

Ascites in the state of Qatar: aetiology and diagnostic value of ascitic fluid analysis

Khan F Y

ABSTRACT

Introduction: Ascites is common and represents an important feature of liver disease and other diseases. The aim of this study is to determine the causes of ascites in Qatar, and to evaluate the value of ascitic fluid analysis in different types of ascites.

Methods: This is a descriptive, prospective study of all patients admitted to the medical department at Hamad General Hospital with ascites between January 2004 and January 2005.

Results: Of the 104 patients enrolled in the study, 70 (67.3 percent) were males and 34 (32.7 percent) were females, with a mean age of 52.9 (+/-14.8) years. Liver cirrhosis was the most frequent cause of ascites in 62 patients (59.6 percent), while chronic alcoholism was the main cause of liver cirrhosis. Other frequent causes of ascites were malignant ascites in 12 patients (11.5 percent), malignancy-related ascites in ten patients (9.6 percent), and tuberculous peritonitis in eight patients (7.7 percent). Based on the serum-ascites albumin gradient (SAAG), different causes of ascites were divided into two main groups. The first group was characterised by a mean SAAG of 1.1 or higher, and the second group was characterised by a mean SAAG of less than 1.1. The most common cause of high gradient ascites was liver cirrhosis, while the most common causes of low gradient ascites were carcinomatous peritonitis and tuberculous peritonitis. The mean ascitic lactate dehydrogenase (LDH) level was higher in cancer patients than in tuberculous patients (p-value is less than 0.05), while the mean ascitic glucose concentration was significantly lower in peritoneal tuberculosis

than in carcinomatous peritonitis (p-value is less than 0.05).

Conclusion: Liver cirrhosis is the main cause of ascites in Qatar. SAAG is a better distinguishing marker for separating ascites related to portal hypertension from other causes of ascites without portal hypertension. In patients with low gradient ascites, ascitic fluid glucose and LDH level are useful indicators for separating tuberculous from malignant ascites.

Keywords: ascites, carcinomatous peritonitis, paracentesis, serum-ascites albumin gradient, tuberculosis

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INTRODUCTION

Accumulation of ascitic fluid is caused most often by cirrhosis of the liver and is the most common complication of that disease. However, it may also be due to cancer, heart failure, TB, pancreatic disease, or other causes.⁽¹⁾ The development of ascites heralds a progressive deterioration in a patient's clinical condition, and only 50% of affected patients survive two years after onset.⁽²⁾ In Qatar, ascites has not been studied before. The traditional classification of ascites into "exudative" and "transudative" involves estimation of ascitic fluid total protein, which is ≥ 2.5 g/dL in exudates and < 2.5 g/dL in transudates.⁽³⁾ This classification, however, is unable to correctly identify the aetiological factors responsible for its causation^(4,5) and has been challenged on various occasions in different clinical conditions, especially in cirrhotic patients on prolonged diuretic therapy,⁽⁶⁾ and patients with cardiac ascites,⁽⁷⁾ malignant ascites,⁽⁸⁾ and spontaneous bacterial peritonitis.⁽⁹⁾ Moreover, it offers little insight into the pathophysiology of ascitic fluid formation.⁽¹⁰⁾

The difference between the serum and ascites albumin concentration (serum-ascites albumin gradient [SAAG]) is thought to directly reflect the colloid osmotic

Department of
Medicine,
Hamad General
Hospital,
Hamad Medical
Corporation,
P O Box 3050,
Doha,
Qatar

Khan FY, MD
Senior Specialist

Correspondence to:
Dr Fahmi Yousef
Khan
Tel: (974) 527 5989
Fax: (974) 439 2273
Email: fakhanqal@
yahoo.co.uk

pressure gradient and, indirectly, the degree of portal hypertension.⁽¹¹⁾ Pare et al suggested that SAAG is a better discriminator of portal hypertension than ascites protein concentration.⁽¹²⁾ Indeed, SAAG is now considered a useful physiological and clinical tool in the work-up of ascites.⁽¹³⁾ This prospective study was undertaken to define the causes of ascites and to evaluate the significance of ascitic fluid analysis in Qatar, and to compare the results with previously-reported studies.

METHODS

The entire country of Qatar is served by one medical corporation in Doha, Hamad Medical Corporation. It is a tertiary referral centre with a total capacity of 1,600 beds covering all medical and surgical disciplines including six intensive care units for adults. The patient population includes locals as well as expatriates mainly from other Arab countries and Asia.⁽¹⁴⁾ This prospective observational study was conducted at Hamad General Hospital. It involved patients admitted with primary diagnosis of ascites, from January 15, 2004 to January 14, 2005. Detailed history and clinical examinations were performed in all patients, in particular those with a history of abdominal distention, abdominal pain, jaundice, fever, stigmata of liver disease, heart failure and abdominal masses. To be accepted in this study, all patients had to undergo a diagnostic abdominal paracentesis and written consent was obtained.

Patients underwent abdominal paracentesis in the first 24 hours after the admission. Under aseptic conditions, a 22-gauge needle was used, in the left lower abdominal quadrant, and the samples of ascitic fluid were immediately sent to the biochemical, cytological and microbiological laboratories for analysis. At the same time, blood samples were taken for simultaneous ascitic fluid and blood determination of the levels of total protein, albumin, lactate dehydrogenase (LDH) and glucose. Smears of ascitic fluid were fixed and stained with Haematoxylin-eosin and Papanicolaou, and microscopically examined for their cellular content. The sediment from ascitic fluid was cultured for mycobacteria. Peritoneal biopsy (biopsy with laparoscopy) was sent to microbiological and histopathological laboratories for the diagnosis of tuberculous and carcinomatous peritonitis. Hepatitis B virus markers and screening for Hepatitis C virus antibodies were done in all patients.

The diagnosis of cirrhotic ascites was suspected when the patient developed ascites in the setting of clinical hepatic failure due to liver cirrhosis. These were divided into ascites due to uncomplicated and complicated liver cirrhosis. Complicated liver cirrhosis includes hepatocellular carcinoma and spontaneous bacterial peritonitis (SBP).

Diagnosis of liver cirrhosis was reached by clinical

assessment, laboratory findings, ultrasonography, and/or other imaging features, and when possible, by histopathology. Hepatocellular carcinoma was diagnosed by a combination of high serum alpha-fetoprotein (> 400 ng/ml) with focal intrahepatic lesion(s) seen by abdominal ultrasound and computed tomography (CT) of the abdomen and if necessary, by histopathology. The diagnosis of SBP was based on an ascitic fluid white blood cell count of more than 0.5×10^9 cells/L, with a neutrophil count of at least 0.25×10^9 cells/L with or without positive ascitic fluid bacterial culture.

Malignant ascites included those caused by peritoneal carcinomatosis. It is associated with malignant cells in the ascitic fluid as demonstrated by cytologic study and/or peritoneal biopsy specimen. On the other hand, malignancy-related ascites occurring as a result of portal hypertension due to massive hepatic metastasis by malignant cells in a patient with known malignancy but in whom the ascitic fluid cytological study and peritoneal biopsy specimen did not demonstrate malignancy. The diagnosis of tuberculous ascites required one of the following: first, positive culture for *Mycobacterium tuberculosis* from ascitic fluid or peritoneal biopsy specimen; second, positive smear for acid-fast bacilli from ascitic fluid or peritoneal biopsy specimen; third, caseating granuloma on peritoneal biopsy specimen.

The diagnosis of heart failure ascites was suspected when the patient developed ascites in the setting of clinical congestive heart failure with an enlarged heart, distended neck veins, and cardiac gallop that improved with therapy for the congestive heart failure. Cardiac failure was diagnosed clinically as well as by echocardiography. Chylous ascites was defined as the presence of ascitic fluid with high fat (triglyceride) content higher than 200 mg/dL, while ascites was considered eosinophilic if it contained more than 5% eosinophils.

The diagnosis of nephrotic syndrome ascites was suspected when the patient developed ascites in the presence of nephrotic syndrome (it means a urine protein excretion rate of more than 3.5 g/1.73 m² per 24 hours), while uraemic ascites occurred in a patient with uraemia for which there was no other explanation. Renal failure, nephritic and nephrotic syndrome diagnoses were based on biochemical, urine and ultrasonographical findings.

Results are expressed as mean \pm standard deviation. Student's t-test was used for statistical analysis of the data and $p < 0.05$ was considered statistically significant. Data analysis was performed using a software Epi Info version 2000 (Atlanta, GA, USA). Accuracy of test results was investigated by using positive predictive value (PPV) and negative predictive value (NPV). To calculate the PPV and NPV of SAAG, a value of < 1.1 g/dL was assigned as diagnostic for non-portal hypertension ascites. Thus, diagnostic results < 1.1 g/dL were considered as positive

Table I. Distribution of ascites among different nationalities by age group and gender.

Nationality	20–25 years		26–35 years		36–45 years		46–55 years		56–65 years		> 65 years		Total n (%)	95% confidence interval
	M	F	M	F	M	F	M	F	M	F	M	F		
Bangladeshi	0	0	0	0	2	0	3	0	0	0	0	0	5 (4.8)	1.6–10.9
Egyptian	0	0	0	0	2	0	7	0	4	1	0	1	15 (14.4)	8.3–22.7
Indian	0	0	0	0	0	0	2	0	1	0	0	0	3 (2.9)	0.6–8.2
Indonesian	0	0	0	2	0	0	0	0	0	0	0	0	2 (1.9)	0.2–6.8
Iranian	0	0	0	0	0	0	0	0	1	0	3	0	4 (3.8)	1.1–9.6
Jordanian	0	0	0	0	0	0	0	0	2	0	1	1	4 (3.8)	1.1–9.6
Nepali	2	0	1	0	0	0	1	0	0	0	0	0	4 (3.8)	1.1–9.6
Pakistani	0	2	1	1	1	1	3	1	2	0	0	0	12 (11.5)	6.1–19.3
Palestinian	0	0	0	0	0	0	0	0	1	1	0	1	3 (2.9)	0.6–8.2
Filipino	0	0	0	0	0	0	0	0	2	0	0	0	2 (1.9)	0.2–6.8
Qatari	0	1	1	1	3	3	4	4	7	2	6	7	39 (37.5)	28.2–47.5
Saudi	0	0	0	0	0	0	0	1	0	1	0	0	2 (1.9)	0.2–6.8
Sri Lankan	0	0	0	1	0	0	0	0	0	0	0	0	1 (1.0)	0.0–5.2
Sudani	0	0	1	0	1	0	0	1	1	0	2	0	6 (5.8)	2.1–12.1
Yemeni	0	0	1	0	0	0	0	0	1	0	0	0	2 (1.9)	0.2–6.8

M: male; F: female.

while results ≥ 1.1 g/dL were negative. The PPV of SAAG was calculated by dividing the total number of non-portal hypertension with true positives by the total number of individuals with positive results in each category (true positives + false positives); while the NPV of SAAG was calculated by dividing the total number of portal hypertension with true negatives by the total number of individuals with negative results in each category (true negatives + false negatives). On the other hand, to calculate the PPV and NPV of total protein ≥ 2.5 g/dL, a value of ≥ 2.5 g/dL was assigned as diagnostic for non-portal hypertension ascites. Thus, investigation results ≥ 2.5 g/dL were considered as positive while results < 2.5 g/dL were regarded as negative; then the PPV and NPV of total protein were calculated as above.

RESULTS

The total number of patients included in this study was 104. 70 (67.3%) were males and 34 (32.7%) were females, with a mean age of 52.9 ± 14.75 years. There were 39 (37.5%) Qataris, the remaining 65 (62.5%) were of different nationalities. The distribution of ascites among different nationalities by age group and gender in this study are summarised in Table I. Abdominal paracentesis was performed smoothly in all patients without any complications.

Liver cirrhosis was the most frequent cause of ascites in 62 (59.6%). Other most frequent causes were malignant ascites in 12 patients (11.5%), malignancy-related ascites in ten patients (9.6%), tuberculous peritonitis in eight patients (7.7%), heart failure in seven patients (6.7%),

nephrotic syndrome in three patients (2.9%), chylous ascites in one patient (1.0%) and eosinophilic ascites in one patient (1.0%). Liver cirrhosis was subdivided into two groups: uncomplicated liver cirrhosis in 40 patients and complicated liver cirrhosis due to hepatoma and SBP in 22 patients (11 hepatoma and 11 SBP). Causes of ascites between Qatari and non-Qatari residents in relation to gender are shown in Table II.

Chronic alcoholism was found to be the main cause of liver cirrhosis in this study. Other causes are chronic viral hepatitis (types B, and C) and miscellaneous causes including cryptogenic cirrhosis, autoimmune hepatitis, Wilson's disease and haemochromatosis (Table II). In malignant ascites, ovarian cancer was found in four patients (33.3%), colon cancer in two patients (16.7%), gastric cancer in two patients (16.7%), breast cancer in one patient (8.3%), urinary bladder cancer in one patient (8.3%), renal cancer in one patient (8.3%), and primary peritoneal cancer in one patient (8.3%). In malignancy-related ascites, gall bladder cancer was found in five patients (50%), breast cancer in two patients (20%), pancreatic cancer in one patient (10%), gastric cancer in one patient (10%), and thyroid cancer in one patient (10%).

Measurement of SAAG divided ascites into two main groups: the first group was characterised by mean gradients greater than or equal to 1.1 g/dL, and the second group was characterised by mean gradients less than 1.1 g/dL. High SAAG correlates with portal hypertension. The most common cause of high gradient ascites was liver cirrhosis in 62 patients (78.4%). Other

Table II. Causes of ascites among Qatari and non-Qatari residents in relation to gender (January 2004–January 2005).

Causes of ascites	Qatari n (%)		Non-Qatari n (%)		Total n (%)
	M	F	M	F	
Liver cirrhosis					
Alcoholic liver disease	15 (51.7)	0 (0)	14 (48.3)	0 (0)	29 (100)
Chronic viral hepatitis (types B and C)	2 (8.3)	6 (25)	12 (50)	4 (16.7)	24 (100)
Miscellaneous	0 (0.0)	3 (33.3)	5 (55.6)	1 (11.1)	9 (100)
Malignant ascites	0 (0)	5 (41.7)	4 (33.3)	3 (25)	12 (100)
Malignancy-related ascites	1 (10)	2 (20)	5 (50)	2 (20)	10 (100)
Tuberculous ascites	1 (12.5)	0 (0)	4 (50)	3 (37.5)	8 (100)
Heart failure	2 (28.6)	2 (28.6)	2 (28.6)	1 (14.2)	7 (100)
Nephrotic syndrome	0 (0)	0 (0)	1 (33.3)	2 (66.7)	3 (100)
Chylous ascites	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)
Eosinophilic ascites	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)

M: male; F: female; Miscellaneous: cryptogenic cirrhosis, autoimmune hepatitis, Wilson's disease, haemochromatosis and undetermined.

Table III. Diagnostic value of SAAG and ascitic total protein.

	Portal hypertension n = 79 (%)	Non-portal hypertension n = 25 (%)	Positive predictive value (%)	Negative predictive value (%)
Ascitic total protein level \geq 2.5 g/dL	13 (16)	22 (88)	63	95
SAAG <1.1 g/dL	3 (4)	22 (88)	88	96

Table IV. Comparison of the concentrations of serum albumin, ascitic albumen, SAAG, ascitic LDH and ascitic glucose in TB and cancer patients.

Disease parameter	Tuberculosis	Malignancies	Differences
Serum albumen (g/dL)	3.50 \pm 0.56	3.15 \pm 0.31	Not significant
Ascitic albumen (g/dL)	2.76 \pm 0.40	2.25 \pm 0.65	Not significant
SAAG (g/dL)	0.56 \pm 0.32	0.90 \pm 0.75	Not significant
Ascitic LDH (U/L)	570 \pm 287	1,549 \pm 1,054	p < 0.05
Ascitic glucose (mmol/L)	4.61 \pm 0.68	6.30 \pm 2.10	p < 0.05

causes include massive hepatic metastasis in ten patients (12.7%), and heart failure in seven patients (8.9%). On the other hand, the most common causes of low SAAG were carcinomatous peritonitis in 12 patients (48%), and tuberculous peritonitis in eight patients (32%). Other causes include nephrotic syndrome in three patients (12%), chylous ascites in one patient (4%) and eosinophilic ascites in one patient (4%). The positive and negative predictive values of SAAG and ascitic total protein are shown in Table III.

The mean ascitic total protein concentration in patients with liver cirrhosis was a low total protein concentration of 1.45 \pm 0.96 g/dL, while patients with congestive heart failure had a relatively high total protein concentration of 2.8 \pm 0.65 g/dL (p < 0.001). The mean ascitic LDH level was higher in cancer patients than in tuberculous patients

(p < 0.05). A cut-off value of 800 U/L has positive and negative predictive values of 92% and 88%, respectively. But in peritoneal TB, mean ascitic glucose concentration was significantly lower than cancer patients (p < 0.05). A cut-off value of 4.7 mmol/L has positive and negative predictive values of 77% and 91%, respectively (Table IV). Although SAAG in SBP was > 1.1 g/dL, all cases of SBP showed SAAG values < 2.0 g/dL (Table V). The ascitic fluid characteristics of various diseases in this study are shown in Table V.

DISCUSSION

Ascites is one of the most common clinical problems confronting a physician in Qatar. It has an incidence rate of 15 per 100,000 and an average of 90 cases is diagnosed annually. Expatriates formed the majority (62.5%) of

Table V. Ascitic fluid characteristics in various diseases.

Causes of ascites	Protein (g/dL)	SAAG (g/dL)	LDH (U/L)	Glucose (mmol/L)	Cells/ μ L		Other tests
					RBC	WBC	
Uncomplicated liver cirrhosis	1.6 \pm 1.44	2.9 \pm 2.25	110 \pm 39.66	7.32 \pm 1.12	< 100	< 500 neutrophils	Ultrasound, other imaging or liver biopsy
SBP	2.1 \pm 2.16	1.60 \pm 0.17	180 \pm 56.18	6.12 \pm 2.22	< 100	> 500 neutrophils	Neutrophil \geq 250/ μ L, \pm ascitic fluid culture
Hepatoma	1.5 \pm 3.33	2.8 \pm 2.36	210 \pm 31.14	6.03 \pm 2	< 100	< 500 neutrophils	Alpha foetoprotein > 400 ng/mL Abdomen ultrasound and CT
Malignant ascites	2.5 \pm 0.65	0.90 \pm 0.75	1,549 \pm 11	6.32 \pm 2.12	>10,000	> 1,000 lymphocytes	Cytology, peritoneal biopsy for histopathology
Malignancy-related ascites	1.4 \pm 2.44	2.9 \pm 2.25	110 \pm 99.66	7.32 \pm 1.12	< 200	< 1,000 lymphocytes	Screen for primary cancer
Tuberculous ascites	2.76 \pm 0.40	0.56 \pm 0.32	570 \pm 29	4.61 \pm 0.68	<10,000	> 1,000 lymphocytes	Peritoneal biopsy, for acid fast bacilli, culture and histopathology
Heart failure	1.2 \pm 3.22	2.8 \pm 2.25	56 \pm 29.12	7.12 \pm 2.20	< 100	< 250 neutrophils	Echocardiography
Nephrotic syndrome	2.5 \pm 0.65	0.7 \pm 0.23	88 \pm 12	9.44 \pm 1.13	< 200	< 250 neutrophils	Urine protein excretion > 3.5 g/1.73 m ² per 24 h
Chylous ascites	4.9	0.6	121	4.9	150	230 neutrophils	Ascitic triglyceride > 200 mg/dL is diagnostic
Eosinophilic ascites	3.8	0.9	650	6.3	852	4,500 eosinophils	Look for the cause of eosinophilia

RBC: red blood cells; WBC: white blood cells

cases presenting with ascites in this study. As expected, the causes of ascites in this study were similar to those in developed countries,⁽¹⁵⁻¹⁷⁾ except that the number of peritoneal TB cases was higher, 7.7%, compared to 0.7%–1.7%.^(16,17) In agreement with other reports,^(15,16) SAAG showed high accuracy for the diagnosis of ascites, as it has positive and negative predictive values of 88% and 96%, respectively, compared to 63% and 95% for ascitic total protein, respectively. Patients with cirrhosis have a low ascitic total protein concentration (1.45 \pm 0.96 g/dL) while patients with congestive heart failure, in whom hepatic synthetic function is essentially preserved, have a relatively high ascitic total protein concentration (2.8 \pm 0.65 g/dL) ($p < 0.001$). Thus, the mean ascitic fluid total protein concentration is a useful marker to differentiate the main causes of ascites in patients with a high SAAG.

In the present study, the main causes of low gradient ascites were found to be peritoneal carcinomatosis, tuberculous peritonitis and nephrotic syndrome, which are in agreement with other reports.⁽¹⁷⁾ The mean ascitic fluid LDH and glucose concentrations were helpful in the differential diagnosis of low gradient (malignancy and peritoneal TB) ascites. The mean ascitic (LDH) level was higher in cancer patients than tuberculous peritonitis ($p < 0.05$) while in peritoneal TB, mean ascitic glucose concentration was significantly lower than in cancer patients ($p < 0.05$). Similar observations have been also reported in other studies.^(12,18,19) In addition, a cut-off

value of ascitic glucose \leq 4.7 mmol/L was found to have positive and negative predictive values for tuberculous peritonitis of 77% and 91%, respectively, while a cut-off value of ascitic LDH \geq 800 U/L had positive and negative predictive values for malignant ascites of 92% and 88%, respectively.

In a survey done in the United States, 11 of 20 patients with liver cirrhosis died of tuberculous peritonitis, without any suspicion of TB before death.⁽²⁰⁾ Since tuberculous peritonitis is a treatable infectious disease and has a good prognosis, TB should always be considered the first diagnosis in patients with low gradient ascites. Unfortunately, in cirrhotic patients, tuberculous peritonitis can simulate ascites from liver disease or spontaneous bacterial peritonitis. The diagnosis is difficult in these patients because the ascitic fluid may not be of the exudative type as a result of the low albumin level in serum, and lymphocytes do not predominate in all cases.⁽²¹⁾

In conclusion, liver cirrhosis is the main cause of ascites in Qatar, while chronic alcoholism is the main cause of liver cirrhosis. Differential diagnosis of ascites should be based on the SAAG, which is a better distinguishing marker for separating ascites related to portal hypertension from other causes of ascites without portal hypertension. During the initial evaluation of patients with low gradient ascites, ascitic fluid glucose and LDH level are useful indicators for separating

tuberculous from malignant ascites. Consequently, low LDH and glucose levels indicate TB, while high LDH and glucose levels suggest cancer as the major cause.

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