. Bacterial peritonitis is classified into spontaneous bacterial peritonitis and secondary bacterial peritonitis. The diagnosis of spontaneous bacterial peritonitis is established with an ascitic PMN count greater than 250 cells/mm^3 with or without a positive ascitic fluid bacterial culture, and the absence of an intra-abdominal source of infection [3, 11]. Ascitic fluid neutrophil count>250 cells/mm^3 in the absence of a positive culture is known as culture negative neutrocytic ascites (CNNA) [4]. Clinical courses of both SBP with a positive ascitic fluid bacterial culture and CNNA were similar [4]. Negative ascitic fluid culture was found in up to 60 % of patients with increased ascites neutrophil counts and clinical manifestations suggestive of spontaneous bacterial peritonitis [33–35], thus, CNNA is now also regarded as SBP in some guidelines [3, 11]. Secondary bacterial peritonitis is defined as the presence of ascitic fluid neutrophil count of greater than 250/mm^3, and extravasation of contrast material or peritoneal free air on radiography or computerized tomography, and/or perforation of the intestinal wall demonstrated at surgery [28, 36]. The ascitic fluid should be cultured at the bedside in aerobic and anaerobic blood culture bottles before initiation of antibiotics [3, 5, 11–13]. Antibiotics should be started empirically (before obtaining culture results) in all patients with an ascites PMN count >250/mm^3 [3, 11]. Bacterascites was diagnosed by a positive ascitic culture and PMN count below 250 cells/mm^3 [37]. Recent studies demonstrated patients with bacterascites had poor clinical outcomes, including acute kidney injury, progression to acute-on-chronic liver failure and the mortality [38, 39].

Optional ascitic fluid analysis

Ascitic cholesterol

Previous studies demonstrated that ascitic cholesterol exhibited excellent diagnostic performance in the differentiation of cirrhosis from malignant ascites, and the value of ascitic cholesterol was superior to that of SAAG. Thus, ascitic cholesterol was used as a marker of malignant ascites

Table 4: Ascitic cholesterol in discriminating the causes of ascites.

Ascitic cholesterol ≥45 mg/dL	Ascitic cholesterol <45 mg/dL
Peritoneal carcinomatosis	Sterile cirrhosis[a]
Tuberculous peritonitis	Infected cirrhosis[b]
Pancreatic ascites	Cardiac ascites
Secondary bacterial peritonitis	Nephrotic syndrome
Connective tissue diseases	Liver failure
Eosinophilic gastroenteritis	Budd-Chiari syndrome
Dialysis-related ascites	Hepatic sinusoidal obstruction syndrome

[a]Cirrhotic ascites without spontaneous bacterial peritonitis, [b]cirrhotic ascites with spontaneous bacterial peritonitis.

[40–42]. However, a high level of ascitic cholesterol was also observed in the patients with purulent peritonitis, congestive heart failure and tuberculous peritonitis, which confined the value of ascitic cholesterol in diagnosing peritoneal carcinomatosis [41, 43]. In consider of this, the measurement of ascitic cholesterol concentration was considered as unhelpful in differential diagnosis of ascites [10]. Then, our multicenter, prospective study demonstrated ascitic cholesterol was an excellent discriminator for differentiating portal hypertension from non-portal hypertension, a high ascitic cholesterol (≥45 mg/dL) indicated non-portal hypertensive ascites (Tables 4 and 5; Figures 2 and 3). Importantly, there is higher sensitivity for a high ascitic cholesterol in detecting non-portal hypertensive ascites, compared with SAAG (sensitivity, specificity and accuracy: 86 %, 94% and 90 % vs. 80 %, 97% and 89 % for ascitic cholesterol and SAAG, respectively) [1]. Underlying etiologies of ascites with a high ascitic cholesterol (≥45 mg/dL) or a low ascitic cholesterol (<45 mg/dL) were described in Tables 4 and 5. In addition, ascitic cholesterol provided a beneficial assistance in the misdiagnosed patients according to SAAG classification. In mixed ascites, ascitic cholesterol is useful in identifying peritoneal lesions. Thus, the determination of ascitic cholesterol is recommended in patients with new onset ascites in clinical practice [1].

Ascitic cytology and tumor markers

Malignant ascites accounts for about 10 % of all cases of ascites [44] and commonly associated with gastric (25.4 %), colorectal (8.5 %), pancreatic (6.6 %), hepatobiliary (7.0 %), gynecological (13.1 %), unknown primary (34.7 %) and other cancers (4.7 %) [45]. Ascitic cytology and tumor markers are used in the differentiation of malignant ascites from benign ascites. The overall sensitivity of cytology for the detection of malignant ascites was 50–96.7 % [45, 46]. In developed countries, cytology should be performed only when patients with a suspicion of malignant ascites due to high expense [10]. Tumor markers offers a putative clinical use in the screening, diagnosis and treatment of various cancers. Tumor markers including CEA, CA15-3, CA19-9, AFP and CA125 have been determined in the diagnosis of malignant ascites [45, 47–49], and the results had demonstrated the detection of serum or ascitic tumor markers was helpful in the differentiation of malignant ascites from benign ascites. Importantly, a high CA125 level was found in malignant and

Table 5: The parameters of ascitic fluid analysis in patients with ascites caused by different etiologies.

	Etiologies of ascites							
	Sterile cirrhosis	**Infected cirrhosis**	**Cardiac ascites**	**Malignant ascites**	**Tuberculous peritonitis**	**Pancreatic ascites**	**Secondary bacterial peritonitis**	**Nephrotic syndrome**
Initial ascitic fluid analysis								
SAAG	≥11 g/L	≥11 g/L	≥11 g/L	<11 g/L	<11 g/L	<11 g/L	<11 g/L	<11 g/L
AFTP	<25 g/L	<25 g/L	≥25 g/L	≥25 g/L	≥25 g/L	≥25 g/L	≥25 g/L	<25 g/L
PMN counts	<250/mm^3	≥250/mm^3					≥250/mm^3	
Optional ascitic fluid analysis								
Ascitic cholesterol	<45 mg/dL	<45 mg/dL	<45 mg/dL	≥45 mg/dL	≥45 mg/dL	≥45 mg/dL	≥45 mg/dL	<45 mg/dL
Tumor markers[a]	Low	Low	Low	High	Low	High CA19-9 in some of patients	CEA>5 ng/mL	Low
LDH	Low	Low	Low	High	High	High	LDH>225 mU/mL	
ADA	Low	Low	Low	Low	High	Low	Low	Low
Amylase	Low	Low	Low	Low or high	Low	High	Low or high	Low
Serum BNP	≤364 pg/mL	≤364 pg/mL	>364 pg/mL	≤364 pg/mL	≤364 pg/mL	≤364 pg/mL	≤364 pg/mL	≤364 pg/mL

Tumor markers: CA 19-9, CEA and CA15-3; CA125 is not helpful in the differential diagnosis of ascites.

Table 6: Summary of ascitic fluid analysis recommended in clinical practice guidelines.

Guidelines	Initial ascitic fluid analysis	Optional ascitic fluid analysis	Publications
AASLD Guideline (2021)	SAAG, AFTP, PMN count	Culture, glucose, cytology, lactate dehydrogenase, amylase	Hepatology 2021; 74:1014–1048
BSG Guideline (2020)	SAAG, AFTP, PMN count	Cytology, amylase, ADA, BNP (serum)	Gut 2021;70:9–29.
JSGE Guideline (2020)	SAAG, AFTP, PMN count, bacterial culture	Cytology, LDH, acid-fast bacilli smear and culture, PCR, ADA, bilirubin, amylase, Gram stain, glucose, triglyceride	J Gastroenterol 2021; 56:593–619
CSH Guideline (2019)	SAAG, AFTP, PMN count	Culture (bacteria, anaerobic bacteria), glucose, lactase dehydrogenase, amylase, Gram's stain, *Mycobacterium tuberculosis* smear and culture, exfoliative cytology, bilirubin, triglycerides	Hepatol Int 2019; 13:1–21
EASL Guideline (2018)	SAAG, AFTP, PMN count, bacterial culture	Amylase, cytology, culture for mycobacteria, cholesterol	J Hepatol 2018; 69:406–460.
KASL Guideline (2017)	SAAG, AFTP, PMN count, bacterial culture	Gram stain, cytology, acid-fast bacilli smear and culture, ADA, LDH, glucose, CEA, ALP, amylase, Triglyceride, Bilirubin, urea, creatinine, Gram stain,	Clin Mol Hepatol 2018; 24:230–277.

AASLD, American Association for the Study of Liver Diseases; BSG, British Society of Gastroenterology; JSGE, Japanese Society of Gastroenterology; CSH, Chinese Society of Hepatology; EASL, European Association for the Study of the Liver; KASL, Korean Association for the Study of the Liver; SAAG, serum-ascites albumin gradient; AFTP, ascitic fluid total protein; PMN, polymorphonuclear; ADA, adenosine deaminase activity; BNP, B-type natriuretic peptide; LDH, lactate dehydrogenase; CEA, carcinoembryonic antigen; ALP, alkaline phosphatase.

benign ascites [45, 48, 50–52]. Therefore, the detection of CA125 is not recommended in patient with ascites [10]. Our results demonstrated ascitic tumor markers possessed (CEA, CA15-3, CA19-9) better diagnostic performance than serum tumor markers [45, 53]. Tumor marker possessed high specificity and low sensitivity in detecting malignant ascites [45, 47, 53]. Thus, the combination of ascitic tumor markers showed better performance than single tumor marker [45, 54]. The combination of cytology and tumor markers increased diagnostic yield [45]. Interestingly, an elevation of CEA (>5 ng/mL) or alkaline phosphatase (>240U/L) in ascitic fluid were observed in patients with secondary bacterial peritonitis [36].

Ascitic lactate dehydrogenase (LDH)

Ascitic LDH has been used as a maker in diagnosing malignant ascites [55, 56]. Ascitic LDH level was significantly higher in malignant ascites (439.1±169.1 U/L) than benign ascites (261.2±135.7 U/L), with 96 % of the sensitivity and 76 % of the specificity in diagnosing malignant ascites [57]. However, high ascitic LDH level was also detected in tuberculous peritonitis, secondary bacterial peritonitis and pancreatic ascites; low LDH level was observed in cirrhotic patients with hepatocellular carcinoma [55, 57–61]. As for the LDH isoenzyme, lower LDH-1 activity and higher LDH-4 and LDH-5 activity were detected in malignant ascites compared with benign ascites, with sensitivity and specificity of 90 and 70 % for LDH-1 activity, 94 and 62 % for LDH-4 activity, and 100 and 56 % for LDH-5 activity, respectively [57]. Low specificity revealed the limitation of LDH and LDH isoenzyme in distinguishing malignant ascites from benign ascites. Conversely, some researchers found ascitic LDH level are a useful indicator for separating tuberculous from malignant ascites [62]. Furthermore, Greene et al. found serum-to-ascites LDH ratio was able to distinguish cirrhotic ascites from malignant ascites with greater than 86 % accuracy [63].

Ascitic adenosine deaminase (ADA) and culture for mycobacteria

Adenosine deaminase (ADA) is an enzyme found in erythrocytes, lymphocytes, and the cerebral cortex. Ascitic ADA has been used as a diagnostic marker for tuberculous peritonitis (TBP) [64–67]. Ascitic fluid ADA levels ≥40 IU/L yielded 100 % of sensitivity and 96.0 % of specificity in the diagnosis of tuberculous peritonitis [64]. It is a challenge to differentiate tuberculous peritonitis from malignant ascites since tuberculous peritonitis and malignant ascites share similar profiles [68, 69]. Our team and other researchers demonstrated ascitic ADA was a good discriminator between tuberculous peritonitis and peritoneal carcinoma, with diagnostic accuracy of 91.72 % at a cut-off value of 22.5 IU/L [53, 66]. Importantly, Yi-Jun et al. found that cirrhotic patients without tuberculous peritonitis had a lower ascitic ADA level than patients with tuberculous peritonitis [70]. Smear and ascitic culture for mycobacteria are also used in the diagnosis of tuberculous peritonitis. The sensitivity of smear for mycobacteria is approximately 0 %; the sensitivity of fluid culture for mycobacteria is approximately 50 % [71].

However, culture for mycobacteria should probably be ordered only when there is a high pretest probability of occurrence of the disease under consideration due to high expense [10].

Ascitic glucose

Since glucose diffuses easily across membranes, the concentration of glucose in ascitic fluid is similar to that in the serum under normal conditions [17, 72]. Glucose in ascites is consumed by bacteria, white blood cells or cancer cells; glucose concentration decreases in tuberculous peritonitis, spontaneous bacterial peritonitis, secondary bacterial peritonitis and malignant ascites [72, 73]. Additionally, low glucose level in ascites was found in rheumatoid-related ascites due to impaired glucose transport across membranes [74, 75]. Kamran et al. demonstrated the concentration of ascitic glucose was significantly lower in exudate ascites than that in transudate ascites (165.8±140.0 mg/mL vs. 437.9±258.7 mg/mL, $p<0.001$) [76]. Particularly, ascitic glucose in tuberculous peritonitis was significantly lower than that in malignant ascites (71±13.82 mg/mL vs. 101.4±17.2 mg/mL, $p<0.001$) [77]. However, the overlap in ascitic glucose concentration between exudate ascites and transudate ascites, or between tuberculous peritonitis and malignant ascites, confined its value. Huseyin et al. found no significant difference in ascitic glucose concentration between high (>11 g/L) SAAG group and low (<11 g/L) SAAG group (12,366±1,008 mg/mL vs. 2016±4,554 mg/mL, $p>0.05$) [78]. All these revealed limited values of ascitic glucose concentration in differential diagnosis of ascites.

Ascitic amylase

Pancreatic ascites is the accumulation of protein-dense, amylase-rich intraperitoneal fluid, which occurs during the course of pancreatitis, and is associated with rupture of a pseudocyst or the disruption of a pancreatic duct [18]. In pancreatic ascites, ascitic amylase level is typically over 1000 U/L or greater than six times the serum amylase, with mean values exceeding 4000 U/L in a recent cohort of 80 patients [11, 79]. However, increased amylase in ascites was also found in patients with malignancy, gastric ulcer, gastrointestinal perforation, upper abdominal surgery, bowel obstruction, mesenteric vascular disease, biliary obstruction, and acute cholecystitis [17, 80]. Importantly, Measurement of amylase isoenzymes provides an assistance in the differentiation of pancreatic diseases from non-pancreatic diseases. In amylase-rich pleural effusions, pancreatic isoenzyme was observed in the patients with pancreatitis, and salivary isoenzyme was seen in patients with carcinoma and other pleural inflammatory conditions [81].

Triglyceride

Chylous ascites is defined as the extravasation of milky chyle rich in triglycerides into the peritoneal cavity [82]. Triglyceride concentration above 200 mg/dL supports the diagnosis of chylous ascites [20, 82, 83]. Chylous ascites usually occurs due to trauma and rupture of the lymphatics or increased peritoneal lymphatic pressure secondary to obstruction. The underlying etiologies for chylous ascites have been classified as traumatic, congenital, infectious, neoplastic, postoperative, cirrhotic or cardiogenic [19]. Sometimes, cloudy/turbid ascites caused by bacterial infection, pancreatitis, or perforated bowel, has similar appearance with chylous ascites. A high concentration of triglycerides is necessary to distinguish chylous ascites from cloudy/turbid ascites.

Serum B-type natriuretic peptide (BNP)

Serum B-type natriuretic peptide (BNP) plays an important role in the diagnosis of heart failure [84]. Farias AQ et al. demonstrated that serum BNP yielded sensitivity of 98 %, specificity of 99 %, and diagnostic accuracy of 99 % at a cutoff of >364 pg/mL in diagnosing heart failure-related ascites [85]; while ascitic BNP yielded sensitivity of 71 %, specificity of 99 %, and diagnostic accuracy of 94 % at a cutoff of >229 pg/mL. These indicated serum BNP is an excellent marker which discriminates heart failure as a cause of ascites from other causes of ascites [85]. Thus, serum BNP is recommended in BSG guidelines (2020) when heart failure-related ascites is suspected [11].

Other analytes

Other ascitic fluid analyses have been investigated. Vascular endothelial growth factor (VEGF) is a powerful angiogenic factor produced by tumor cells, it has been shown to play a critical role in the formation of malignant ascites [86]. Some researchers found ascitic VEGF level in malignant ascites was significantly higher than that in benign ascites [87]. Particularly, patients with ovarian cancer had higher ascitic VEGF level than those with gastric and colon cancer. Additionally, there was no significant difference in ascitic VEGF concentration between tuberculous peritonitis and cirrhotic ascites [87]. Study by Cheng et al. showed VEGF yielded a sensitivity of 81.2 % and a specificity of 80.2 % at a cutoff value of 560 pg/mL in the discrimination between malignant ascites and benign ascites [88]. While Dong et al. found a sensitivity of 91.3 % and a specificity of 90.9 %, at a cutoff value of 119.44 pg/mL [87]. Therefore, VEGF is a useful

parameter for the differential diagnosis of malignant and benign ascites. However, further investigations are necessary to confirm an optimum cut-off value.

High-resolution ^{1}H NMR spectroscopy of body fluids has emerged as an important tool for differential diagnosis of ascites. In a study with 70 ascitic fluid specimens, ^{1}H NMR spectroscopy was used to obtain a metabolic profile through quantitative estimation of 14 metabolite. Then, a model containing β-hydroxybutyrate, lactate, citrate, and tyrosine was established and the results showed the model 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 [72]. However, the assay does not apply to clinical practice due to high expense and unavailability in most hospital.

Potential analytical errors in ascites fluid analysis

Appropriate collection of ascitic fluid sample is prerequisite for laboratory investigation of ascites. Separate bottles containing ascitic fluid sample should be sent to each of the laboratory (cell count, biochemistry, cytology, microbiology). Plane tube is used for biochemistry test, cytology; EDTA tube is used for automated cell count; standard blood culture bottles are used for culture. Inappropriate sample collection gives rise to the error in ascitic fluid analysis. Ascitic fluid culture requires the bedside inoculation of the fluid into blood culture bottles to increase its sensitivity [5, 11, 89]. The interventions might result in inaccurate biochemical analysis of ascitic fluid. Albumin infusion and diuretic therapy may affect the measurement of AFTP. Ascites and serum samples should be collected on the same day for the calculations of SAAG. In addition, anti-infectives change the cell count and bacteria culture in ascitic fluid, thus, the ascitic fluid should be obtained before the initiation of anti-infective agents. Serum and ascitic BNP levels are altered after the use of cardiotonic drugs and the diuretics.

Conclusions

Ascitic fluid analysis has been widely used in defining the etiology of ascites. Routine ascitic fluid analysis should include the serum ascites albumin gradient (SAAG), total protein concentration, cell count and differential. Optional ascitic fluid analysis includes cholesterol, fluid culture, cytology, tumor markers, lactate dehydrogenase, adenosine deaminase (ADA), triglyceride, amylase, glucose, brain natriuretic peptide (BNP), etc. In our review, diagnostic values of the parameters in ascitic fluid analysis were evaluated. Then, diagnostic algorithm for patients with new-onset ascites was established (Figure 3).

Research ethics: Not applicable.
Informed consent: Not applicable.
Author contributions: Li Du, Ning Wei, Rakhi Maiwall and Yuhu Song reviewed the literature; Yuhu Song established the design and conception of the paper; all authors have contributed to write this review and approved the final version.
Competing interests: The authors state no conflicts of interest.
Research funding: National Natural Science Foundation of China (No. 82070631).
Data availability: Not applicable.

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Supplementary Material: This article contains supplementary material (https://doi.org/10.1515/cclm-2023-1112).