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Original Article

Subtype analysis of the malignancy-related ascites contributes to raise discriminative ability of tumor markers in ascites

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Abstract: The discriminative ability of the ascites tumor markers to diagnose malignancy-related ascites has long been controversial. The aim of this study is to establish cut-off values and testify the diagnostic power of ascites CA125, CA19-9 and CEA in the differentiation of non-malignancy and malignancy-related ascites. A retrospective cohort study was conducted and 105 patients with ascites were enrolled and divided into malignancy and non-malignancy groups. Clinical characteristics were compared and ascites CA125, CA19-9 and CEA were evaluated for their diagnostic capacities via ROC curve analyses. Diagnostic capacities were further evaluated after subset analysis by secretion status of serum tumor markers. Logistic regression was used to build the multi-variate model. Concentrations of ascites CA125, CA19-9 and CEA were higher in malignant than non-malignant group. The AUCs for ascites CA125, CA19-9, CEA and multi-variate model were 0.671, 0.695, 0.802 and 0.799. The diagnostic cut-off value, sensitivity and specificity were 2145 IU/mL, 33.3% and 97.2% for CA125; 78 U/mL, 41.5% and 95.7% for CA19-9; 3.6 IU/mL, 57.6% and 96.1% for CEA; and 1.0, 48.5% and 97.1% for multi-variate model. Subtype analysis showed improved diagnostic capacity for secretory malignancy-related ascites vs. non-malignancy related ascites. The AUCs of ascites CA125, CA19-9, CEA and multi-variate model increased to 0.725, 0.805, 0.903 and 0.901, respectively. Meanwhile, choosing the same cut-off values and specificities yielded higher sensitivities and NPVs for all three tumor markers and the multi-variate model. Subtype analysis of the malignancy-related ascites contributes to raise the discriminative ability of ascites tumor markers.

Keywords: Ascites, malignancy, tumor markers, diagnose, cut-off value

Introduction

Ascites, also known as hydroperitoneum, is the accumulation of fluids in the peritoneal cavity. Ascites is grossly categorized by portal hypertensive and non-portal hypertensive. Liver cirrhosis is recognized as the main cause of portal hypertensive ascites and accounts for up to 85% of all ascites cases [1, 2]. Non-portal hypertensive etiologies usually include peritoneal carcinomatosis (less than 12% of all ascites cases) and peritoneal tuberculosis (PTB) (up to 2% of all ascites cases) [1]. Malignancy-related ascites, however, is a broad definition that cannot be simply classified into portal or non-portal hypertensive etiologies. Major mechanisms of malignancy-related ascites include peritoneal carcinomatosis (53%), portal hypertension caused by liver metastases (13%), hepatocellular carcinoma complicated with cirrhosis (13%), and lymphoma causing chylous ascites (7%) [3, 4]. The presence of malignant cells in the ascites is the most important strategy for differentiating malignancy-related ascites from non-malignancies. However, the sensitivity of this test is unsatisfactory due to the low chance of malignant cells disseminating into ascites such as in hepatocellular carcinoma and pancreatic carcinoma [3, 5]. Also, tumor markers in the ascites are reported to be either low sensitive or specific for making differentiation [6]. Failing to subtype malignancy-related ascites by the existence of tumor markers in the serum is considered as a major reason [7].

Table 1. Clinical manifestations between the 3 studied groups

Characteristics	Malignancies (n=34)	Liver Cirrhosis (n=40)	PTB (n=31)	*P* values
Age	57.91±9.14	60.15±13.75	45±17.20	<0.001
Gender (male/female)	17/17	23/17	16/15	NS
Duration of symptoms				NS
<1 month	7 (20.59%)	11 (27.50%)	12 (38.71%)	
≥1 month	27 (79.41%)	29 (72.50%)	19 (61.29%)	
Fever	3 (8.82%)	1 (2.50%)	21 (33.87%)	<0.001
Distention	22 (64.71%)	30 (75.00%)	20 (64.51%)	NS
Abdominal pain	10 (29.41%)	2 (5.00%)	6 (19.35%)	<0.05
Weight loss	12 (35.29%)	9 (22.50%)	8 (25.80%)	NS
Loss of appetite	8 (23.53%)	10 (25%)	9 (29.03%)	NS
Night sweating	0 (0.00%)	0 (0.00%)	2 (6.45%)	<0.05*

Continuous variables were presented as mean ± SD. *The test were performed by the Fisher exact test, others were performed by Pearson χ^2 test. Abbreviations, PTB, peritoneal tuberculosis.

In this study, we described the clinical characteristics of malignancy-related ascites. Ascites tumor markers and multi-variate model were evaluated for their diagnostic capacities by receiver operating characteristic (ROC). Cut-off values providing high specificities were established and each tumor marker was assessed for diagnostic performance. Furthermore, ROC and area under the curve (AUC) were analyzed after malignancy-related ascites were subtyped into secretory and non-secretory groups according to the existence of tumor markers in the serum.

The aim of this study is to prove that subtyping malignancy-related ascites can improve the capacity of diagnosing malignancy-related ascites.

Materials and methods

Patients and sample collection

A total of one hundred and five ascites patients were enrolled from January 2007 to December 2013. They were either diagnosed with liver cirrhosis, PTB or malignant tumors. All patients underwent laboratory tests including serum and ascites biochemical tests, serum and ascites tumor markers, ascites cell count, ascites adenosine deaminase (ADA) and ascites cytology. PTB was diagnosed based on clinical characteristics, sputum examinations for acid-fast bacilli (AFB), and/or histopathological examination of granuloma from the peritoneal biopsy specimens. Malignancy-related ascites was diagnosed when cancer cells were detected from ascitic fluids or peritoneoscopic biopsy specimen. Hepatic cirrhotic ascites was diagnosed when patients developed severe liver disease that can lead to cirrhosis with further confirmation from liver function test or radiology. In liver cirrhosis group, patients with a history of tuberculosis and malignancies were excluded. All ascites specimens were collected by paracentesis. Fluid was stored at -20°C and tumor markers were measured by the department of the clinical laboratory in our hospital, including cancer antigen (CA) 125, CA19-9, and carcinoembryonic (CEA) using electrochemiluminescence immunoassay (Roche cobas E601; Roche diagnostics, Mannheim Germany).

This protocol was approved by the ethics committee (ethics committee of Zhongshan Hospital of Fudan University, Shanghai, China). Written informed consent was obtained from all study participants.

Statistics

Data were analyzed using SPSS 18.0 (SPSS Inc., Chicago, IL). Values for continuous variables were presented as mean ± SD. Categorical variables were compared using the Fisher exact test or Pearson χ^2 test. Continuous variables were compared by using one way ANOVA. Multivariate model was analyzed using multi-variate logistic regression for ascites CA125, CA19-9 and CEA. ROC curves were created and AUCs were calculated to determine the predictive power. Subsequently, sensitivity, specificity, negative and positive predictive values of the obtained cut-offs were calculated for the determination of ascitic fluid etiologies. The optimal cut-off value was defined as the cut-off corresponding to the point on the ROC curve closest to the sensitivity =1 when specificity was higher than 0.95. For all analyses, a *P* value of <0.05 (two-tailed) was treated as statistically significant.

Table 2. Laboratory findings in the serum and ascitic fluids between the 3 studied groups

	Malignancies (n=34)	Liver Cirrhosis (n=40)	PTB (n=31)	*P* values
Ascites				
Lymphocyte (%)	74.67±18.99	73.92±21.02	80.29±19.91	NS
Albumin (g/L)	30.05±7.97	8.23±7.12***	29.82±5.16	<0.001
ADA (IU/L)	31.50±13.22	16.53±6.53	72.52±25.74***	<0.001
CA125 (IU/mL)	2645.60±2045.97***	689.88±475.31	627.90±391.11	<0.001
CA19-9 (U/mL)	1025.0±2327.61*	60.89±273.57	48.82±207.43	<0.05
CEA (ng/mL)	203.37±333.47***	17.061±84.45	0.67±0.60	<0.001
Serum				
Albumin (g/L)	35.71±6.72	28.38±5.76***	34.60±6.04	<0.001
CA125 (IU/mL)	771.04±1155.01	478.55±547.45	395.35±356.14	NS
CA19-9 (U/mL)	510.15±1881.62	79.67±237.23	10.24±7.58	NS
CEA (ng/mL)	8.21±11.27**,*	3.77±2.73	1.45±1.11	<0.01, 0.05
Scr (μmol/L)	73.08±29.75	105.86±81.57****	62.87±15.39	<0.001, 0.05
Ccr (mL/min)	120.96±153.90	78.22±40.22	110.59±33.06	NS
SAAG	8.43±6.41	20.67±5.18***	6.78±5.40	<0.001

Continuous variables were presented as mean ± SD. The tests were performed by one way ANOVA. Abbreviatons, PTB, peritoneal tuberculosis; ADA, adenosinedeaminase; Ccr, creatinine clearence rate; Scr, serum creatinine; SAAG, serum ascites albumin gradient. Significance: NS, not significant; Ascites and serum albumin, ***P<0.001 vs. PTB and Malignancies; Ascites ADA, ***P<0.001 vs. Malignancies and Liver cirrhosis; Ascites CA125, ***P<0.001 vs. PTB and Liver cirrhosis; Ascites CA19-9, *P<0.05 vs. PTB and Liver cirrhosis; Ascites CEA, ***P<0.001 vs. PTB and Liver cirrhosis; Scr, ***P<0.001 vs. PTB, *P<0.05 vs. Malignancies; Serum CEA, **P<0.01 vs. PTB, *P<0.05 vs. Liver cirrhosis; SAAG, ***P<0.001 vs. PTB and Malignancies.

Table 3. Predictive values of ascites tumor markers and mulit-variate model using ROC curve

	Tumor vs. Non-tumor			Secretory tumor vs. Non-tumor		
	AUC	95% CI	*P* values	AUC	95% CI	*P* values
Ascites CA125	0.671	0.538-0.803	0.019	0.725	0.588-0.862	0.006
Ascites CA19-9	0.695	0.589-0.830	0.008	0.805	0.682-0.928	<0.001
Ascites CEA	0.802	0.687-0.917	<0.001	0.903	0.804-1.003	<0.001
Multi-variate model	0.800	0.685-0.912	<0.001	0.901	0.809-0.993	<0.001

Abbreviations, AUC, area under the curve; CI, confidence interval.

Results

One hundred and five ascites patients were enrolled in our study. Among them, thirty-four were malignancy-related ascites. Patients with liver cirrhosis (n=40) and PTB (n=31) were grouped into non-malignant ascites (**Table 1**). Since liver cirrhosis and PTB are two diseases sharing some similarities with malignancy-related ascites [2, 8]. We separated them into two groups rather than one non-malignant ascites group when comparing their clinical and laboratory features. Generally, gender did not differ significantly between these three groups (P> 0.05). Patients diagnosed with PTB were younger (median age was 45 years) than those diagnosed with malignancy or cirrhosis (P<0.001). Abdominal pain may be helpful in differentiating patients with malignancy from patients with cirrhosis (29.41% and 5%, respectively). However, for PTB patients, abdominal pain was also prominent (19.35%) when it affected the large intestine such as ileocecus and colon [9]. Laboratory tests of ascites and serum biomarkers for three groups were presented in **Table 2**. Concentrations of ascites tumor marker CA125, CA19-9 and CEA were higher in malignant cases than in PTB and cirrhosis patients (P<0.001, <0.05 and <0.001, respectively). A stepwise logistic regression analysis (with a forward likelihood ratio method) of these three tumor markers was applied to discriminate between malignancy related and non-malignancy related ascites. The formula used is discriminant function score =0.001×CA125+ 0.011×CEA-1.622. The ROC curves of ascites

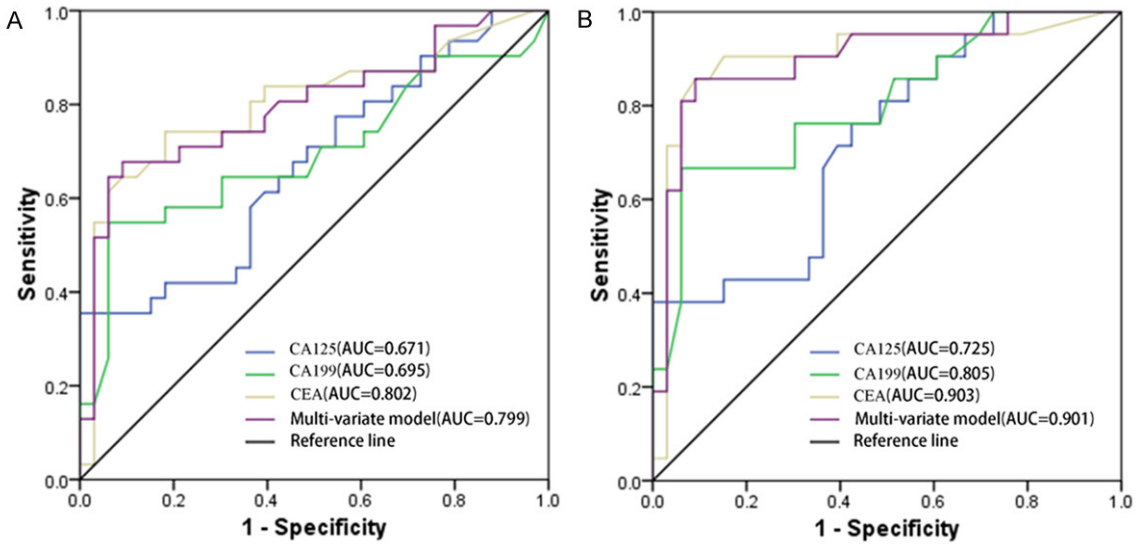

Figure 1. Receiver-operating characteristic curves for ascites CA125, CA19-9, CEA and multi-variate model of malignancy-related ascites vs. non-malignant ascites (A) and secretory tumor ascites vs. non-malignant ascites (B).

Table 4. Analysis of the predictive values of different cut-offs for ascites CA125, CA19-9, CEA and multi-variate model

cut-off value	CA125 (IU/mL)		CA19-9 (U/mL)		CEA (ng/mL)		Multi-variate model	
	>2145		>78		>3.6		>1.0	
	Tumor vs. Non-tumor	Secretory Tumor vs. Non-tumor	Tumor vs. Non-tumor	Secretory Tumor vs. Non-tumor	Tumor vs. Non-tumor	Secretory Tumor vs. Non-tumor	Tumor vs. Non-tumor	Secretory Tumor vs. Non-tumor
Sensitivity	33.3%	34.8%	41.5%	61.9%	57.6%	73.9%	48.5%	56.5%
Specificity	97.2%	97.2%	95.7%	95.7%	96.1%	96.1%	97.1%	97.1%
PPV	91.6%	88.9%	87.5%	86.7%	90.5%	89.5%	94.12%	92.9%
NPV	61.4%	70.0%	72.6%	84.9%	77.8%	89.1%	66%	76.7%

Abbreviations, ADA, adenosinedeaminase; SAAG, serum ascites albumin gradient; PPV, positive predictive value; NPV, negative predictive value.

tumor markers are shown in **Table 3** and **Figure 1**. When predicting malignancy-related ascites vs. non-malignant ascites in the whole study population, the AUCs of ascites CA125, CA19-9 and CEA were 0.671, 0.695 and 0.802, respectively. The AUC of multi-variate model was 0.799, with a diagnostic accuracy of 79.7%, which was significantly higher than AUCs of single ascites tumor marker CA125 and CA19-9 and was approximately equal to that of ascites CEA. Furthermore, in order to raise diagnostic specificity, we picked the specificity of 95% for selecting the cut-off value. For ascites CA125, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 33.3%, 97.2%, 91.6% and 61.4% respectively when the cut-off value was set at >2145 IU/mL; for ascites CA19-9, a cut-off >78 IU/mL resulted in a sensitivity, specificity, PPV and NPV of 41.5%, 95.7%, 87.5% and 72.58%, respectively; for ascites CEA, choosing a cut-off >3.6 IU/mL yielded a sensitivity, specificity, PPV and NPV of 57.6%, 96.1%, 90.47% and 77.78% respectively. Multivariate model showed a sensitivity, specificity, PPV and NPV of 48.5%, 97.1%, 94.12% and 66% respectively at the cut-off value over 1.0 (**Table 4**).

Then, these 34 malignancy-related ascites were classified into secretory (n=23) and non-secretory group (n=11). "Secretory tumors" were defined as malignant tumors with the elevation of serum tumor makers known to secrete, while "non-secretory tumors" were defined as malignancies without the elevation of expected tumor markers in the serum (**Table 5**). The concentrations of CEA and CA19-9 in secretory malignancies were significantly higher than non-malignant cases, while the concentration of ascites CA125 did not show

Table 5. Cause of malignancy-related ascites in this study

Cause	Reported elevation of serum tumor markers	Tumor No. (secretory/ non-secretory)
Gastric cancer	CEA and CA19-9	6/9
Colon cancer	CEA and CA19-9	0/1
Hepatocellular carcinoma	CA19-9 and AFP	2/1
Pancreatic cancer	CEA and CA19-9	1/0
Breast cancer	CEA	2/0
Ovarian cancer	CEA and CA125	4/0
Tumors of unknown origins with peritoneal carcinomatosis	CEA and CA19-9	8/0
Total		23/11

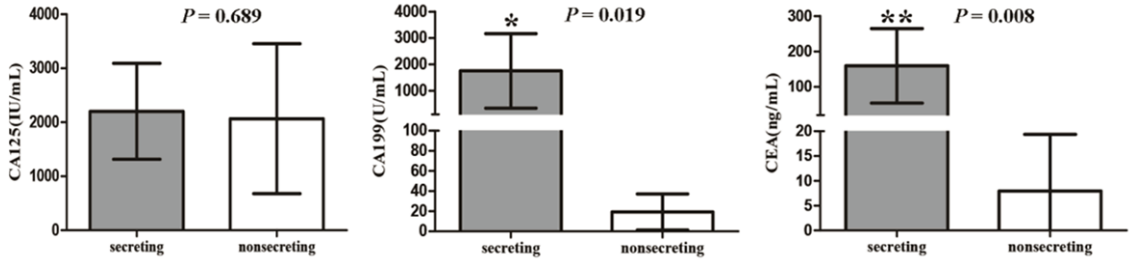

Figure 2. Distribution of ascites tumor markers concentrations of secretory and non-secretory tumor groups. The tests were performed by independent sample *t* test. *, *P*<0.05; **, *P*<0.01.

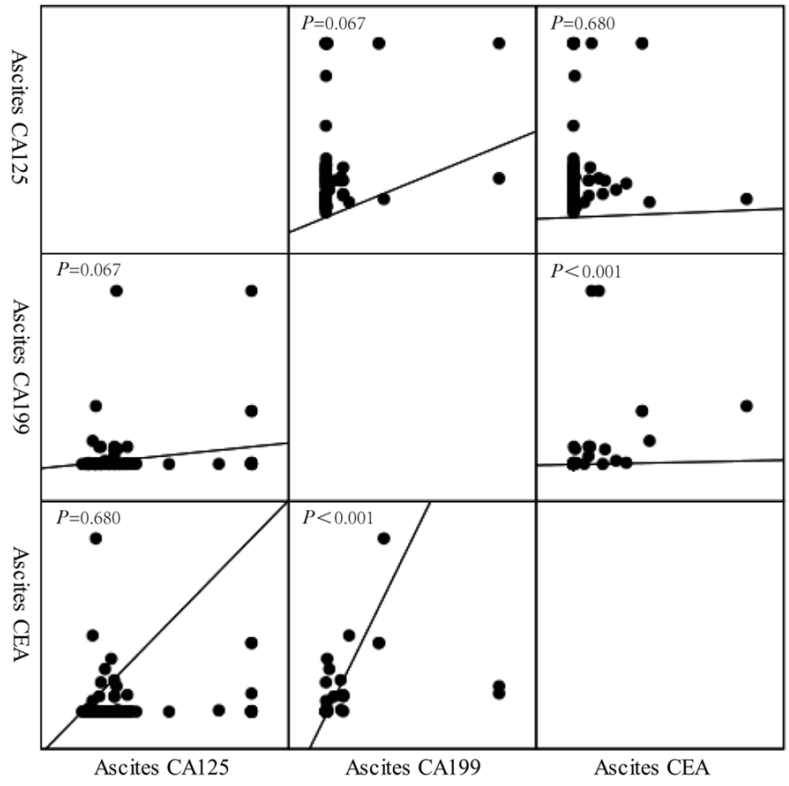

Figure 3. Correlation matrix of the level of ascites tumor marker CA125, CA19-9 and CEA.

statistical difference (**Figure 2**). Subtype analysis between secretory malignancies and non-malignancies showed improved performance of the diagnostic capacity for three tumor markers and multi-variate model. The AUCs of ascites CA125, CA19-9, CEA and multi-variate model increased to 0.725, 0.805, 0.903 and 0.901, respectively (**Table 3**). Meanwhile, choosing the same cut-off values and specificities yielded higher sensitivities and NPVs for all three tumor markers and the multi-variate model (**Table 4**).

Discussion

The usefulness of ascites tumor markers in diagnosing malignancy-related ascites has long been contro-

versial [5-7]. Low sensitivity and specificity are the main reasons hindering them from being powerful tools. In our study, AUCs for ascites CA125, CA19-9 and CEA showed poor predictive powers as those results reported by previous studies [7, 10]. When analyzing predictive values, cut-offs were chosen at a high specificity (>95%) in order to avoid false positives which may lead to unnecessary tests. It turned out that using these ascites tumor markers alone or together did not provide high sensitivity or NPV. Erin J et al. inferred that this may somehow be due to the failure to subgroup the malignant ascites into secretory and non-secretory groups according to the secretion status of the tumor marker antigens in serum [7]. Taking this suggestion by Erin J et al., malignancies were further subtyped into two groups in our study. Of the 34 patients diagnosed with malignant ascites, the locations of the primary tumors were confirmed in 26 patients, with gastrointestinal (n=16), hepatocellular (n=3), pancreatic (n=1), breast (n=2) or ovarian (n=4) malignancies. The tumor cell origins of the remaining eight patients were unable to be found. Among the eleven non-secretory patients, nine were gastric cancer with normal serum CEA and CA19-9. One was liver cancer with normal serum AFP and CA19-9. One was colon cancer with normal serum CEA and CA19-9 (**Table 5**). After subtyping malignancies into secretory and non-secretory groups, both single ascites tumor markers and the multi-variate model showed increased AUCs for secretory tumor vs. non-tumor group. Also, choosing the same specificities at the same cut-offs yielded higher sensitivities and NPVs for all ascites tumor markers as well as multi-variate model.

We included three tumor markers (ascites CA125, CA19-9 and CEA) to the establishment of multi-variate model. Finally, only ascites CA125 and CEA were in the equation while ascites CA19-9 was discarded. This result may be due to the collinearity of CA19-9 and CEA. Originally, CEA is thought to be specific for digestive tract cancers while CA19-9 is a tumor marker for pancreatic cancer and gall bladder cancer [11]. Y Tuzun et al. reported that ascites CEA had correlation with CA19-9 and CA724, while ascites CA125 had correlation with CA153 [6]. In our study, the correlation matrix for levels of ascites tumor markers was illustrated in **Figure 3**. The correlation coefficient between CEA and CA19-9 was 0.404 (P<0.001), while no correlation was found between CA125 and CEA (P=0.680) or between CA125 and CA19-9 (P=0.067). The use of ascites CA125, derived from the mesothelial cells of the peritoneum [11], was deemed as a poor tumor marker in diagnosis due to its low specificity. Ascites CA125 may be elevated in other benign conditions such as liver cirrhosis, inflammation in the abdominal area and etc. [12, 13]. Also, secretory group showed higher levels of ascites CA19-9 and CEA but not ascites CA125 compared to non-secretory group (**Figure 2**). So it's hard to explain why ascites CA125 was kept in our equation regardless of its low specificity. Limited ascites tumor markers used in our study may partly tell the reason. As a matter of fact, more tumor markers in the ascites should be included to reestablish multi-variate models in the future. Also, more ascites patients should be enrolled to verify the diagnostic power of our multivariate model.

Another thing to be noted is the non-secretory tumors. It was reported that certain tumors do not secrete tumor markers that are expected in the serum. For example, one cell type called mucinous ovarian cancer has normal serum CA125 [14]. Also, it is known that a proportion of gastric cancer patients have normal serum CEA [15]. As for CA19-9, less than 7% of the population are Lewis-negative and have undetectable concentrations of CA19-9 despite the presence of a malignancy expecting to secrete it [16]. What's more, of the eleven patients (all tumor origins known) grouped into non-secretory group, there may be certain cases secreting other serum tumor markers which were beyond the scope of tumor marker categories in our study. As a matter of fact, demerits of our study still exist. The diagnostic power of the ascites tumor markers may be somehow underestimated.

In conclusion, this study aimed to testify the diagnostic ability of ascites tumor markers alone or together after classifying the malignancy-related ascites into secretory and non-secretory groups. Increased diagnostic power was obtained after this classification, indicating that previous low sensitivity and NPV of ascites tumor markers in making diagnosis could be largely improved when they were applied to the comparison between non-malig-

nancies and malignancies known to secrete tumor markers in the serum.

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Disclosure of conflict of interest

None.

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