

## ETIOLOGY OF ASCITES AND THE DIAGNOSTIC VALUE OF SERUM-ASCITES ALBUMIN GRADIENT IN NON-ALCOHOL LIVER DISEASE

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This study was designed to determine the different etiologies of ascites and the diagnostic value of serum-ascites albumin gradient (SAAG) in patients with ascites of non-alcoholic liver disease in Southern Saudi Arabia. A total of 132 patients with ascites (96 males and 36 females, mean age 58.8±15.9 years) were studied for the different causes of ascites. In 55 patients with liver disease and 22 patients with nonliver disease (malignancy and peritoneal tuberculosis), we compared SAAG with the three usual parameters of ascitic fluid biochemical analysis used in the differential diagnoses of ascites. The nonliver disease group showed higher ascitic fluid total protein (aTP) concentration (4.77±2.05 versus 1.98±1.56 g/dL), ascitic to serum ratio of total protein (a/sTP) concentration (0.75±0.43 versus 0.26±0.19), ascitic fluid lactic dehydrogenase (aLDH) level (565.4±353.4 versus 254.1±205.03 U/L) and a lower SAAG (0.6±0.30 versus 1.71±0.61).  $P < 0.0001$  for all parameters. The positive predictive values for aTP, a/sTP, aLDH and SAAG to detect ascites due to liver disease were 68%, 76%, 67%, and 80%, respectively, while the negative predictive values were 96%, 96%, 84%, and 98%, respectively. Liver causes accounted for 69.7% of cases, followed by peritoneal tuberculosis 10.6%, malignancy 9.1%, congestive heart failure 7.6%, and nephrotic syndrome 3.0%. SAAG is a useful diagnostic parameter which can be used to separate ascites of liver disease (nonalcoholic) from other causes of ascites, with an efficiency of 91%. SAAG should replace the traditional parameters (aTP, a/sTP, and aLDH) used in the differential diagnosis of ascites. In our series, liver disease is the major cause of ascites, followed by peritoneal tuberculosis. *Ann Saudi Med 1997;17(1):26-28.*

Ascites is the pathologic accumulation of fluid in the peritoneal cavity. The differential diagnosis of ascites is a lengthy one. Major subdivisions are those conditions associated with a normal peritoneum and those in which the disease process involves the peritoneum.

The ascitic fluid total protein and lactic dehydrogenase (LDH) concentration, as well as the ascites-to-serum ratios of protein and LDH, have traditionally been used to classify ascites into exudate and transudate categories.<sup>1</sup> Unfortunately, none of these parameters has been found to be completely discriminating.<sup>2</sup>

The difference between the serum and ascites albumin concentration (albumin gradient or SAAG) is thought to directly reflect the colloid osmotic pressure gradient and, indirectly, the degree of portal hypertension.<sup>3</sup> Pare and co-workers suggested that the serum-ascites albumin gradient (SAAG) is a better discriminator of portal hypertension than ascites protein concentration.<sup>4</sup> Indeed, SAAG is now considered a useful physiological, clinical tool in the work-up of ascites.<sup>5</sup>

Patients with gradients of  $\geq 1.1$  g/dL have portal hypertension while patients with gradients of  $< 1.1$  g/dL do not. The accuracy of such determinations is 97%.<sup>6</sup> "High-albumin gradient" ( $\geq 1.1$  g/dL) and "low-albumin gradient" ( $< 1.1$  g/dL) have replaced the terms "transudative" and "exudative" in the description of ascites in most of the recent publications.<sup>4,7,8</sup>

A strong relationship has been reported to exist between SAAG and the measured portal venous pressure in patients with ascites due to alcoholic liver disease.<sup>3,9</sup> Such a relationship was not found in patients with non-alcoholic liver disease.<sup>10</sup> Few studies are published from Saudi Arabia looking at the different causes of ascites in our area.<sup>11,12</sup>

We have undertaken this study to determine the different etiologies of ascites and the diagnostic value of SAAG in patients with ascites of nonalcoholic liver disease.

### Patients and Methods

This retrospective inpatient-based study was done on all Saudi patients admitted with ascites to Asir Central Hospital, Abha, southern region of Saudi Arabia, over a two-year period. Patients with ascites underwent routine

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TABLE 1. Causes of ascites.

Causes	No. of patients	%
Liver	92	69.7
Hepatitis B cirrhosis	32	24.2
Hepatitis C cirrhosis	27	20.5
Cryptogenic cirrhosis*	28	21.2
Hepatoma	5	3.8
Non-liver	40	30.3
Malignancy	12	9.1
Congestive heart failure	10	7.6
Nephrotic syndrome	4	3.0
Peritoneal tuberculosis	14	10.6
Total	132	100

\*In 12 of 28 patients, anti-HCV test was not done.

TABLE 2. Diagnostic value of ascitic fluid biochemical analysis in ascites of liver disease and ascites due to non-liver disease.

	Liver disease	Nonliver disease*	Predictive value	
			+	%
Number	55	22		
Ascitic total protein level >2.5 g/dL	9 (16%)	19 (86%)	68	96
A/S total protein level ratio >0.50	6 (11%)	19 (86%)	76	96
Ascitic fluid LDH level >400 U/L	7 (13%)	14 (64%)	67	84
SAAG <1.1 g/dL	5 (9%)	20 (91%)	80	98

\*Non-liver disease=malignancy and peritoneal tuberculosis; A/S=ascitic fluid to serum ratio; SAAG=serum-ascites albumin gradient.

admission abdominal paracentesis for analysis of cell count and differential, bacterial culture, cytology and concentration of total protein, albumin, glucose and lactate dehydrogenase (LDH). Simultaneous serum was obtained and tested for total protein, albumin, glucose and LDH.

Ascitic fluid bacterial cultures were performed routinely by bedside inoculation of blood culture bottles.<sup>13</sup> For cytological analysis, the timing of the paracentesis and the handling of the specimen was coordinated with the cytology laboratory. Biochemical analysis of ascitic fluid and serum were performed by Hitachi 704 autoanalyzer, Boehringer Mannheim, Mannheim, Germany. Ascitic cell counts and differential were done manually.

The diagnosis of peritonitis was based on an ascitic fluid white blood cell count of more than  $0.5 \times 10^9$  cells/L, with a neutrophil count of at least  $0.25 \times 10^9$  cells/L with or without positive ascitic fluid bacterial culture. Peritonitis was subclassified into spontaneous bacterial peritonitis (SBP), culture-negative neutrocytic ascites and secondary peritonitis.

The diagnosis of liver cirrhosis was based on the clinical features, presence of portal hypertension and, when available, a liver biopsy. Patients with liver cirrhosis were categorized as having portal hypertension if

esophageal varices were seen during gastroscopy. Cirrhosis was classified as cryptogenic if there were negative HBsAg, anti-HCV and autoimmune serologic tests, as well as normal metabolic studies and no history of alcohol intake.

HBsAg test was done by utilizing commercially available ELISA kits (Abbot Laboratories, Diagnostic Division, Chicago, Ill.). Anti-HCV was checked by using second-generation EIA kit detecting antibodies reacting with C-100, C33c and C22-3 region of HCV (Santoni Diagnostic Pasteurs, Manes La Coquette, France).

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 CT scan of the abdomen.

Diagnosis of peritoneal tuberculosis was based on laparoscopic appearance and peritoneal biopsy. Malignant ascites was based on evidence of primary tumor and/or positive cytologic examination. Cardiac ascites was diagnosed by clinical features and echocardiographic findings and nephrotic ascites by the finding of a nephrotic range of proteinuria.

The Student's *t*-test was used for the statistical analysis of the data. All values are expressed as mean  $\pm$  standard deviation. The predictive values and efficiency were calculated according to Galan and Gambino.<sup>14</sup>

## Results

We reviewed 132 patients with ascites, 96 males and 36 females, with a mean age of  $58.8 \pm 15.9$  years. The different causes of ascites in our series are shown in Table 1. From this table, liver causes accounted for 69.7% of cases with ascites, hepatitis B cirrhosis 24.2%, hepatitis C cirrhosis 20.5%, cryptogenic cirrhosis 21.2%, and hepatoma 3.8%, followed by peritoneal tuberculosis 10.6%, malignancy 9.1%, congestive heart failure 7.6% and nephrotic syndrome 3.0%. Twenty-one (22.8%) patients with liver diseases had clinical and ascitic fluid findings of SBP, only 12 (57.1%) of these had positive ascitic fluid culture. *Escherichia coli* was the most common (58.3%) organism isolated. All liver disease patients, except hepatoma patients, had esophageal varices documented by gastroscopy. Cytology was positive in 70% of patients with malignant ascites and no hepatocellular carcinoma patients had positive cytologic analysis. The causes of malignant ascites included gastric carcinoma in four patients, colon cancer in two patients, pancreatic cancer in two patients, ovarian cancer in two patients and breast cancer in two patients.

Table 2 shows the diagnostic value of four ascitic fluid biochemical parameters used in separating ascites of liver disease from ascites due to nonliver disease (malignancy and peritoneal tuberculosis). Of the 132 patients, 77

patients for both liver and nonliver-related ascites had all four parameters complete for analysis. The ascitic fluid protein concentration was  $1.98 \pm 1.56$  g/dL in patients with liver disease and  $4.77 \pm 2.05$  g/dL in patients with nonliver disease (malignancy and peritoneal tuberculosis) ( $P < 0.0001$ ); ascitic fluid LDH concentration was, respectively,  $565.4 \pm 353.4$  U/L and  $254.1 \pm 205.3$  U/L ( $P < 0.001$ ); the ascitic fluid-to-serum ratio of total protein concentration was, respectively,  $0.26 \pm 0.14$  and  $0.75 \pm 0.43$  ( $P < 0.0001$ ). SAAG was higher in patients with liver disease,  $1.71 \pm 0.61$ , than in patients with nonliver disease (malignancy and peritoneal tuberculosis),  $0.60 \pm 0.30$  ( $P < 0.0001$ ).

As expected, patients with congestive heart failure showed high SAAG (1.12 g/dL) and patients with nephrotic syndrome had low SAAG (0.8 g/dL).

The efficiency of the criteria in correctly diagnosing patients with ascites caused by liver disease and those related to nonliver disease (malignancy and peritoneal tuberculosis) was highest for SAAG,  $< 1.1$  (91%), followed by ascites/serum total protein ratio,  $> 0.5$  (88%), ascitic total protein,  $> 2.5$  g/dL (84%) and ascitic fluid LDH level,  $> 400$  U/L (81%). A SAAG of  $< 1.1$  g/dL was found in five (9%) patients with liver disease.

### Discussion

The causes of ascites in our series were similar to the causes in developed countries,<sup>6,15</sup> except that we had a higher number of peritoneal tuberculosis cases, 10.6%, compared to 0.7%, 1.7%<sup>15</sup> and 3.5%.<sup>16</sup> Another study from the central part of Saudi Arabia showed similar findings in which peritoneal tuberculosis accounted for 10% of their series.<sup>11</sup> Liver disease accounted for most of our patients with ascites; none of these cases were due to alcoholic liver disease, metabolic or autoimmune etiology.

Hoefs first reported a linear correlation ( $r = 0.73$ ,  $P = 0.0001$ ) between SAAG and portal venous pressure in 56 patients with chronic liver disease, 52 of whom had an alcoholic liver disease.<sup>3</sup> Likewise, Rector and Reynolds reported an excellent correlation ( $r = 0.81$ ,  $P < 0.001$ ) between SAAG and portal pressure in 18 patients with alcoholic liver disease.<sup>9</sup> The only study in the literature examining such a relationship, reported by Kajani and co-workers, in 24 patients with chronic nonalcoholic liver disease, showed no correlation ( $r = 0.398$ ) between measured portal venous pressure and SAAG, and three of their patients had a SAAG  $< 1.1$  g/dL.<sup>10</sup> We found five of our liver disease patients with a SAAG  $< 1.1$  g/dL. These were due to viral causes of liver cirrhosis and had no superimposed SBP or hepatocellular carcinoma. In spite of the presence of esophageal varices by gastroscopy, which indicates the presence of portal hypertension, these five patients had low SAAG. Our study suggests that once the

causes of low albumin-gradient ascites, SAAG  $< 1.1$  g/dL (peritoneal tuberculosis, peritoneal carcinomatosis, pancreatitis, nephrotic syndrome and biliary ascites), were excluded, this entity of portal hypertension patients with low SAAG should be considered.

In conclusion, liver disease (69.7%) is the major cause of ascites in our patients, followed by peritoneal tuberculosis (10.5%). Despite the lack of linear correlation between measured portal venous pressure and SAAG in nonalcoholic liver disease,<sup>10</sup> SAAG is still a useful diagnostic biochemical parameter, which can be used to separate ascites of liver disease (nonalcoholic) from other causes of ascites (malignancy and tuberculosis) and should replace the exudate/transudate concept in the differential diagnosis of ascites.

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