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Ascitic and serum levels of tumor biomarkers (CA 72-4, CA 19-9, CEA and CA 125) in discrimination of cause of ascites: a prospective study

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ABSTRACT – Background – The role of ascitic and serum levels of various tumour biomarkers in the discrimination of cause of ascites is not well established. **Objective –** To evaluate the role of serum and ascitic levels of tumor biomarkers (CA 72-4, CA 19-9, CEA and CA 125) in discrimination of cause of ascites. **Methods –** A prospective study was conducted in consecutive patients presenting with ascites. Serum and ascitic levels of CA 19-9, CA 125, CA 72-4 and carcinoembryonic antigen (CEA) were determined at the presentation. The patients with cirrhotic ascites, tuberculous peritonitis (TBP) and peritoneal carcinomatosis (PC) were eventually included in analysis. **Results –** Of the 93 patients (58 males, mean age 47 years) included, the underlying cause was cirrhosis in 31, PC in 42 and peritoneal tuberculosis in 20. The best cutoff for discriminating benign and malignant ascites for serum CEA, CA 19-9 and CA 72-4 were 6.7 ng/mL, 108 IU/mL and 8.9 IU/mL, respectively. The best cutoff for discriminating benign and malignant ascites for ascitic CA 125, CEA, CA 19-9 and CA 72-4 were 623 IU/mL, 8.7 ng/mL, 33.2 IU/mL and 7 IU/mL, respectively. **Conclusion –** The performance of single biomarker for the prediction of underlying PC is low but a combination of serum CA 19-9 and CA 72-4 best predicted the presence of peritoneal carcinomatosis.

Keywords – Tuberculous peritonitis; peritoneal carcinomatosis; peritoneal tuberculosis; malignant ascites; cirrhosis; portal hypertension.

INTRODUCTION

Ascites, a pathologic accumulation of fluid in the peritoneal cavity, can be caused by diverse etiologies[1,2]. The mechanism of ascites formation could be related to a disbalance between plasma flowing in and out of blood and lymphatic vessels from increased capillary permeability, venous pressure, lymphatic obstruction, decreased serum protein and occasionally, protein exudation from the peritoneum[3,4]. Currently, cytological analysis plays a pivotal role in differentiating malignant from benign ascites. However, sensitivity of cytology for diagnosis of peritoneal carcinomatosis (PC) is 40–70%[5-7]. Further, cytology does not have an important role in diagnosis of benign causes like tuberculous peritonitis (TBP) or cirrhotic ascites. It is especially difficult to discriminate peritoneal carcinomatosis (PC) from TBP because of similar clinical and radiological presentation.

Tumor markers are bioactive substances in body fluids or tissues that are produced, secreted or shed off from tumor cells, or substances which are produced by host cells as a reaction to tumor tissues[8]. These markers have been assayed in serum and found useful in diagnosing various malignancies and are also secreted in peritoneal fluid. Their measurement in peritoneal fluid has often been used to increase the specificity and sensitivity of cytological examination in ascitic fluid. However, apart from malignancies, they have been found to be elevated in certain benign conditions like gastritis, diverticulitis, cirrhosis and pancreatitis[9]. While carcinoembryonic antigen (CEA), CA-125 and CA19-9 have already been studied in patients with ascites, the role of CA 72-4 in discrimination of etiology of ascites is uncertain[10]. The present study aimed at studying the role of CA 72-4 along with CEA, CA 19-9 and CA-125 for the discrimination of underlying etiology in patients with ascites.

METHODS

Setting

The study was a prospective observational study conducted in the Departments of General Surgery and Gastroenterology at a tertiary care center in North India. The study was approved by the Institute's Ethics' Committee and written informed consent was taken from the participants. Further, separate consent was taken prior to any invasive procedure like paracentesis.

Patients and diagnosis

We considered consecutive patients presenting with ascites for inclusion. The patients between 12 to 80 years of age in whom un-

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derlying cirrhosis, tuberculosis or peritoneal carcinomatosis were considered as cause were included in the study. Patients refusing to give consent, cases where ascites could not be tapped due to minimal volume of fluid or a contraindication and cases of perforation peritonitis were excluded from the study.

Cirrhotic ascites was defined as ascites in patients with chronic liver disease (CLD) having a high serum ascites albumin gradient (>1.1 gram/dL) and evidence of cirrhosis as confirmed by presence of nodular / irregular outline of liver and/or other features of portal hypertension (esophageal or gastric varices). Tubercular ascites was diagnosed on basis of either microbiological positivity (acid fast bacilli/ tubercular polymerase chain reaction testing / Gene Xpert or Culture) in ascitic fluid or other tissues or histopathological findings of caseating granulomas from any tissue or if clinical presentation was consistent with TBP, level of ADA in ascites was elevated (>32 U/L) or there was a presence of granulomas (without caseation) in any tissue with exclusion of other causes and demonstration of response to therapy with reduction / resolution of ascites[11]. Peritoneal carcinomatosis was diagnosed with a positive cytology for malignant cells with a known or unknown primary malignancy.

Patient follow-up

Two samples each of serum and ascitic fluid were collected, centrifuged and stored for subsequent assay of CA-125, CEA, CA19-9 and CA 72-4. Samples of ascitic fluid were obtained from the left lower abdominal quadrant under aseptic conditions using a 22-gauge needle and sent for biochemical investigations. Ultrasound guided ascitic tap was done if required. Malignant or nonmalignant ascites were confirmed with history, examination, cytology, histopathological examination, ADA or imaging. Non-malignant conditions mainly included chronic liver disease and tuberculosis. The diagnosis of these conditions was established either by imaging or tissue examination as clinically indicated. Finally, tumor markers were analyzed in each group and compared statistically.

Statistical analysis

The data was analyzed using Statistical Package for the Social Sciences: IBM SPSS Statistics for Windows, Version 24.0. NY. Levels of tumor markers were analyzed among the three groups of TBP, malignant ascites and cirrhotic ascites stating their medians and Inter-Quartile Ranges as necessary. The data were checked for normality using Kolmogorov-Smirnov test. Comparison was done among the groups- malignant and benign (CLD and tuberculosis) ascites, and malignant and tuberculous ascites using nonparametric test- Mann Whitney Test. Possible cutoff values of various serum and ascitic biomarkers were determined using the receiver operating characteristic (ROC) curves. A combination of markers that had a significant area under curve in the ROC curves was used to calculate combined sensitivity and specificity of the markers. Positive predictive value and negative predictive values were also calculated for these combinations.

RESULTS

Patients and diagnosis

The study was conducted from July 2018 to December 2019 and 111 patients were assessed for inclusion. A total of eighteen patients were excluded from the study– five had ascites due to unrelated causes (chronic kidney disease and ruptured amoebic abscess); single cause of ascites could not be ascertained for the other 10 (three lost to follow up; one had an inconclusive result; ascites could be attributed to more than one diagnosis in the other six patients); dry tap in three patients. A total of 93 patients were finally included and analyzed (FIGURE 1).

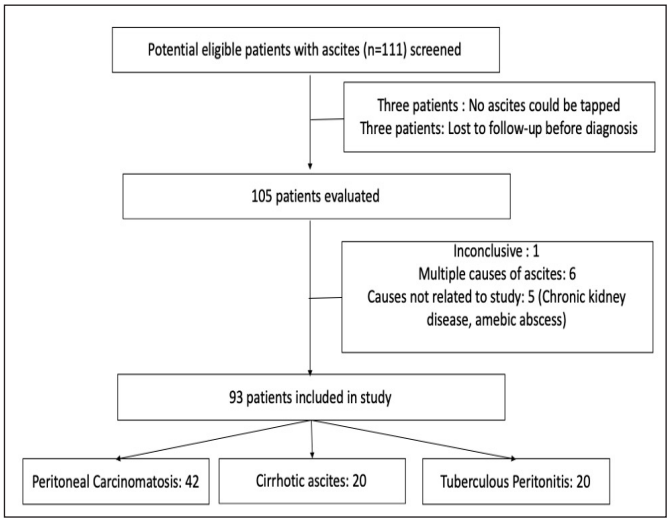

FIGURE 1. Flow chart showing the flow of the study participants and final diagnosis.

Of the 93 patients included, 58 (62%) were males and the mean age was 47 years (14–81). (TABLE 1). The etiology of the ascites in the study population was CLD in 31, tuberculosis in 20 and peritoneal carcinomatosis in 42 patients. (TABLE 1). The underlying causes of peritoneal carcinomatosis were gallbladder carcinoma – 14 (33%), gastric carcinoma – 7 (16.8%), colorectal carcinoma – 6 (14.3%), cholangiocarcinoma – 4 (9.5%), esophageal cancer – 2 (4.8%), duodenal carcinoma – 2 (4.8%) and two cases of unknown primary and one case each of gastrointestinal stromal tumour, ovarian malignancy, pancreatic adenocarcinoma, appendiceal adenocarcinoma and mesothelioma.

Tumour biomarkers in various groups

The median values of tumor markers in serum in the malignant group were 5.0 ng/mL, 131 IU/mL, 234.9 IU/mL and 9.5 IU/mL for CEA, CA 19-9, CA-125 and CA 72-4 respectively (TABLE 2). The median values of the tumor markers in benign etiology (CLD or TBP) were 2.8 ng/mL, 16.5 IU/mL, 280.9 IU/ml and 2.7 IU/mL for serum CEA CA19-9, CA-125 and CA 72-4 respectively. The levels of serum CEA, CA19-9 and CA72-4 were significantly different in malignant and benign ascites (TABLE 2).

In ascitic fluid, the median values of CEA, CA19-9, CA-125 and CA 72-4 were 14.6 ng/mL, 47.8 IU/mL, 472.5 IU/mL and 10.7 IU/mL respectively in the malignant group. The median values in the group with benign ascites were 1.0 ng/mL, 4.6 IU/mL, 353.7 IU/mL and 3.9 IU/mL for CEA, CA19-9, CA-125 and CA 72-4 respectively. All tumor markers were significantly higher in the malignant etiology group.

The group with tuberculous ascites was assessed separately and compared with the malignant group (TABLE 2). The median values for all the tumor markers except serum CA-125, in the malignant group were found to be statistically significantly higher than the tuberculosis group.

TABLE 1. Baseline characteristics of study groups.

Characteristic	Cirrhotic ascites (n=31) n (%)	Peritoneal carcinomatosis (n=42) n (%)	Tuberculous peritonitis (n=20) n (%)	Total (n=93) n (%)
Male gender	29 (94)	20 (48)	9 (45)	58 (62)
Age (mean ± SD and range)	47±12.6 (21–71)	54±12.9 (24–81)	31±12.6 (14–60)	47 (14–81)
Abdominal pain	5 (16)	33 (80)	14 (70)	52 (56)
Abdominal distension	29 (94)	33 (80)	15 (75)	77 (83)
Abdominal lump	0 (0)	1 (2)	1 (5)	2 (2)
Fever	5 (16)	2 (5)	12 (60)	19 (20)
Jaundice	9 (29)	7 (17)	1 (5)	17 (18)
Haematemesis/melaena	7 (23)	2 (5)	1 (5)	10 (11)
Loss of weight	1 (3)	29 (71)	7 (35)	37 (40)
Altered bowel habits	1 (3)	8 (19)	8 (40)	17 (18)
Vomiting	0 (0)	8 (19)	5 (25)	13 (14)
Alcoholic	22 (71)	4 (10)	1 (5)	29 (31)
Icterus	14 (45)	10 (24)	2 (10)	26 (28)
Abdominal distension	30 (97)	36 (86)	19 (95)	85 (91)
Abdominal lump	0 (0)	7 (17)	0 (0)	7 (8)
Flaps	2 (6)	0 (0)	0 (0)	2 (2)

TABLE 2. Comparative analysis of investigations between various causes of ascites.

	Malignant vs benign ascites		
Investigation	**Malignant (n=42) median (IQR)**	**Benign (n=51) median (IQR)**	***P* value**
Serum markers			
CEA (ng/mL)	5.0 (19.1)	2.8 (3.5)	0.01
CA19-9 (IU/mL)	131.3 (1067.5)	16.5 (33.8)	0.00
CA-125 (IU/mL)	234.9 (266.8)	280.9 (345.4)	1.00
CA 72-4 (IU/mL)	9.5 (25.0)	2.7 (5.1)	0.00
Ascitic fluid markers			
CEA (ng/mL)	14.6 (249.75)	1.0 (1.3)	0.00
CA 19-9 (IU/mL)	47.8 (994.0)	4.6 (8.4)	0.00
CA 125 (IU/mL)	472.5 (639.6)	353.7 (343.8)	0.02
CA 72-4 (IU/mL)	10.7 (59.7)	3.9 (3.5)	0.00
Malignant vs tuberculosis	**Malignant (n=42) median (IQR)**	**Tuberculosis (n=20) median (IQR)**	***P* value**
Serum markers			
CEA (ng/mL)	5.0 (19.1)	2.0 (1.5)	0.00
CA19-9 (IU/mL)	131.3 (1067.5)	6.9 (22.0)	0.00
CA-125 (IU/mL)	234.9 (266.8)	136.2 (321.7))	0.10
CA 72-4 (IU/mL)	9.5 (25.0)	3.7 (6.1)	0.00
Ascitic fluid markers			
CEA (ng/mL)	14.6 (249.75)	1.3 (5.7)	0.01
CA 19-9 (IU/mL)	47.8 (994.0)	5.2 (17.8)	0.00
CA 125 (IU/mL)	472.5 (639.6)	254.3 (342.6)	0.01
CA 72-4 (IU/mL)	10.7 (59.7)	4.1 (4.5)	0.00

Cutoff for tumor biomarkers using ROC curves

AUC analysis of ROC curves were used to determine the best cut-off for prediction of cause of ascites. Serum cut off values decided to differentiate malignant and benign ascites were - 6.7 ng/mL, 108 IU/mL and 8.9 IU/mL which had a sensitivity of 44%, 54% and 51% and a specificity of 91%, 94% and 98% for serum CEA, CA19-9 and CA 72-4 respectively; cut off values for markers in ascitic fluid were 8.7 ng/mL, 33.2 IU/mL, 623 IU/mL and 7 IU/mL with a sensitivity of 66%, 56%, 42% and 63% and a specificity of 88%, 88%, 84% and 88% for CEA, CA19-9, CA 125 and CA 72-4 respectively (TABLE 3). Area under the curve was significant for all tumor markers except serum CA-125. (FIGURE 2) The maximum area under the curve was seen for ascitic CEA at a value of 0.778 (95%CI- 0.676–0.880) followed by ascitic CA19-9 at 0.770 (95%CI- 0.667–0.874).

TABLE 3. Cut off values for various markers.

Tumor marker	Malignant vs benign		
	Cut off value	Sensitivity (%)	Specificity (%)
Serum Markers			
CEA (ng/mL)	6.7	44	91
CA 19-9 (IU/mL)	108	54	94
CA 72-4 (IU/mL)	8.9	51	98
CA19-9 + CA 72-4		71	92
Ascitic Fluid Markers			
CEA (ng/mL)	8.7	66	88
CA 19-9 (IU/mL)	33.2	56	88
CA-125(IU/mL)	623	42	84
CA 72-4 (IU/mL)	7	63	88
CA 19-9+ CA 72-4		74	78
CEA+ CA19-9+ CA 72-4		86	74
Malignant vs tuberculosis			
Serum markers			
CEA (ng/mL)	4	50	95
CA 19-9 (IU/mL)	108	55	95
CA 72-4 (IU/mL)	8.2	55	95
CA 19-9 + CA 72-4		71	90
Ascitic fluid markers			
CEA (ng/mL)	8.7	68	80
CA 19-9 (IU/mL)	33.2	58	85
CA-125(IU/mL)	577	45	85
CA 72-4 (IU/mL)	9.3	58	95
CA 19-9 + CA72-4		74	70
CEA + CA19-9 + CA 72-4		86	55

Cut off values to differentiate between tuberculous and malignant ascites were also determined using the ROC curves (FIGURE 3). Serum values of 4 ng/mL, 108 IU/mL and 8.2 IU/mL were decided for CEA, CA19-9 and CA 72-4 which had a sensitivity of 58%, 55% and 55% respectively; specificity was 90%, 95% and 95% respectively. Ascitic fluid cut off levels were 8.7 ng/mL, 33.2 IU/mL, 577 IU/mL and 9.3 IU/mL with a sensitivity of 68%, 58%, 45% and 58%, and specificity of 80%, 85%, 85% and 95% for CEA, CA19-9, CA-125 and CA 72-4 respectively. Area under the curve was maximum for serum CA19-9- at a value of 0.78 (95%CI- 0.675–0.900) and significant for all markers except serum CA-125.

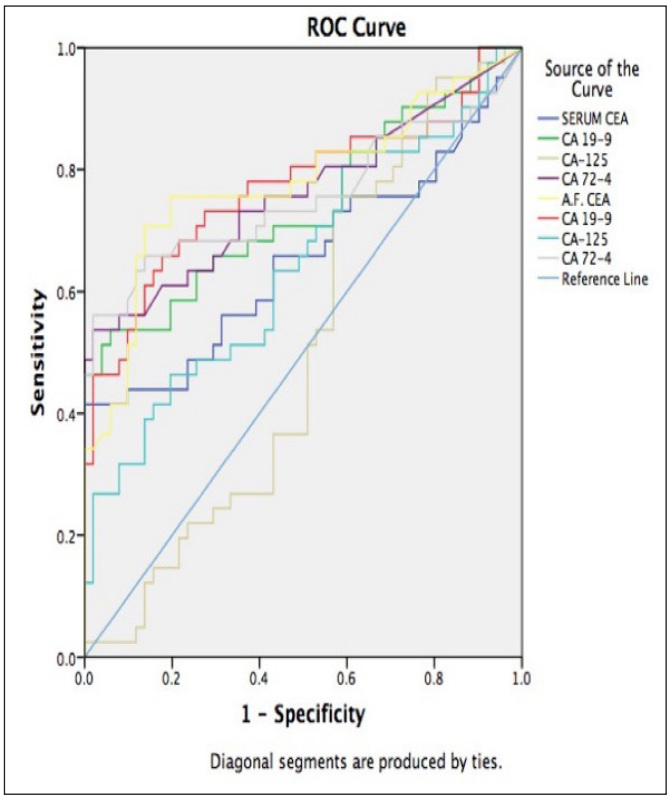

FIGURE 2. AUROC for biomarkers for discriminating malignant from benign cause of ascites.

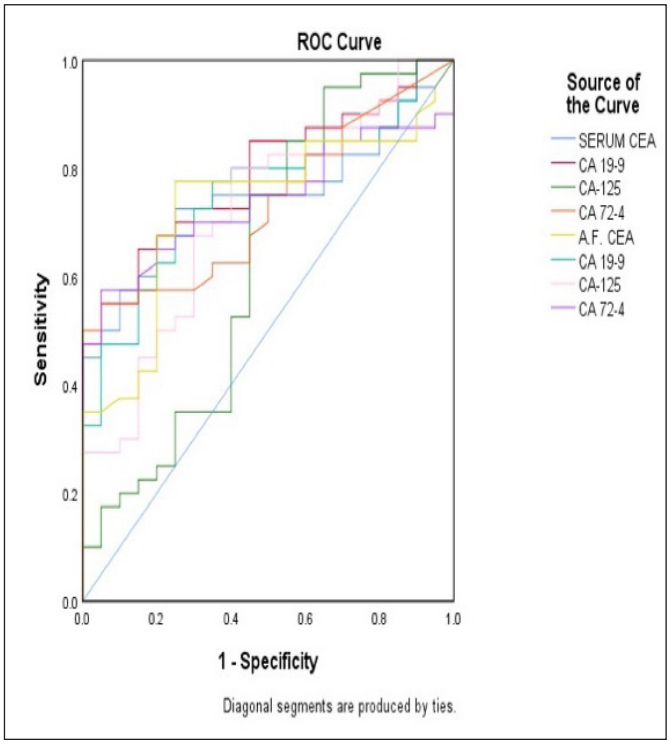

FIGURE 3. AUROC for discriminating peritoneal carcinomatosis from tuberculous peritonitis.

A combination of serum CA19-9 and CA 72-4 achieved a sensitivity of 71%, specificity of 92%, positive predictive value of 88% and negative predictive value of 80% to differentiate malignant vs benign etiology. Ascitic CEA, CA 19-9 and CA 72-4 had a combined sensitivity of 86%, specificity of 74%, positive predictive value (PPV) of 73% and negative predictive value (NPV) of 86%

In malignant vs tubercular etiology, serum CA 19-9 and CA 72-4 had a sensitivity of 71% and specificity of 90%; the PPV and NPV were 94% and 60% respectively. Ascitic CEA, CA 19-9 and CA 72-4 achieved a sensitivity of 86%, specificity of 55%, PPV of 80% and NPV of 65%.

DISCUSSION

In the present prospective study, we compared various tumor markers (CEA, CA 125, CA 19-9, CA 72-4) in serum and ascites between the three most important etiologies of ascites (tuberculosis, cirrhosis and peritoneal carcinomatosis). Although the levels of most tumor biomarkers (except CA 125) were significantly higher in the malignant group, the sensitivity for the diagnosis was modest when high specificity was chosen. Significantly, in negative malignant cytology (14/42 patients), it was noticed that the levels of at least one biomarker was raised beyond our determined cutoffs. This goes to say that assay of tumor marker levels in patients with an undetermined cause of ascites can help in arriving at a definite diagnosis with the caveat that a single tumour biomarker may not provide a definitive discriminative ability in all cases. Similar results have been reported in previous studies wherein a panel of tumor markers improves the sensitivity and specificity of malignant cytology[9,10,12-15].

Previous studies have indicated that tuberculous peritonitis and peritoneal carcinomatosis have similar clinical and radiological presentation[12]. The diagnosis of TBP is difficult as the yield of microbiological tests is low. Therefore, there is an unmet need to have better biomarkers to discriminate between these two entities. Based on the ROC curves, we analyzed a panel of markers with significant area under curves and found an increase in sensitivity without a significant decrease in specificity with a combination of serum CA 19-9 and CA 72-4 in differentiating malignant ascites from other etiologies. CA-125 was not found to be a useful marker in our study in determining the etiology of ascites. Fang Liu also studied sensitivity and specificity of a combination of CEA, CA 19-9 and CA-125 in differentiating malignant from benign ascites along with their ascites/serum ratio gaining a maximum sensitivity of 98% with a low specificity of 33.5%[13]. Sari et al. found that tumor markers had a low sensitivity- 38% for ascitic CEA and 19% for ascitic CA19-9. However, they found a high specificity of 98.1% and 94.5% for these markers but attributed it to a smaller sample size of 76 patients[14]. Similar study by Fang Liu concluded that a panel of markers CEA, CA 19-9 and CA-153 increased the diagnostic yield along with malignant cytology in determining the cause of ascites[15]. Another study by Gulyas found a combination of cytology, CEA and cholesterol to be 100% specific and 88% sensitive in diagnosing peritoneal carcinomatosis[16]. Ferroni et al. evaluated the tumor markers CEA, CA 19-9, CA 72-4 and CA 125 in benign and malignant (pleural, peritoneal and peroicardial) effusions and found that CA 72-4 and CEA together would help in diagnosing unknown effusions[17]. These studies have focused on differentiating malignant ascites from benign ascites, not evaluating tuberculous ascites as a separate entity as done in our study. In another report comparing the levels of CEA and CA 125 in TB peritonitis, peritoneal carcinomatosis (ovarian vs non ovarian) a composite index-CEA x CA-125 values was found to have a sensitivity and specificity of 91% and 99% respectively. They concluded that CEA and the composite index could help in distinguishing peritoneal carcinomatosis from TB peritonitis[18].

All studies done until date have emphasized the use of a panel of markers in diagnosing the etiology of ascites and its utility in cytology negative ascites. Our findings corroborate this, however, we have focused also on tuberculous ascites and tried to eliminate the use of all the markers for workup and found a combination of serum CA 19-9 and CA 72-4 to be useful. Ascitic markers have been found to be more sensitive than the serum markers in differentiating between malignant and other causes of ascites. Serum CA-125 was not found to be a good marker in determining the cause of ascites, ovarian malignancies were very few in number[19]. Our study has some limitations including the limited number of patients and the exclusion of those cases in which the underlying cause was not related to cirrhosis, malignancy or tuberculosis. However, the strengths are an adequate follow-up and clear characterization of the cause. Although there is a heterogeneity in the underlying causes of peritoneal carcinomatosis, this represents the actual situation encountered by the clinicians.

In conclusion, routine use of tumour biomarkers can be avoided in discriminating benign and malignant ascites. However, in difficult cases it is better to use multiple tumour markers because the performance of a single biomarker for discrimination of benign and malignant ascites and also for discrimination of TBP and PC is below par. A panel of serum CA 199 and CA 72 4 had the best discriminative ability for TBP and PC in our patients while the use of CA 125 should be avoided. The use of multiple markers is suggested when the performance of an individual biomarker may be relevant to a specific underlying cause of peritoneal carcinomatosis or when it could help diagnose the entire spectrum of malignancies responsible for peritoneal carcinomatosis.

Authors' contribution

Jain T: conception, data collection, initial draft and revisions. Ram S: biochemical work; manuscript revision. Kumar H and Saroch A: resources, patient management, manuscript revisions. Sharma V and Singh H: conceived and designed, organized resources, patient management, manuscript editing; both are equal senior authors.

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RESUMO – Contexto – O papel dos níveis ascíticos e séricos de vários biomarcadores de tumores na discriminação da causa das ascites não está bem estabelecido. **Objetivo –** Avaliar o papel dos níveis séricos e ascíticos de biomarcadores tumorais (CA 72-4, CA 19-9, CEA e CA 125) na discriminação da causa das ascites. **Métodos –** Estudo prospectivo foi realizado em pacientes consecutivos que apresentaram ascite. Foram determinados níveis do soro e ascítico de CA 19-9, CA 125, CA 72-4 e antígeno carcinoembrínico (CEA). Os pacientes com ascites cirróticas, peritonite tuberculosa e carcinomatose peritoneal (CP) foram eventualmente incluídos na análise. **Resultados –** Dos 93 pacientes (58 homens, média de idade 47 anos) incluídos, a causa básica foi cirrose em 31, CP em 42 e tuberculose peritoneal em 20. O melhor corte para discriminação de ascites benignas e malignas para soro CEA, CA 19-9 e CA 72-4 foram 6,7 ng/mL, 108 UI/mL e 8,9 UI/mL, respectivamente. O melhor corte para discriminação de ascites benignas e malignas para CA 125 ascitico, CEA, CA 19-9 e CA 72-4 foram 623 UI/mL, 8,7 ng/mL, 33,2 UI/mL e 7 UI/mL, respectivamente. **Conclusão –** O desempenho do biomarcador único para a previsão do CP subjacente é baixo, mas uma combinação de soro CA 19-9 e CA 72-4 melhor previu a presença de carcinomatose peritoneal.

Palavras-chave – Peritonite tuberculosa; carcinomatose peritoneal; tuberculose peritoneal; ascites malignas; cirrose; hipertensão portal.

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