Diagnostic value of carcinoembryonic antigen in malignancy-related ascites : systematic review and meta-analysis

Mitra Ahadi[1], Shahrzad Tehranian[2], Bahram Memar[3], Hassan Vossoughinia[1], Masoumeh Salari[4], Elaheh Eskandari[4], Mohammadreza Farzanehfar[1], Ramin Sadeghi[2]

(1) Gastroenterology Department, Ghaem Hospital, (2) Nuclear Medicine Research Center, (3) Pathology Department, Emam Reza Hospital, (4) Internal Medicine Department, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran.

Abstract

Background and study aims : **There is a common misconception that malignant ascites is equivalent to peritoneal carcinomatosis. It seems that malignancy-related ascites is a more appropriate description of malignant ascites, which is difficult to confirm. Carcinoembryonic antigen, a glycoprotein tumor marker shed by malignant cells, increases in a wide range of gastrointestinal malignancies. We carried out the current meta-analysis to determine carcinoembryonic antigen accuracy in the diagnosis of malignancy-related ascites.**

Patients and methods : **Pudmed/Medline and SCOPUS were searched using these search terms : malignan* AND ascites AND (CEA OR carcinoembryonic). The outcome of interest was carcinoembryonic antigen accuracy in the differentiation of malignancy-related ascites and nonmalignant ascites.**

Results : **Seven studies were included in this systematic review. Pooled diagnostic indices using random-effects model were as follows : sensitivity 43.1% [381-48.3] ; specificity 95.5% [93-97.3] ; LR+ (positive likelihood ratio) 7.33 [4.58-11.73] ; LR- (negative likelihood ratio) 0.6 [0.54-0.68] ; and DOR (diagnostic odds ratio) 12.93 [7.58-22].**

Conclusions : **Carcinoembryonic antigen of the ascitic fluid does not seem to be sensitive enough to diagnose malignancy-related ascites. However, due to high specificity, the positive predictive value of this marker is high and the higher the level of carcinoembryonic antigen, the more likely it is to be malignancy-related. Nevertheless, a negative test result cannot definitely rule out the malignancy.** (Acta gastroenterol. belg., **2014**, 77, **418-424**).

Key words : ascites, carcinoembryonic antigen, malignancy, meta-analysis, systematic review.

Introduction

Ascites occurs due to a wide range of both benign and malignant diseases, with a significant proportion resulting from hepatic cirrhosis. In 7% of cases, malignancies account for ascites formation or are a contributing factor (1). It is a misconception that malignant ascites is equivalent to peritoneal carcinomatosis. Malignant diseases lead to ascites formation through at least six mechanisms including peritoneal carcinomatosis, extensive hepatic metastases developing portal hypertension, peritoneal carcinomatosis accompanied by massive hepatic metastasis, hepatocellular carcinoma and cirrhosis, malignancy-induced chylous ascites and Budd-Chiari syndrome as the result of hepatic vein obstruction secondary to malignancy (2). Hence, malignancy-related ascites (MRA) is a better description of malignant ascites.

In most cases, the confirmation of MRA is extremely difficult and an isolated laboratory test is not helpful in diagnosis (3). Therefore, a series of clinical manifestations, blood tests, ascitic fluid analysis, imaging studies and follow-up should be performed. Ascitic fluid analysis should evaluate cell count and differential, serum-ascites albumin gradient (SAAG), culture, total protein, glucose level, lactate dehydrogenase (LDH) concentration and cytology.

Carcinoembryonic antigen (CEA) is a glycoprotein tumor marker shed by malignant cells. Serum CEA concentration is considered an indicator of the malignant disease activity. This tumor marker increases in a wide range of gastrointestinal malignancies. Tumor marker measurement in ascitic and pleural fluids has been used to improve the detection of malignancy-related etiologies for years. It seems that an isolated measurement of CEA concentration or in combination with other tumor markers could be beneficial in the diagnosis of MRA (4, 5). Several studies have revealed different results considering the potential CEA efficacy in the diagnosis of MRA.

We carried out this current systematic review to determine CEA accuracy in the diagnosis of MRA.

Materials and methods

The PRISMA statement was followed for reporting the current systematic review and meta-analysis (6).

Search strategy

A comprehensive search was conducted in Pudmed/Medline and SCOPUS with the following search terms : malignan* AND ascites AND (CEA OR carcinoembryonic). We did not restrict our search based on language and publication date.

Correspondence to : Mohammadreza Farzanehfar, Gastroenterology Department, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran. E-mail : farzanehfm@mums.ac.ir

Submission date : 12/05/2014
Acceptance date : 03/11/2014

Study selection

Two researchers extracted the relevant original articles that assessed the accuracy of the CEA tumor marker to diagnosis MRA. The researchers also independently performed the data extraction at the title and abstract stage or at the full paper stage, if needed. The last search was performed on November 2013. Any disagreement was resolved by final consensus by a third researcher's judgment.

A decision was made to exclude studies containing the following criteria :

– Inaccessible article, which could not be obtained despite sending several emails to the corresponding authors
– Lack of any differentiation of CEA evaluation between ascitic and pleural fluids
– Lack of enough statistical data to calculate the sensitivity or specificity
– A sample size of less than 5 patients

Quality assessment

Quality of the retrieved studies was evaluated applying the Oxford Centre for Evidence Based Medicine Checklist for diagnostic studies (7).

The quality assessment of the studies considers the following :

– Consecutive recruitment
– Prospective design
– Gold standard/application of gold standard to all patients
– Enough explanation of mapping method

Two researchers performed all these evaluations.

Statistical analyses

We followed the recommended standard methods for executing the meta-analysis of diagnostic test evaluations (8). For each study, the following indices were calculated : sensitivity, specificity, negative and positive likelihood ratios (LR-, LR+) and diagnostic odds ratio (DOR). The random-effects model was used to pool the data across studies. Heterogeneity was evaluated by the Cochrane Q test and p-values less than 0.05 were considered statistically significant. The I^2 index was used to quantify the heterogeneity.

In order to evaluate the threshold effect on systematic review results, the Spearman correlation between sensitivity and specificity was used. SROC curve fitting was also used to summarize the overall performance of the test. Furthermore, the area under the curve (AUC) and Q* were also calculated.

Publication bias was evaluated graphically by funnel plots. Egger's regression intercept and trim-fill method were also used to provide the importance of possible publication bias.

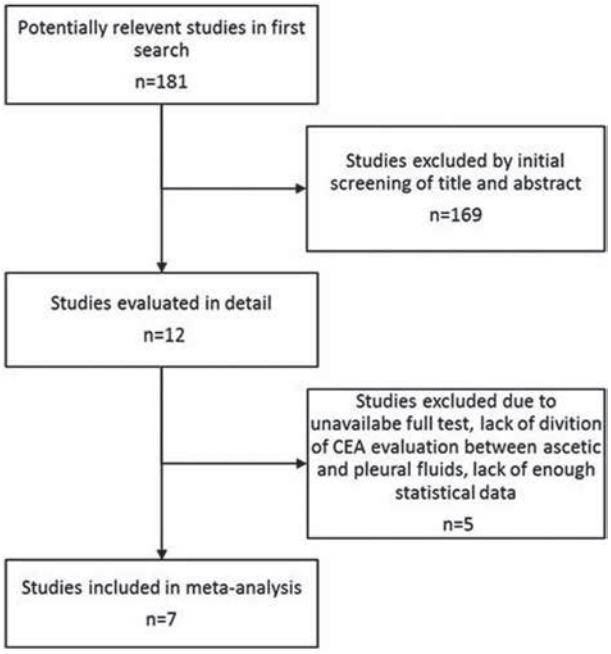

Fig. 1. — Flowchart of study selection process

Results

Quality of reporting and study characteristics

Figure 1 displays the PRISMA flowchart of the study selection process of our systematic review. Finally, seven published articles were included in the systematic review (3-5, 9-12).

Table 1 shows the quality assessment of the selected studies. In Table 2, the summary of the findings from individual studies are described including total number of patients, number of malignancy-related ascites, number of nonmalignant ascites, type of malignancy, benign diseases, study cut-off, sensitivity, specificity and true positive and true negative results.

Pooled diagnostic indices using the random-effects model were as follows : sensitivity 43.1% [381-48.3] ; specificity 95.5% [93-97.3] ; LR+ 7.33 [4.58-11.73] ; LR- 0.6 [0.54-0.68] ; DOR 12.93 [7.58-22]. Figures 2 and 3 show the meta-analyses of sensitivity and specificity in addition to heterogeneity indices of each analysis.

Figure 4 shows the SROC of the meta-analysis. The AUC was 0.75 and Q* was 0.69.

Figure 5 shows the funnel plot of sensitivity pooling. Egger's regression intercept was -0.54 ($p = 0.85$). The trim and fill method was also applied, but no study could be trimmed due to the symmetry of the funnel plot.

Figure 6 shows the funnel plot of specificity pooling. Egger's regression intercept was 2.25 ($p = 0.008$). Adjusted pooled specificity using the trim and fill method showed 1.2% decrease after trimming 3 studies to achieve a symmetric plot.

Table 1. — **The quality assessment in the selected studies**

First author/country/ publication year	Quality assessment			
	Consecutive recruitment	Prospective design	Gold standard/application of gold standard to all patients	Enough explanation of the mapping method
Kaleta/ US 2013	N/A*	Yes	Cytology, biopsy and long-term follow-up /yes**	Yes
Tuzun/turkey 2009	Yes	Yes	Ascetic fluid cytology, fine needle aspiration cytology or specimens obtained by laparoscopy, endoscopy or laparotomy along with histopathological evaluation/ yes**	Yes
Gulyás/Sweden 2001	Yes	Yes	Cytology, necropsy and/or by histology within one year of receipt/yes**	Yes
Torresini/Brazil 2000	Yes	Yes	Cytology, follow-up/yes**	Yes
Chen/Taiwan 1994	N/A	Yes	Histology (with specimen obtained from autopsy, laparoscopy, peritoneoscopy or sonoguided biopsy or ascetic fluid cytology, ultrasonography or computed tomography/ yes**	Yes
Gerbes/Germany 1991	Yes	Yes	Histology, ultrasonography, computed tomography, peritoneoscopy, peritoneal biopsy or autopsy and follow-up/yes**	Yes
Loewenstein/US 1978	Yes	Yes	Radiology, cytopathology, endoscopy, biochemistry, histology and physical findings/yes**	Yes

*N/A : not available.
**Yes : No further evaluation were performed if the initial tests confirmed the diagnosis.

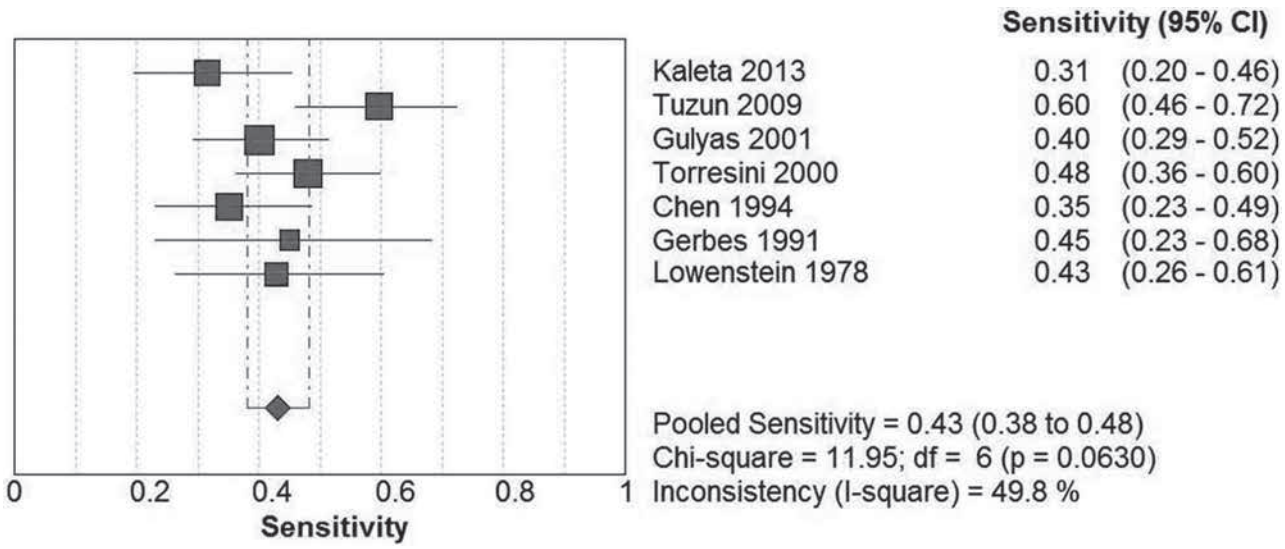

Fig. 2. — Forest plot of the sensitivity pooling

Threshold effect analysis showed the Spearman correlation coefficient of 0.32 (p = 0.48) between the logit of true positive and false positive rates. We could recalculated the diagnostic indices using low (5 or below) and high (more than 5) values of ascitic fluid CEA positivity cut-off values. Pooled sensitivity for low and high cut-off values were 43.9% [38.2-49.7] and 40.2% [34-46.7], respectively. Pooled specificity for low and high cut-off values were 93.1% [89.9-95.5] and 97.2% [94.6-98.8], respectively.

Discussion

Tumor marker investigation has been widely used to distinguish between malignancy-related ascites and non-malignant causes. In the current systematic review, we evaluated available literatures on the diagnostic value of CEA in detecting MRA.

According to this study, CEA measurement in ascitic fluid had a pooled specificity of 95.5% with the LR+ of 7.33, showing patients with MRA have a higher

Table 2. — **Characteristics of the included studies**

First author/country/ publication year	Sample size	Number of malignancy-related ascites	Number of nonmalignant-related ascites	Types of malignancy	Nonmalignant disease	Cut off (ng/ml)	Sensitivity (%)	Specificity (%)	True positive	True negative
Kaleta/ US 2013	137	54	83	Bladder, breast, Gastrointestinal, hepatocellular carcinoma, leiomyosarcoma, leukemia, lung lymphoma, melanoma, mesotheliom, neuroendocrine tumor, pancreas, peritoneal carcinomatosis, renal	Chronic liver disease, portal hypertension	3.5	31.5	95.2	17	79
Tuzun/ Turkey 2009	107	57	50	Gastric, breast , colon, non-Hodgkin lymphoma, ovary, malignant mesotheliomas, pancreas adenocarcinoma, germ cell tumor, adenocarcinoma of primary unknown origin	Cirrhosis, tuberculous peritonitis, acute pancreatitis, granulomatous peritonitis	4.3	60	90	34	45
Gulyás/ Sweden 2001	130	80	50	Ovary, liver, gastric, large intestine, pancreas, lung, gall bladder, breast, kidney	Cirrhosis, pancreatitis, cardiac decompensation	5	40	100	32	5
Torresini/ Brazil 2000	130	75	55	Colon, primary unknown, pancreas, gastric, ovary, breast, esophagus, biliary tract, kidney, nonepithelial tumors	Chronic hepatic disease, hemoperitoneum, cardiac failure, cardiorenal failure, pancreatitis, peritoneal fluid, bile peritoneum, postsurgical ascites, mesenteric occlusion	11	48	94.8	9	28
Chen/ China 1994	123	57	66	Gastric, pancreas, colon, ovary, lung, gall bladder, thyroid, urinary bladder, unknown origin, hepatocellular cancinoma	Cirrhosis	5	35	92	20	61
Gerbes/ Germany 1991	48	20	28	Ovary, gastric, breast, bladder, kidney, hepatocellular carcinoma, adenocarcinoma of unknown origin, liposarcoma, leukemia	Cirrhosis, ovarian overstimulation, pancreatitis, peritoneal tuberculosis, Budd-Chiari syndrome, systemic lupus erythematosus	2.5	45	100	9	28
Loewenstein/ US 1978	105	35	70	Gastrointestinal, breast, ovary, lung, lymphoma, unknown origin	Alcoholic liver disease, congestive heart failure, peritonitis, nonalcoholic liver disease, nephrotic syndrome, vasculitis, hemodialysis, pancreatitis, myxedema benign, chronic chylous ascites	10	45	98	15	69

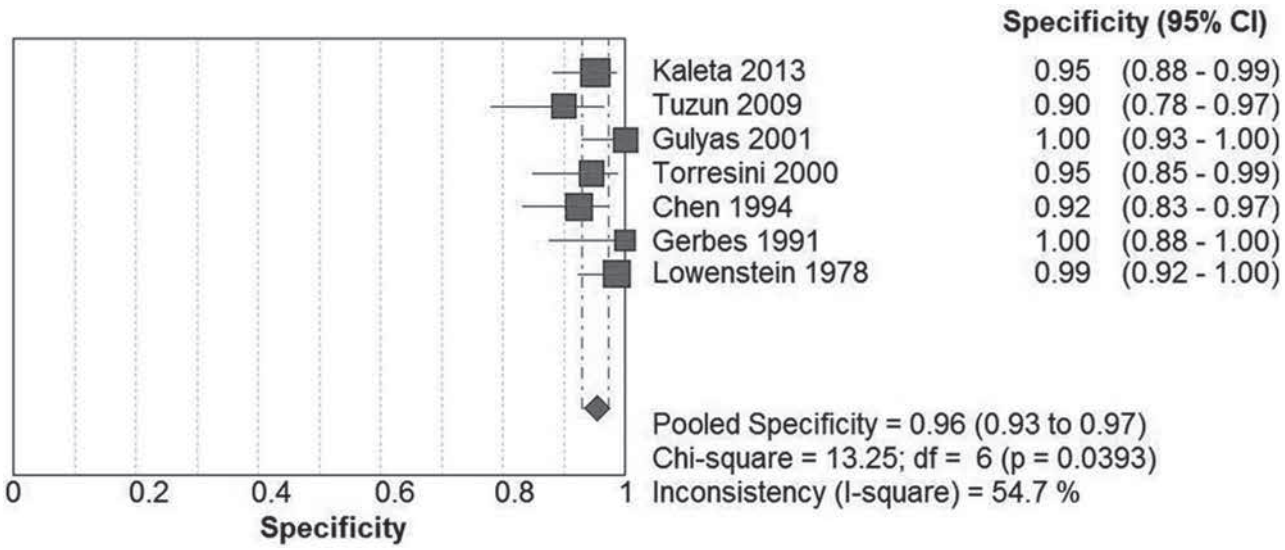

Fig. 3. — Forest plot of the specificity pooling

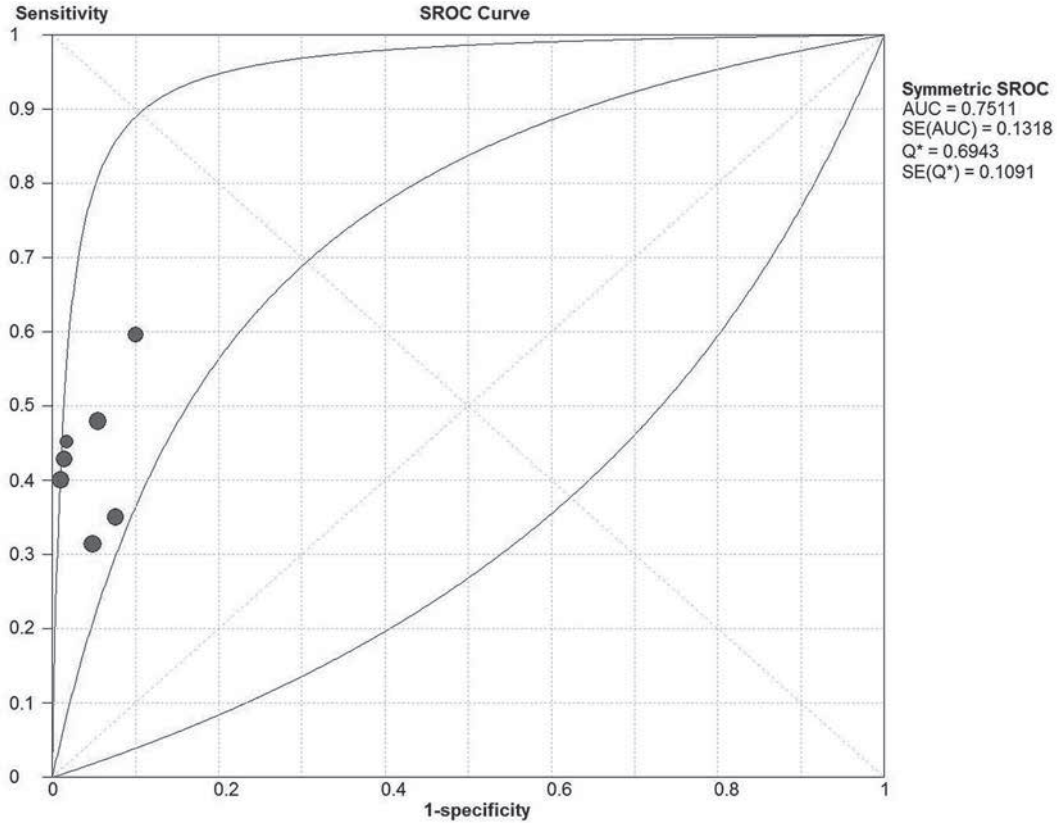

Fig. 4. — SROC curve of the meta-analysis

possibility of positive CEA values in ascitic fluid (approximately 8 times) compared to patients with nonmalignant diseases.

Furthermore, this study revealed that CEA measurement had a low sensitivity (43.1%) and LP- of 0.6 in the diagnosis of MRA. This result indicated that low values of ascitic fluid CEA are unable to confirm nonmalignant ascites. Therefore, patients may have a malignancy even with the negative CEA results.

We also calculated the diagnostic indices considering low (5 or below) and high (more than 5) cut-off values. Pooled specificity for low and high cut-off values were 93.1% [89.9-95.5] and 97.2% [94.6-98.8], respectively, but pooled sensitivity was 43.9% [38.2-49.7] at low

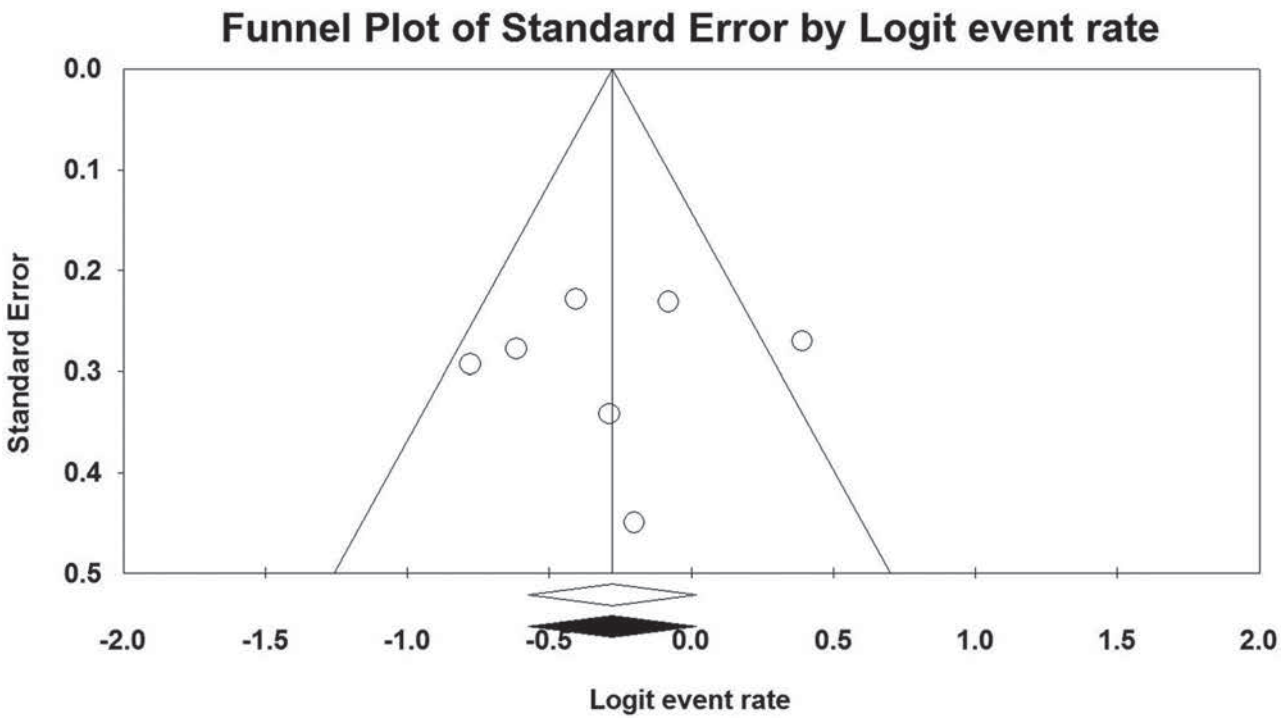

Fig. 5. — Funnel plot of the sensitivity pooling

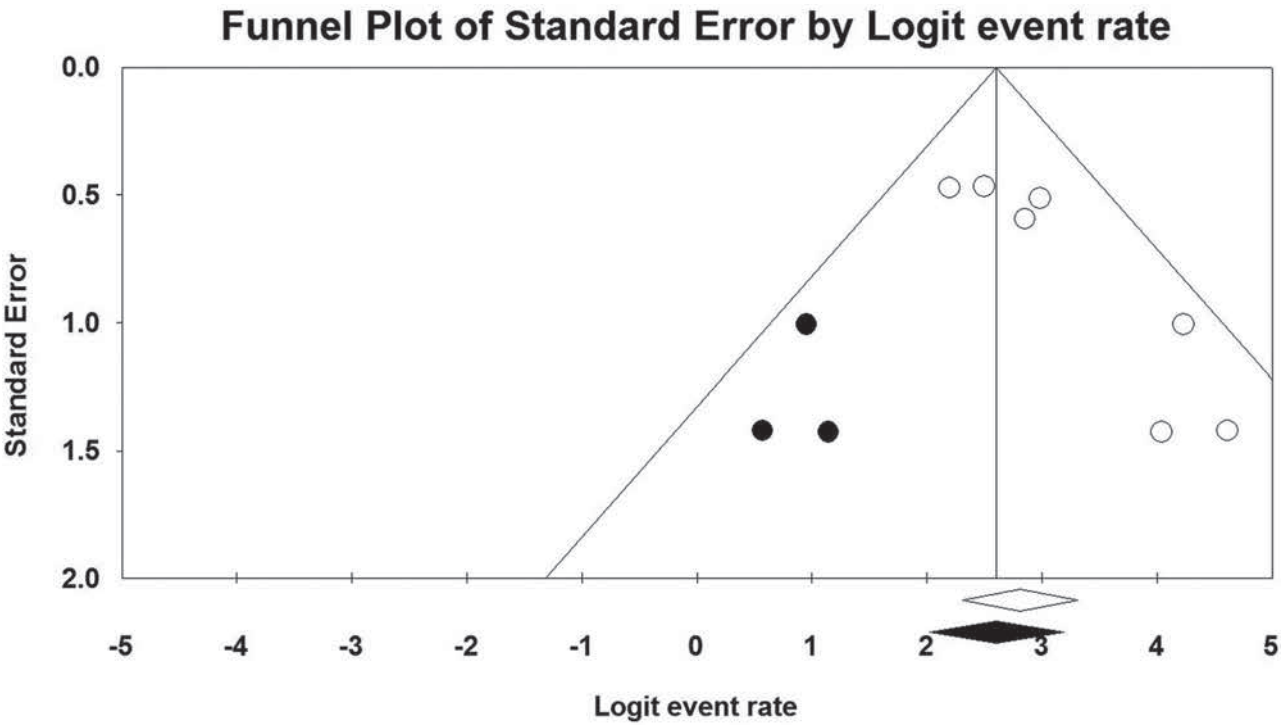

Fig. 6. — Funnel plot of the specificity pooling

cut-off values and 40.2% [34-46.7] at high cut-off values. This shows that cut-off values higher than 5 seems to yield the highest positive predictive value. Based on these results, increasing the cut-off values will lead to higher CEA specificity in the diagnosis of MRA, which conversely will decrease the sensitivity.

DOR expresses the test accuracy in terms of the sensitivity and specificity, ranges from zero to infinity. Higher DOR are a better indicator of discriminatory performance of the test (13). The analysis of ascitic fluid CEA, elevated in a variety of malignancies, has been proposed as a productive test in MRA detection (14). In our study,

DOR of 12.93 [7.58-22] indicated that CEA measurement in ascitic fluid could be beneficial in the differential diagnosis of MRA. More studies are required to establish the preference of ascitic fluid CEA measurement in MRA over serum CEA (15).

Limitations

The current meta-analysis has some limitations. The quality of the included studies is the major limitation of our study. As shown in Table 1, the gold standard test applied to the patients is a combination of several tests as well as follow-up. This can introduce some bias into the included studies.

Publication bias is also a major consideration in all systematic reviews. We evaluated publication bias by several methods and none of them showed the presence of possible important publication bias. Hence, it seems that publication bias is not a major concern in our systematic review.

Heterogeneity of the included studies is another limitation of our study (I^2 of 49.8 and 54.7% for sensitivity and specificity pooling). Due to this heterogeneity, the results of our systematic review should be interpreted with caution. However, some of the heterogeneity of the included studies could be explained by a threshold effect. Threshold effect is a major source of heterogeneity in diagnostic meta-analysis. As we have shown above, the threshold effect is present in the current systematic review, acting as a source of heterogeneity.

Conclusion

CEA of the ascitic fluid does not seem to be sensitive enough to diagnose MRA. However, due to high specificity, the positive predictive value of this marker is high and the higher the level of CEA, the more likely it is to be malignancy related. A negative test result cannot definitely rule out the malignancy.

References

1. RUNYON B.A., MONTANO A.A., AKRIVIADIS E.A., ANTILLON M.R., IRVING M.A., MCHUTCHISON J.G. The serum-ascites albumin gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites. *Annals of internal medicine*, 1992, **117** (3) : 215-20. PubMed PMID : 1616215.
2. RUNYON B.A., HOEFS J.C., MORGAN T.R. Ascitic fluid analysis in malignancy-related ascites. *Hepatology*, 1988, **8** (5) : 1104-9. PubMed PMID : 3417231.
3. TUZUN Y., YILMAZ S., DURSUN M., CANORUC F., CELIK Y., CIL T. *et al*. How to increase the diagnostic value of malignancy-related ascites : discriminative ability of the ascitic tumour markers. *The Journal of international medical research*, 2009, **37** (1) : 87-95. PubMed PMID : 19215677.
4. LOEWENSTEIN M.S., RITTGERS R.A., FEINERMAN A.E., KUPCHIK H.Z., MARCEL B.R., KOFF R.S. *et al*. Carcinoembryonic antigen assay of ascites and detection of malignancy. *Annals of internal medicine*, 1978, **88** (5) : 635-8. PubMed PMID : 646247.
5. GULYAS M., KAPOSI A.D., ELEK G., SZOLLAR L.G., HJERPE A. Value of carcinoembryonic antigen (CEA) and cholesterol assays of ascitic fluid in cases of inconclusive cytology. *Journal of clinical pathology*, 2001, **54** (11) : 831-5. PubMed PMID : 11684715. Pubmed Central PMCID : 1731306.
6. LIBERATI A., ALTMAN D.G., TETZLAFF J., MULROW C., GOTZSCHE P.C., IOANNIDIS J.P. *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions : explanation and elaboration. *BMJ*, 2009, **339** : b2700. PubMed PMID : 19622552. Pubmed Central PMCID : 2714672.
7. Oxford Centre for Evidence-based Medicine Levels of Evidence [Access date June 2013]. Available from : http://www.cebm.net/index.aspx?o=1025.
8. DEVILLE W.L., BUNTINX F., BOUTER L.M., MONTORI V.M., DE VET H.C., VAN DER WINDT D.A. *et al*. Conducting systematic reviews of diagnostic studies : didactic guidelines. *BMC medical research methodology*, 2002, **2** : 9. PubMed PMID : 12097142. Pubmed Central PMCID : 117243.
9. CHEN S.J., WANG S.S., LU C.W., CHAO Y., LEE F.Y., LEE S.D. *et al*. Clinical value of tumour markers and serum-ascites albumin gradient in the diagnosis of malignancy-related ascites. *Journal of gastroenterology and hepatology*, 1994, **9** (4) : 396-400. PubMed PMID : 7948823.
10. GERBES A.L., JUNGST D., XIE Y.N., PERMANETTER W., PAUMGARTNER G. Ascitic fluid analysis for the differentiation of malignancy-related and nonmalignant ascites. Proposal of a diagnostic sequence. *Cancer*, 1991, **68** (8) : 1808-14. PubMed PMID : 1913524.
11. TORRESINI R.J., PROLLA J.C., DIEHL A.R., MORAIS E.K., JOBIM L.F. Combined carcinoembryonic antigen and cytopathologic examination in ascites. *Acta cytologica*, 2000, **44** (5) : 778-82. PubMed PMID : 11015979.
12. KALETA E.J., TOLAN N.V., NESS K.A., O'KANE D., ALGECIRAS-SCHIMNICH A. CEA, AFP and CA 19-9 analysis in peritoneal fluid to differentiate causes of ascites formation. *Clinical biochemistry*, 2013, **46** (9) : 814-8. PubMed PMID : 23454392.
13. SHI H.Z., LIANG Q.L., JIANG J., QIN X.J., YANG H.B. Diagnostic value of carcinoembryonic antigen in malignant pleural effusion : a meta-analysis. *Respirology*, 2008, **13** (4) : 518-27. PubMed PMID : 18422869.
14. KILUK M.S., ROLKOWSKI R., ZAWADZKI R.J., WOJTUKIEWICZ M.Z. [Usefulness of CEA, CA 15-3 and CA 125 tumor markers in the differential diagnostics of peritoneal effusion]. *Polski merkuriusz lekarski : organ Polskiego Towarzystwa Lekarskiego*, 2002, **13** (76) : 298-301. PubMed PMID : 12557435. Przydatnosc markerow nowotworowych CEA, CA 15-3 i CA 125 w diagnostyce plynow wysiekowych w jamie brzusznej.
15. TUZUN Y., CELIK Y., BAYAN K., YILMAZ S., DURSUN M., CANORUC F. Correlation of tumour markers in ascitic fluid and serum : are measurements of ascitic tumour markers a futile attempt ? *The Journal of international medical research*, 2009, **37** (1) : 79-86. PubMed PMID : 19215676.