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ORIGINAL ARTICLE

# Clinical pattern of ascites due to malignancy in Qatar

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## ABSTRACT

**Background:** The clinical characteristics of ascites due to malignancy are not fully known, and it appears as a variable entity with different types of clinical presentation and with a difficult diagnosis.
**Objectives**: the aim of this study is to describe the clinical pattern of ascites due to malignancy in Qatar and to evaluate the diagnostic efficacy of serum/ascitic albumin gradient in differentiating different types of ascites caused by malignancy.
**Methods:** a descriptive prospective study of patients admitted to Hamad general hospital with ascites due to malignancy.
**Results:** The total number of patients included in this study was 22 patients. Based on serum ascitic albumen gradient, ascites due to malignancy was divided into two main groups; first, with serum/ascitic albumin gradient < 1.1 g/dL, second, serum/ascitic albumin gradient ≥ 1.1 g/dL. The firs group was consistent with carcinomatous peritonitis (Malignant ascites), while the second group represented tumors metastasizing to the liver leading to portal hypertension (malignancy related ascites). Ovarian carcinoma was the most common primary tumour in patients with malignant ascites while gall bladder cancer was most common primary tumour in patients with malignant related ascites.
**Conclusion:** serum/ascitic albumin gradient is effective in differentiating between malignant and malignancy related ascites. Along with the currently available, largely unsatisfactory treatment alternatives, these data might change our present clinical management of ascites due to malignancy.

**Key words:**
Malignant ascites, malignancy related ascites, carcinomatous peritonitis.

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## Introduction

Cancer accounts for about 10% of all cases of ascites and usually caused by ovarian, endometrial, breast, oesophageal, gastric, colorectal, lung, pancreatic, hepatobiliary and primary peritoneal carcinomas.[1], [2], [3] It has been shown that around 10 to 15% of all patients with gastrointestinal cancer develop ascites at some stage of their disease. Generally, the presence of malignant ascites is associated with poor prognosis, regardless of the cause. [4] It is a poor prognostic indicator, with a median survival time ranging from 1 to 4 months.[5]

Analysis of ascites plays a major role in the diagnostic workup of ascites due to malignancy.
The incidences of ascites due to cancer vary from country to other, In Qatar it represents 21% of ascites cases. [6] Data on clinical patterns and outcome of ascites due to malignancy in the state of Qatar are still incomplete. This prospective study was conducted to describe the clinical patterns and outcome of ascites due to malignancy in the state of

Qatar and to compare the results with previously reported studies.

## Methods and Patients

This prospective observational hospital based study was conducted at Hamad Medical Corporation (HMC), State of Qatar, which is a small country with an area of 11,521.0 Sq. km extending into the Persian Gulf from the eastern coast of Arabian Peninsula and has an estimated population size of 744,029 according to 2004 census and is densely populated at the capital city of Doha. HMC serves as a tertiary referral center with many hospitals, covering all medical and surgical disciplines including 6 intensive care units. So far, there are no private hospitals admitting patients with cirrhotic ascites. This study was conducted during one year, started from January 15, 2004 to January 14, 2005 at Hamad General Hospital. The aim of this study was to describe the clinical pattern of ascites due to malignancy in Qatar and to evaluate the diagnostic efficacy of serum/ascitic albumin gradient in differentiating different types of ascites caused by malignancy**.** It includes all patients admitted to the medical department of Hamad General Hospital with primary diagnosis of ascites due to malignancy and who had peritoneal paracentesis performed during admission. Detailed history and clinical examinations performed, in all patients, in particular those with a history of malignant disease. Routine hematological and biochemical investigations of serum were performed in all patients. 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. Peritoneal biopsy (biopsy with laparoscopy) was sent to histopathological laboratories for the diagnosis of carcinomatous peritonitis. Patients were included in the study if they had had underwent abdominal paracentesis and had signed a consent form.

The development of ascites in patients with history of either intra-abdominal or extra-abdominal malignancy in the absence of liver cirrhosis and other causes of nonmalignant ascites was accepted as being ascites due to malignancy**.**

Malignant ascites (carcinomatous peritonitis):An ascites associated with malignancy in the peritoneal space as demonstrated by cytologic study and/or peritoneal biopsy specimen. Malignancy related ascites (massive hepatic metastasis): Ascites occurring as a result of portal hypertension due to hepatic infiltration by malignant cells in a patient with known malignancy but in whom the ascitic fluid cytologic study and peritoneal biopsy specimen did not demonstrate malignancy. (Malignant origin of the ascites in these patients was usually confirmed by one or more of cytological examination, imaging, laparoscopy or laparotomy).

**Table/Fig 1**
**Causes of ascites due to malignancy among Qatari and non-Qatari residents in relation to gender**

| | Qatari n (%) | | Non-Qatari n (%) | | Total |
|---|---|---|---|---|---|
| | M | F | M | F | N (%) |
| Malignant ascites | 0(0) | 5(41.7) | 4(33.3) | 3(25) | 12 (54.5) |
| Malignancy related ascites | 1(10) | 2(20) | 5(50) | 2(20) | 10 (45.5) |
| Total | 1(4.5) | 7(31.9) | 9(40.9) | 5(22.7) | 22 (100) |

**Table/Fig 2**
**Diagnostic value of SAAG ascitic total protein**

| | Malignant ascites N=12 | Malignancy related ascites N= 10 | Positive predictive value (%) | Negative predictive value (%) |
|---|---|---|---|---|
| Ascitic total Protein > 2.5 g/dL | 11 | 1 | 91.6 | 90 |
| SAAG <1.1 g/dL | 12 | 0 | 100 | 100 |

## Data analysis

Data were analyzed with soft ware EpiInfo 2000. Quantitative variables are expressed as mean ± standard deviations. Fisher exact test or Chi Square test were used when appropriate to compare between categorical groups. Results were considered significant if the P-value is less than 0.05. 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 malignant (non portal hypertension) ascites. Thus, diagnostic results < 1.1 g/dL were considered as positive 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 malignant (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.

**Table/Fig 3**
**Comparison of the concentrations of ascitic total protein, SAAG, ascitic LDH, ascitic glucose and ascitic cytopathology in malignant and malignancy related ascites**

| | Malignant ascites N=12 | Malignancy related ascites N= 10 | Differences |
|---|---|---|---|
| Ascitic total Protein (g/dL) | 2.5 ± 0.65 | 1.4±2.44 | P<0.05 |
| SAAG (g/dL) | 0.9±0.75 | 2.9±2.25 | P<0.05 |
| LDH (U/L) | 1549±11 | 110±99.66 | P<0.05 |
| Glucose (mmol/L) | 6.32±2.12 | 7.32±1.12 | Not significant |
| Cytopathology (+ve for malignancy) | 9 | 0 | P<0.05 |

## Results

The total number of patients included in this study was 22 patients. 12 (54.5%) were females and 10 (45.5%) were males with a mean age of 52.9±14.75 years. There were 8 (36.4%) Qataris; the remaining 14 (63.6%) were of different nationalities. Table 1 shows causes of ascites due to malignancy among Qatari and non-Qatari residents in relation to gender.

Based on serum-ascitic albumin gradient, ascites due to malignancy was divided into two groups: first, with serum/ascitic albumin gradient (SAAG) < 1.1 g/dL, second, serum/ascitic albumin gradient ≥ 1.1 g/dL. The first group was consistent with carcinomatous peritonitis (malignant ascites), while the second group represented tumors metastasizing to the liver leading to portal hypertension (malignant related ascites). Moreover, ascitic total protein was high (≥ 2.5 gm/dL) in 11 (91.6%) patients of the first group, while it was low (< 2.5 g/dL) in 9 (90%) patients of the second group. The positive and negative predictive values of serum/ascites albumin gradient and ascitic total protein are shown in Table/Fig 2.

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%). On the other hand, causes of malignant related ascites included gall bladder cancer 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%). Out of 22, 13 (59%) patients, presented with ascites, which required further investigations to find the primary tumour.

Cytopathological study of ascitic fluid in malignant ascites was positive in nine (75%) patients; while peritoneal biopsy (biopsy with laparoscopy) was required to confirm peritoneal carcinomatosis in the remaining three. On the other hand, malignant related ascites has disappointingly low yield; the frequency of positive result was zero. Table/Fig 3 shows the comparison between malignant and malignancy related ascites.

After one year follow up, two patients with malignancy related ascites [one male and one female], and one male patient with malignant ascites were died, to result in a one-year mortality rate of 13.6%.

## Discussion

Two-thirds of cases of ascites due to malignancy are caused by peritoneal carcinomatosis, while the most common tumors causing peritoneal carcinomatosis are primary adenocarcinomas of the ovary, uterus, pancreas, stomach, colon, lung, or breast. The remaining one-third is due to lymphatic obstruction or portal hypertension due to hepatocellular carcinoma or diffuses hepatic metastases. [7], [8]

In our study, ascites was caused by peritoneal carcinomatosis in 12 (54.5%) patients, whereas it was caused by malignant related ascites in the remaining 10 (45.5%) patients. We did not encounter any case of hepatocellular carcinoma causing ascites in this series. This may be due to low incidence of primary hepatocellular carcinoma in Qatar. There is a predominance of the female patient population (12 of 22) similar to previous studies[4], [7] and this is accounted for by the predominance of the ovarian and breast cancer entity.

In Thirteen (59%) of our patients, the presence of ascites was the first clinical sign of an underlying neoplastic process, which coincides with other reports.[4], [9], [10] These patients were mainly the ovarian and the GI cancer groups, while patients with breast cancer tended to develop ascites due to their cancers months or years after their primary cancer had been diagnosed and treated.

In agreement with other reports [7], [8], [11], [12], [13], ascitic fluid analysis of our patients with peritoneal carcinomatosis demonstrated a low serum /ascites-albumin gradient (< 1.1 mg/dL) in all patients, and an elevated white cell count with a lymphocyte predominance. In malignant ascites, ascitic fluid cytology was diagnostic in 50% to 90% in reported series. [2,8,11,14] laparoscopy can be used to obtain a tissue diagnosis. [15] In our study cytology was positive in over 75%, and laparoscopy was required in three patients with negative cytology to confirm the diagnosis of peritoneal carcinomatousis.

As noted in this study, serum/ascitic albumin gradient seems to be an effective tool in differentiating between malignant and malignancy related ascites in clinical practice, serum/ascitic albumin gradient showed high accuracy for the diagnosis of malignant ascites, as it has positive and negative predictive value of 100% and 100% respectively, compared to 91.6% and 90% for ascitic total protein.

This fact affects the management line of ascites. Malignancy related ascites can be controlled by administering higher doses of spironolactone similar to those seen in patients suffering form liver cirrhosis. [2], [9]

In many studies,[2], [10], [16], [17] ovarian carcinoma is the primary tumour in the majority of cancer patients with malignant ascites. The commonest cancer of origin leading to malignant ascites in our series was ovarian carcinoma; it represented 33.3% of the total patient population. We did not encounter any case of cancer of unknown primary (CUP), although previous studies had been reported the number of malignant ascites due to an unknown primary cancer (CUP) in the range of (8.1% - 22.6%). [2], [4], [9]

Imaging diagnostics such as CT, MRI or ultrasonography are able to detect even small amounts of fluid in the abdominal cavity but they cannot differentiate between a benign or malignant form of ascites. Despite this limitation, they are valuable techniques for discovering a primary tumour or metastases. [2]

In conclusion, it is crucial to differentiate between malignant and malignancy related ascites in clinical practice. This fact will influence not only our understanding but the clinical management of these devastating conditions. Serum/ascitic albumin gradient is effective in differentiating between malignant and malignancy related ascites, since it is related to the genesis of this type of ascites. Moreover, cytological evaluation of ascitic fluid is helpful in the detection of malignant ascites; it was positive in 75% of our patients.

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