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The role of oxidative stress parameters in the differential diagnosis of malignant and benign ascites

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Abstract. – OBJECTIVE: Ascites is the pathological fluid accumulation in the peritoneal cavity and there are mainly two reasons for its etiology. These are malignant diseases such as hepatoma or pancreas cancer and benign diseases such as liver cirrhosis and heart failure. In this study, we investigated the diagnostic utility of arylesterase (ARES), paraoxonase (PON), stimulated paraoxonase (SPON), catalase (CAT) and myeloperoxidase (MPO) in the differential diagnosis of malignant and benign ascites.

PATIENTS AND METHODS: This study was conducted between February and September 2016. Patients with acute infection, those taking vitamin supplements and antioxidant medication, smoking, and drinking alcohol were excluded from the study.

RESULTS: The study population consisted of 60 patients: 36 had benign (60%) and 24 had malignant (40%) ascites. The mean age of the patients was 63.3 years. MPO levels (14.2 *vs*. 4.2; *p*=0.028) were found to be higher and PON (2.6 *vs*. 4.5; *p*<0.001), SPON (10.7 *vs*. 23.9; *p*<0.001), ARES (615.7 *vs*. 823.5, *p*<0.001) and CAT (13.3 *vs*. 36.8; *p*=0.044) were found to be lower in malignant patients compared to benign patients. There was a positive correlation between PON, SPON, and ARES levels, and a negative correlation between MPO levels and SPON, ARES, and CAT levels. MPO levels showed superior diagnostic performance compared to ARES and CAT levels (*p*<0.05) for predicting malignancy but showed no diagnostic superiority compared to PON and SPON levels (*p*>0.05).

CONCLUSIONS: PON, SPON, ARES, CAT, and MPO can be used with high sensitivity and specificity in the differential diagnosis of malignant and benign ascites.

Key Words:
Serum arylesterase, Paraoxonase, Catalase, Myeloperoxidase.

Introduction

Ascites is the pathological fluid accumulation in the peritoneal cavity and there are mainly two reasons for its etiology. These are malignant diseases such as hepatoma or pancreas cancer and benign diseases such as liver cirrhosis and heart failure[1,2]. Knowing the causes of ascites and making a differential diagnosis is very important for choosing an appropriate treatment. However, clinical differentiation of malignant and benign ascites is often not possible. Cytology used in the differential diagnosis is often inadequate[3]. A peritoneal biopsy is an invasive procedure with a high complication rate. Therefore, different methods have been tried in the differential diagnosis of malignant and benign ascites.

Antioxidant markers have anti-inflammatory and anti-oncogenic properties and are decreased in malignant diseases[4,5]. Conversely, oxidative markers have pro-inflammatory and oncogenic properties and are increased in malignant diseases[6]. Arylesterase (ARES), paraoxonase (PON), and stimulated paraoxonase (SPON) are esterase enzymes that have antioxidant properties[7,8]. Serum PON and ARES activities were found to be lower in patients with cancer than in control groups[9,10]. Similarly, catalase (CAT) has anti-inflammatory properties, and is decreased especially in adenocarcinoma cases[11]. Myeloperoxidase (MPO) is an enzyme secreted from neutrophils and has preoxidative and pro-inflammatory properties. Although it is a useful enzyme, it is thought to cause many diseases through tissue damage following extracellular release[12]. In cancer cases, it helps in both the etiology and progression of the disease[13].

These parameters have been studied in serum, but there are also some publications[14] in which ox-

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idative stress markers were studied in body fluids. However, there is no study in the literature that investigated the use of these parameters in the differential diagnosis of malignant and benign ascites. For this reason, we investigated the diagnostic utility of these parameters in the differential diagnosis of malignant and benign ascites in this study.

Patients and Methods

This study was conducted on patients admitted to our hospital with malignant and benign ascites. The etiologic factors of ascites were recorded from patient files. Patients with indefinite etiology were excluded from the study. Also, patients with acute infection, those taking vitamin supplements and antioxidant medication, smoking, and drinking alcohol, and participants younger than 18 years old at the time of admission were excluded from the study. At the time of admission, a 10-cc sample of ascitic fluid was taken from patients whose ascites had already been sampled for other reasons (to investigate infection or etiology of ascites). Ascites samples were stored at -80°C. Then ARES, PON, SPON, CAT, and MPO parameters were studied in the same sequence. Participants' laboratory results were recorded from patients' files at the time of admission.

PON levels were measured with the colorimetric method using a commercial kit (Rel Assay Diagnostics, Şehitkamil, Gaziantep, Turkey, REF. No: RL0031, LOT No: JE14028P). Measurements of PON activity were performed in the absence (basal activity) and presence of NaCl (salt-stimulated activity-SPON). The increase of absorbance at 412 nm at 37 °C was recorded as the activity of paraoxon hydrolysis (diethyl-p-nitrophenyl phosphate). The amount of generated p-nitrophenol was calculated from the molar absorptivity coefficient (18.290 M-1 cm-1) at a pH of 8.5[15]. PON activity was expressed as U/L serum. ARES level was also measured with a commercial kit (Rel Assay Diagnostics, Şehitkamil, Gaziantep, Turkey, REF. No: RL0055, LOT No: JR13017AR) *via* the colorimetric method. Measurement of ARES activity was performed using phenylacetate as the substrate. Enzymatic activity was calculated from the molar absorptivity coefficient (1,310 M-1 cm-1) of the produced phenol. One unit of ARES activity was defined as 1 μmol phenol generated/min under the above-defined assay conditions and expressed as kU/L serum[16].

Catalase activity was gauged by Goth's method[17]. A sample (0.2 ml) was propagated in 1.0 ml substrate (65 μmol per H_2O_2 in 60 mmol/L sodium-potassium phosphate buffer, pH 7.4) at 37°C for 60 seconds. The enzymatic reaction was ceased with 1.0 ml of 32.4 mM ammonium molybdate, and the yellow complex of molybdate and H_2O_2 was measured at 405 nm. One unit of catalase dissociates 1 μmol of H_2O_2 min^{-1} under these conditions. Results were expressed in kU/L.

Myeloperoxidase activity was measured by a modification of the o-dianisidine method[18] based on kinetic measurement at 460 nm with the rate of the yellow in orange product formation from the oxidation of o-dianisidine with myeloperoxidase in the presence of H_2O_2. One unit of myeloperoxidase was defined as that degrading 1 μmol of H_2O_2 min-1 at 25°C. A molar extinction coefficient of 1.13×104 of oxidized o-dianisidine was used for the calculation. Myeloperoxidase activity was expressed in IU/mL.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM Corp., Armonk, NY, USA) and Medcalc 11.4.2 (MedCalc Software, Mariakerke, Belgium). The normal distribution of the data was assessed by the Kolmogorov-Smirnov test. Numerical variables with normal distribution were shown as mean ± standard deviation, and numerical variables without normal distribution were shown as median (min-max). Categorical variables were expressed as numbers and percentages. The comparison of numerical variables between benign and malignant patient groups was assessed by *t*-test (numerical variables exhibiting normal distribution) and Mann-Whitney U test (numerical variables exhibiting anormal distribution) in independent samples. Chi-square and Fisher's exact Chi-square test were used to compare categorical data. The relationship between numerical variables was analyzed by Spearman correlation analysis. Diagnostic evaluation of PON, SPON, ARES, CAT, and MPO levels for assessing malignant diseases compared to benign diseases was done by ROC Curve analysis. Estimates were determined according to the Youden index method. $p<0.05$ value was accepted as statistically significant.

This study was designed in accordance with the Brazil version of the 2013 Helsinki Declaration and has been approved by the Research Ethics Committee of the Board of Turkey Ankara City Hospital Training.

Results

The study population consisted of 60 patients with 36 benign (60%) and 24 malignant (40%) ascites. The mean age of the patients was 63.3 ± 11.6 years. 51.7% of the patients were male and 48.3% were female. The mean age and sex ratio did not differ between benign and malignant patients. Cryptogenic cirrhosis (41.7%) in the benign group and hepatocellular cancer HCC (41.7%) in the malignant group were the most common etiologic factors (Table I).

The laboratory findings of the patients are shown in Table II. According to this median ascites lactate dehydrogenase LDH (115 *vs.* 69.5; p=0.005) and median MPO (14.2 *vs.* 4.2; p=0.028) were higher in malignant patients compared to benign patients. Median ascitic fluid glucose (116 *vs.* 141; p=0.003) PON (2.6 *vs.* 8.5; p<0.001), median SPON (10.7 *vs.* 23.9; p<0.001), median ARES (615.7 *vs.* 823.5, p<0.001) and median CAT (13.3 *vs.* 36.8; p=0.044) were lower in malignant patients compared to benign patients.

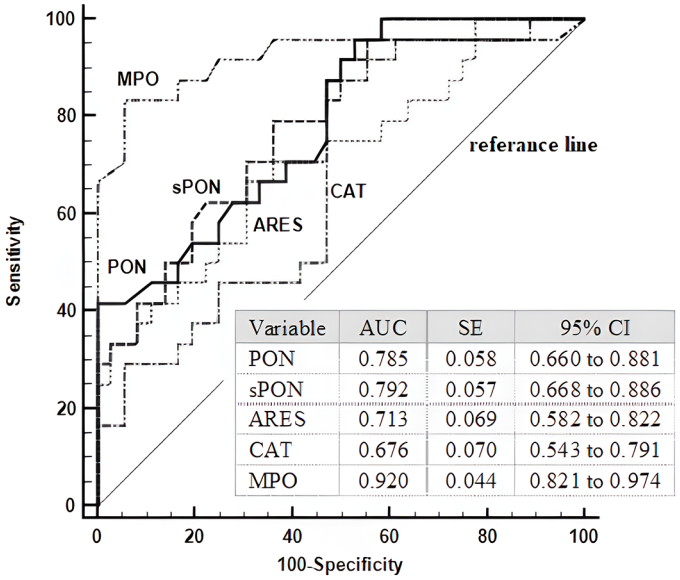
Findings related to PON, SPON, ARES, CAT, and MPO levels are shown in Table III. A positive correlation was found between PON levels and SPON (r=0.870; p<0.001), ARES (r=0.505; p<0.001), and albumin levels (r=0.496; p<0.001). There was a positive correlation between SPON and ARES (r=0.776, p<0.001) and albumin levels (r=0.573; p<0.001), and a negative correlation between SPON and MPO levels (r = -0.319 p=0.013). There was a positive correlation between ARES and albumin levels (r=0.962; p=0.002) and a negative correlation between ARES and MPO levels (r= -0.492; p<0.001). A negative correlation was found between CAT and MPO levels (r= -0.338; p=0.005).

MPO levels showed superior diagnostic performance compared to ARES and CAT levels (p<0.05) for predicting malignancy but showed no diagnostic superiority compared to PON and SPON levels (p>0.05) (Figure 1).

Table I. Age of patients, duration of marriage and mean postoperative pregnancy period.

Variables	Total population n=60	Benign n=36	Malignant n=24	p
Age, years	63.3±11.6	62.7±11.6	64.2±11.8	0.626
Gender, n (%)				
Female	29 (48.3)	17 (47.2)	12 (50.0)	0.995
Male	31 (51.7)	19 (52.8)	12 (50.0)	
Ascites etiology, n (%)				
Cryptogenic cirrhosis	15 (25.0)	15 (41.7)	-	-
Hepatitis B cirrhosis	6 (10.0)	6 (16.7)	-	
Hepatitis C cirrhosis	2 (3.3)	2 (5.6)	-	
Alcoholic cirrhosis	4 (6.7)	4 (11.1)	-	
Budd Chiari	2 (3.3)	2 (5.6)	-	
Veno-occlusive	2 (3.3)	2 (5.6)	-	
Biliary cirrhosis	1 (1.7)	1 (2.8)	-	
Cardiac cirrhosis	4 (6.7)	4 (11.1)	-	
Malignant	24 (40.0)	-	24 (100.0)	
Malignant etiology, n (%)				
Pankreas CA	4 (16.7)	-	4 (16.7)	-
Cholangio CA	2 (8.3)	-	2 (8.3)	
Stomach CA	1 (4.2)	-	1 (4.2)	
Over CA	3 (12.5)	-	3 (12.5)	
HCC	10 (41.7)	-	10 (41.7)	
Breast CA	1 (4.2)	-	1 (4.2)	
Others	3 (12.5)	-	3 (12.5)	

Categorical variables were expressed as number (%). Numerical variables with normal distribution were expressed as mean ± standard deviation. CA: Cancer, HCC: Hepatocellular carcinoma.



Variable	AUC	SE	95% CI
PON	0.785	0.058	0.660 to 0.881
sPON	0.792	0.057	0.668 to 0.886
ARES	0.713	0.069	0.582 to 0.822
CAT	0.676	0.070	0.543 to 0.791
MPO	0.920	0.044	0.821 to 0.974

Pairwise comparison of ROC curves

PON ~ sPON	
ΔAUC	0.007
p	0.716
PON ~ ARES	
ΔAUC	0.072
p	0.145
PON ~ CAT	
ΔAUC	0.109
p	0.249
PON ~ MPO	
ΔAUC	0.135
p	0.068
sPON ~ ARES	
ΔAUC	0.079
p	0.156
sPON ~ CAT	
ΔAUC	0.116
p	0.210
sPON ~ MPO	
ΔAUC	0.128
p	0.081
ARES ~ CAT	
ΔAUC	0.030
p	0.733
ARES ~ MPO	
ΔAUC	0.207
p	0.008
CAT ~ MPO	
ΔAUC	0.244
p	0.007

Figure 1. Demonstration of factors predicting malignancy by ROC curve analysis. AUC: Area the curve, SE: Standart error, CI: Confidence interval, PON; Paraoxonase, SPON: Stimulated paraoxonase, ARES: Arylesterase, ΔAUC: Difference Area under the curve.

Table II. Laboratory findings of patients.

Variables	Total population n=60	Benign n=36	Malignant n=24	*p*
Hemoglobin	10.6±2.2	10.3±2.1	11±2.2	0.216
Platelet (x103)	116 (22-858)	112 (27-858)	122 (22-419)	0.624
INR	1.4 (1-3.8)	1.4(1-3.8)	1.3 (1-3.4)	0.511
Albumin	2.6±0.6	2.6±0.6	2.5±0.6	0.561
Glucose	106.5 (47-301)	110.5 (70-301)	99.5 (47-181)	0.277
LDH	240 (95-1,599)	228 (95-435)	262 (139-1,599)	0.090
Ascites WBC	278.3±84.6	277.8±86.6	279.2±83.3	0.951
Ascites PMNL	100 (0-200)	100 (0-200)	100 (0-200)	0.883
Ascites LDH	74 (20-583)	69.5 (20-138)	115 (31-583)	0.005*
Ascites glucose	135.5 (0-301)	141 (85-301)	116 (0-172)	0.003*
Ascites albumin	0.6 (0.1-2.4)	0.6 (0.1-2.4)	0.7 (0.1-2.3)	0.584
PON	6.5 (0-77.1)	8.5 (0.3-77.1)	2.6 (0-8.9)	<0.001*
SPON	20.6 (3.7-296.2)	23.9 (5.8-271.2)	10.7 (3.7-40.2)	<0.001*
ARES	715 (67.6-881.7)	823.5 (375.9-881.7)	615.7 (67.6-742.5)	<0.001*
CAT	16.5 (0.1-568.4)	36.8 (0.4-568.4)	13.3 (0.1-210.1)	0.021*
MPO	6.4 (0-289.7)	4.2 (0-181.5)	14.2 (0-289.7)	0.028*

Numerical variables with normal distribution were expressed as mean ± standard deviation. Numerical variables without normal distribution are shown as median (min-max). *p<0.05. PON: Paraoxonase, SPON: Stimulated paraoxonase, ARES: Arylesterase, CAT: Catalase, MPO: Myeloperoxidase, INR: International normalizde ratio, LDH: Lactate dehydrogenase, WBC: White blood count, PMNL: Polymorphonuclear leukocyte.

Discussion

Ascites is the pathological fluid accumulation in the peritoneal cavity that leads to important clinical problems in patients. Moreover, the differential diagnosis of malignant and benign ascites is often difficult because of the inadequacy of cytology. In this study, the diagnostic utility of oxidative and non-oxidative markers in patients with ascites was investigated and as the MPO level was found to be higher; ARES, PON, SPON, and CAT levels were found to be lower in the malignant ascites group compared to benign ascites group. PON, SPON, and CAT levels with high specificity; ARES and MPO with high specificity and sensitivity have been shown to predict malignancy. To the best of our knowledge, this is the first study to examine the diagnostic utility of oxidative and non-oxidative markers in the differential diagnosis of malignant and benign ascites.

Oxidative stress in malignant diseases, characterized by an increase in free radicals and associated cellular damage is thought to play an important role in the etiology and progression of the disease[19]. In these patients, oxidation-induced free radicals arise in lipid structures and oxidative imbalance develops. PON and SPON are enzymes that are primarily synthesized from the liver and show beneficial effects against a large number of diseases and contribute to the improvement of the oxidative imbalance mentioned above. ARES is an esterase enzyme encoded by the same gene and having similar effects[20]. Previous studies[21] have shown that PON, SPON, and ARES values decrease significantly in cancer patients with a decrease in the resultant antioxidant effect. It was reported that PON and ARES levels were decreased in cases of thyroid cancer, then immediately increased after the cancer was operated and the esterase enzymes directly correlated with cancer[10]. All the results mentioned above were obtained by studying these parameters in serum samples. Our study is different from the above studies as it was done by examining ascitic fluid. Moreover, in these studies, it was said that PON, SPON, and ARES were lower in malignant diseases, but detailed information about the use of these parameters in the differential diagnosis of malignant and benign ascites was not given. We have shown that these parameters can be used for the diagnostic differentiation of ascites by setting the predictive value for each parameter studied. In our study, PON, SPON, and ARES were found to be effective in predicting malignancy with high specificity and sensitivity. Contrary to our findings, there are some articles[22] indicating that higher PON levels may play a role in the development of cancer. All these parameters have antioxidative properties and the idea of their decreased in cancer patients is more acceptable since oxidation and free radicals play an important role in the etiology of cancer.

In our study, CAT levels were also found to be lower in patients with malignant ascites parallel to PON, SPON, and ARES. CAT is an antioxidant enzyme that acts by controlling intracellular hydrogen peroxide levels. CAT activity has been shown to decrease in most cancer cases[23]. Studies of bladder cancers have conflicting results regarding CAT activity. In some studies, CAT activity increased in malignant diseases[24] and decreased in others[25]. However, Corrocher et al[26] found significantly decreased CAT activity in the tissues of patients with HCC[26]. In our study, 40% of patients with malignant ascites have HCC in the etiology. For this reason, the patients' profiles and results of the above study support our findings.

MPO is a well-known oxidative marker. Previous studies[27] with cancer patients have shown that as the cancer stage increases, MPO increases, resulting in increased oxidative and decreased survival. However, in many of these studies, MPO has been studied in tissue. An important advantage of our study was to investigate MPO levels in ascitic fluid which is easily accessible. In majority of the above studies, the association of these parameters with cancer was shown but not much was mentioned about its usefulness for diagnostic differentiation. Our study showed that increased MPO levels predict mortality with high sensitivity and specificity. MPO was found superior to all other parameters except PON in diagnostic differentiation. These results show that these parameters especially MPO and PON can be used especially in distinguishing between malignant and benign ascites.

Our main limitation was the cross-sectional design of our study and the fact that the lipid parameters of the oxides were not studied.

Conclusions

This study showed that PON, SPON, ARES, CAT, and MPO can be used in the differential di-

Table III. Findings related to PON, SPON, ARES, CAT and MPO levels.

	PON		SPON		ARES		CAT		MPO	
Vatiables	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***
PON	-	-	-	-	-	-	-	-	-	-
SPON	0.870	<0.001*	-	-	-	-	-	-	-	-
ARES	0.505	<0.001*	0.776	<0.001*	-	-	-	-	-	-
CAT	0.219	0.192	0.194	0.201	0.169	0.189	-	-	-	-
MPO	-0.368	0.003*	-0.319	0.013*	-0.492	<0.001*	-0.338	0.005*	-	-
Age	-0.229	0.178	-0.197	0.131	-0.177	0.274	-0.093	0.481	0.112	0.396
Hemoglobin	0.182	0.165	0.185	0.156	0.107	0.417	0.195	0.136	0.133	0.36
Platelet	0.187	0.226	0.192	0.223	0.197	0.121	-0.207	0.113	0.155	0.237
INR	0.143	0.247	-0.041	0.841	-0.146	0.385	0.087	0.886	0.070	0.594
Albumin	0.496	<0.001*	0.573	<0.001*	0.962	0.002*	-0.183	0.163	0.119	0.367
Glucose	0.228	0.164	0.217	0.105	0.235	0.071	0.145	0.286	-0.19	0.146
LDH	-0.205	0.185	-0.193	0.133	-0.183	0.163	0.184	0.159	0.129	0.178
Ascites WBC	-0.104	0.674	-0.100	0.385	0.036	0.787	0.085	0.518	0.046	0.725
Ascites LDH	0.117	0.596	-0.165	0.255	-0.119	0.115	0.095	0.513	0.134	0.306
Ascites glucose	0.111	0.338	0.194	0.248	0.062	0.652	0.064	0.638	-0.084	0.554
Ascites albumin	0.158	0.256	0.123	0.359	0.211	0.143	0.010	0.944	0.185	0.142

*p<0.05. PON: Paraoxonase, SPON: Stimulated paraoxonase, ARES: Arylesterase, CAT: Catalase, MPO: Myeloperoxidase, INR: International normalizde ratio, LDH: Lactate dehydrogenase, WBC: White blood count

agnosis of malignant and benign ascites with high sensitivity and specificity.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Funding
No financial support was received for this study.

Ethics Approval
Ankara City Hospital Ethics Committee, Decision Date/No: 24.03.2021/E2-21-316. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

Informed Consent
Informed consent was obtained from all participants included in the study.

Authors' Contributions
Concept – A.A.S., O.E. and E.B.B.; Design - A.A.S., O.E. and E.B.B.; Supervision – A.A.S., O.E. and E.B.B.; Data collection &/or processing – A.A.S. and O.E.; Analysis &/or interpretation – A.A.S., O.E. and E.B.B.; Literature search – A.A.S., O.E. and E.B.B.; Data collection &/or processing – A.A.S., O.E. and E.B.B.; Writing - A.A.S., O.E. and E.B.B.; Critical review – A.A.S., O.E. and E.B.B.

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