Diagnostic utility of oxidative and non-oxidative markers for spontaneous bacterial peritonitis in non-malign ascites

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Abstract

***Objective* : In this study, we aimed to investigate the diagnostic availability of oxidant and antioxidant parameters in ascites for spontaneous bacterial peritonitis (SBP).**

***Material and method*s : This study was carried out between July and October 2018 with 25 patients with SBP and 24 patients without SBP. Patients with acute infection, those taking vitamin supplements and antioxidant medication, smoking and drinking alcohol, and patients without ascites culture were excluded from the study.**

***Results* : In patients with SBP compared those without SBP median paraoxonase (3.1 vs 15.6 ; p <0.001), median stimulated paraoxonase (12.6 vs 53.1 ; p <0.001), median arylesterase (769,9 vs 857,5 ; p = 0,003) and median catalase (10 vs 22,2 ; p = 0,003) were found to be lower and median myeloperoxidase (8.1 vs 1.1 ; p <0.001) were found to be higher. There was a positive correlation between paraoxonase levels and stimulated paraoxonase levels, arylesterase levels and catalase levels, there was a negative correlation between paraoxonase levels and myeloperoxidase levels. Paraoxonase levels 3.7 and lower, stimulated paraoxonase levels 25.8 and lower, arylesterase levels 853.4 and lower, catalase levels 11.8 and lower and myeloperoxidase levels 2.7 and more predicted the the presence of SBP with high specificity and high sensitivity. Paraoxonase and stimulated paraoxo-nase levels were found to have superior performance in predicting the presence of SBP compared to arylesterase levels (p <0.05).**

***Conclusion* : In this study it was shown that paraoxonase, stimulated paraoxonase, arylesterase, catalase and myeloperoxidase activities can be used for the diagnosis and severity of SBP.** (Acta gastroenterol. belg., **2020**, 83, **279-284**).

Key words : serum arylesterase, paraoxonase, catalase, myeloperoxidase.

Introduction

Ascites is pathological fluid collection in the peritoneal cavity. Cirrhosis and accompanying portal hypertension are the most common causes of ascites in the world (1,2). Patients with cirrhosis and ascites are predisposed to bacterial infections due to reduced defense mechanisms (3). The most common of these bacterial infections – and one of the most serious one – is spontaneous bacterial peritonitis. Spontaneous bacterial peritonitis (SBP) is the infection of ascites without any interference, visceral perforation, and abscess, or any acute source of infection, such as acute pancreatitis (4). SBP is a clinical condition that can cause morbidity and sometimes mortality in cirrhotic patients. Neutrophil and white blood cell counts in ascites are frequently used in the diagnosis of SBP (5). However, this procedure may cause false negative results when samples are transported to the laboratory (6). Culture of ascites is an insensitive and late diagnosis method. In addition, ascites fluid cultures may be negative in 10-60% of patients with SBP (7-8). Therefore, new parameters are needed to be used in the diagnosis of SBP.

Serum arylesterase (ARES) and paraoxonase (PON) are esterase enzymes and have antioxidant properties (9-10). In previous studies, PON and ARES were found to be significantly lower in thromboembolic and inflammatory processes (11). In addition, these enzymes are reported to be protective against bacterial endotoxins by making lipopolysaccharide inactivation (12,13). Similarly, catalase (CAT) is an enzyme with anti-inflammatory properties. In previous studies, it is observed that catalase level decreases in inflammatory events (14). Myeloperoxidase (MPO) is an enzyme that is secreted from neutrophils and has a preoxidant-proinflammatory property and its level increases in cases of infection (15).

There are not many studies in the literature about the diagnostic utility of these parameters in ascites. In this study, we aimed to investigate the diagnostic availability of oxidant and antioxidant parameters in ascites for spontaneous bacterial peritonitis.

Materials and methods

This study was carried out between July and October 2018 with 49 patients who had ascites due to portal hypertension. Ascites cultures for SBP diagnosis were sent from all patients. 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. As a gold standard for the diagnosis of SBP, positive ascites culture was based on. There may be patients that were diagnosed SBP with a negative culture result and a high

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neutrophil count, but positive ascites culture without a secondary cause is the gold standard for SBP. Therefore, only patients with positive ascites culture were included in this study to avoid confusion in the diagnosis of SBP. 25 patients that diagnosed as SBP with positive ascites culture and 24 patients that diagnosed as non-SBP with both negative ascites culture and ascites neutrophil counts less than 250 were included in the study.

Biochemical parameters

At the time of admission, 10 cc ascitic sample was taken from patients whose ascites had already sampled for another reason (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 patient files.

Measurement of ARES, PON, SPON, CAT and MPO

Measurements of PON and ARES : Ascites ARES level was measured with a commercial kit (Rel Assay Diagnostics, Turkey, REF. No : RL0055, LOT No : JR13017AR) via colorimetric method. Ascites PON levels were also measured with the colorimetric method using a commercial kit (Rel Assay Diagnostics, Turkey, REF. No : RL0031, LOT No : JE14028P). %CV : 5. Linearity : 0-750 U/L. 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 (14). PON activity was expressed as U/L. Measurement of ARES activity was performed using phenylacetate as the substrate. Enzymatic activity was calculated from the molar absorptivity coefficient (1310 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 (16).

Measurements of catalase activity assay : Catalase activity was gauged by Goth's method (17). 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.

Measurements of myeloperoxidase : Ascites 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 is 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 SPSS Inc., Chicago, IL) and Medcalc 11.4.2 (MedCalc Software, Mariakerke, Belgium). The normal distribution of the data was evaluated with the Kolmogorov Smirnov test. Numerical variables with normal distribution were shown as mean ± standard deviation and numerical variables which were not normally distributed were shown as median (min-max). Categorical variables were expressed as numbers and percentages. The comparison of the numerical variables between the groups with and without SBP was evaluated with independent samples T test (in numerical variables with normal distribution) and Mann Whitney U test (in non-normally distributed numerical variables). Chi-square and Fisher's exact chi-square test were used to compare categorical data. The relationship between numerical variables was investigated by Spearman correlation analysis. The diagnostic evaluation of PON, SPON, ARES, catalase and myeloperoxidase levels in predicting patients with SBP compared with non-SBP patients was performed by ROC Curve analysis. Estimation values were determined according to Youden index method. $P < 0.05$ was considered statistically significant.

Results

The study population consisted of 49 patients (24 with non-SBP (49%) and 25 with SBP (51%). The mean age of the patients was 59.7 ± 14.4 years. 53.1% of the patients were male and 46.9% were female. The mean age and sex ratio did not differ in patients with SBP and without SBP. The most common etiologic factor in both groups was cryptogenic cirrhosis (Table 1).

Laboratory findings of the patients are shown in Table 2. According to this findings ; median platelets (178 vs 101,5 ; p = 0,015), median WBC (10,4 vs 4,5 ; p <0,001), median CRP (31 vs 14 ; p = 0,004), mean ascites WBC (866,4 ± 257,2 vs 262,5 ± 77,0 ; p <0,001), median ascites neutrophils (500 vs 100 ; p <0,001), median LDH (102,5 vs 58 ; p = 0,001) and median myeloperoxidase (8.1 vs 1.1 ; p <0.001) were found to be higher in patients with SBP compared those without SBP, median PON (3.1 vs 15.6 ; p <0.001), median SPON (12.6 vs 53.1 ; p <0.001), median ARES (769,9 vs 857,5 ; p = 0,003) and median catalase (10 vs 22,2 ; p = 0,003) were found to be lower in patients with SBP compared those without SBP.

Table 1. — **Demographic and etiologic findings of patients**

Variables	Total population n=49	SBP - n=24	SBP + n=25	p
Age	59,7±14,4	62,3±12,9	57,1±15,5	0,211
Sex				
Female	23(46,9)	13(54,2)	10(40,0)	0,396
Male	26(53,1)	11(45,8)	15(60,0)	
Etiology of ascites				
Cryptogenic cirrhosis	24(49,0)	11(45,8)	13(52,0)	0,620
Cirrhosis due to hepatitis B	7(14,3)	3(12,5)	4(16,0)	
Cirrhosis due to NASH	5(10,2)	3(12,5)	2(8,0)	
Alcoholic cirrhosis	4(8,2)	3(12,5)	1(4,0)	
Budd Chiari syndrome	4(8,2)	1(4,2)	3(12,0)	
Cirrhosis due to hepatitis C	3(6,1)	2(8,3)	1(4,0)	
Biliary cirrhosis	2(4,1)	1(4,2)	1(4,0)	

Categorical variables were shown as number (%). Normally distributed numerical variables were shown as mean ± standard deviation. Abbreviations : SBP : Spontaneous bacterial peritonitis ; NASH : Non-alcoholic steatohepatitis.

Table 2. — **Laboratory findings of patients**

Variables	Total population	SBP +	SBP -	p
Hemoglobin	10,4±2	10,8±2,1	9,8±1,8	0,082
Platelets ($x10^3$)	113(19-858)	178(26-858)	101,5(19-276)	0,015*
WBC ($x10^3$)	7(1,3-23)	10,4(1,3-23)	4,5(1,6-11,1)	<0,001*
INR	1,5(1-4,1)	1,5(1-4,1)	1,4(1-2,8)	0,133
Glucose	110(70-301)	113(75-285)	106,5(70-301)	0,342
LDH	234(95-573)	241(95-573)	214(126-390)	0,174
Sedimentation	33(2-135)	40(2-97)	29(2-135)	0,949
CRP	16(0,4-191)	31(1,5-191)	14(0,4-88)	0,004*
WBC count of ascites	570,6±199,6	866,4±257,2	262,5±77,0	<0,001*
Neutrophils count of ascites	300(0-700)	500(300-700)	100(0-200)	<0,001*
Ascites LDH	74,5(16-2615)	102,5(28-2615)	58(16-157)	0,001*
Ascites glucose	137(0-301)	137(0-234)	138,5(85-301)	0,725
PON	6,5(0,3-77,1)	3,1(0,3-35,8)	15,6(2,9-77,1)	<0,001*
SPON	23(2,8-271,2)	12,6(2,8-134,4)	53,1(9,3-271,2)	<0,001*
ARES	818,1(375,9-881,7)	769,9(375,9-877,4)	857,5(689,3-881,7)	0,003*
Catalase	16,3(0,4-582,7)	10(0,4-178,3)	22,2(6,8-582,7)	0,003*
Myeloperoxidase	3,9(0,1-181,5)	8,1(0,3-181,5)	1,1(0,1-17,9)	<0,001*

Normally distributed numerical variables were shown as mean ± standard deviation. Numerical variables not showing normal distribution were shown as median (min-max). * P <0.05. Abbreviations : WBC : White blood cell count ; INR : International normalized ratio ; LDH : Lactate dehydrogenase ; CRP : C-reactive protein ; PON : Paraoxanase ; SPON : Soluble paraoxanase ; ARES : Arylesterase.

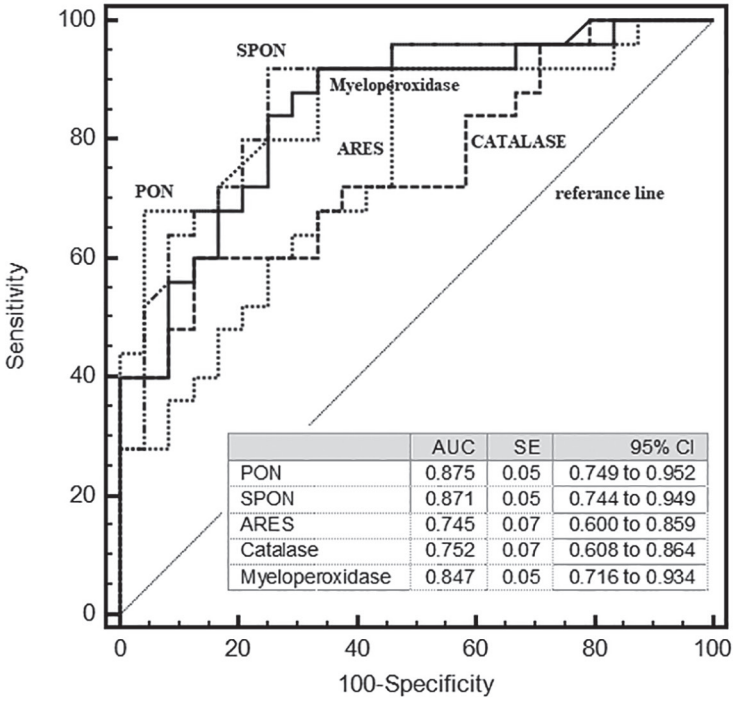
The findings related to PON, SPON, ARES, catalase and myeloperoxidase levels are shown in Table 3. There was a positive correlation between PON levels and SPON levels (r = 0.969 ; p <0.001) and ARES levels (r = 0.858 ; p <0.001), and there was a negative correlation between PON levels and myeloperoxidase levels (r = -0.387 ; p = 0.006), WBC (r = -0.396 ; p = 0.005), ascites WBC (r = -0,666 ; p <0.001), ascites neutrophils (r = -0.598 ; p <0.001)). There was a positive correlation between SPON levels and ARES levels (r = 0.844 ; p <0.001) and catalase (r = 0.281 ; p = 0.050), and there was a negative correlation between SPON levels and myeloperoxidase levels (r = -0.394 ; p = 0.005), WBC (r = -0.389). ; p = 0.006), ascites WBC (r = -0.615 ; p <0.001), ascites neutrophils (r = -0.564 ; p <0.001). There was a negative correlation between ARES levels and ascites WBC (r = -0.444 ; p = 0.001), ascites neutrophils (r = -0.355 ; p = 0.012). There was a negative correlation between catalase levels and myeloperoxidase levels (r = -0,375 ; p = 0,008), platelets (r = -0,298 ; p = 0,038), ascites WBC (r = -0,322 ; p = 0,024) and ascites neutrophils (r = -0,470 ; p = 0.001). There was a positive correlation between myoloperoxidase levels and platelets (r = 0.542 ; p <0.001), WBC (r = 0.282 ; p = 0.049), ascites WBC (r = 0.539 ; p <0.001), ascites neutrophils (r = 0.604 ; p <0.001) and ascites LDH (r = 0.390 ; p = 0.009).

PON levels 3.7 and lower predicted the presence of SBP with 68% sensitivity and 95.7% specificity (AUC ± SE : 0,875 ± 0,05 ; + PV : 99,7% ; -PV : 13,6% ; p < 0.001). SPON levels 25.8 and lower predicted the presence of SBP with 75.0% specificity and 75.0% specificity (AUC ± SE : 0.871 ± 0.05 ; + PV : 98.6% ; -PV : 33.0% ; p <0.001). ARES levels 853.4 and lower predicted the the presence of SBP with a specificity of 92.0% and a specificity of 54.2% (AUC ± SE : 0.745 ± 0.07 ; + PV : 97.4% ; -PV : 26.3% ; p <0.001). The

Table 3. — **Findings related to PON, SPON, ARES, catalase and myeloperoxidase levels**

Variables	PON		SPON		ARES		Catalase		Myoloperoxidase	
	r	p	r	p	r	p	r	p	r	p
PON	-	-	0,969	<0,001*	0,858	<0,001*	0,250	0,083	-0,387	0,006*
SPON	0,969	<0,001*	-	-	0,844	<0,001*	0,281	0,050*	-0,394	0,005*
ARES	0,858	<0,001*	0,844	<0,001*	-	-	0,079	0,589	-0,119	0,416
Catalase	0,250	0,083	0,281	0,050*	0,079	0,589	-	-	-0,375	0,008*
Myoloperoxidase	-0,387	0,006*	-0,394	0,005*	-0,119	0,416	-0,375	0,008*	-	-
Age	-0,106	0,468	-0,126	0,390	-0,128	0,383	0,175	0,230	-0,133	0,361
Hemoglobin	-0,060	0,681	-0,007	0,960	-0,043	0,768	-0,068	0,644	0,237	0,101
Platelets	-0,051	0,726	-0,031	0,830	-0,023	0,878	-0,298	0,038*	0,542	<0,001*
WBC	-0,396	0,005*	-0,389	0,006*	-0,259	0,073	-0,066	0,651	0,282	0,049*
INR	-0,143	0,327	-0,168	0,250	-0,124	0,396	-0,034	0,818	-0,204	0,161
Glucose	-0,007	0,964	-0,060	0,680	0,038	0,797	-0,098	0,504	0,082	0,575
LDH	-0,079	0,589	-0,069	0,636	-0,091	0,535	-0,091	0,533	-0,104	0,479
Sedimentation	-0,102	0,494	-0,144	0,333	-0,214	0,149	-0,028	0,854	0,026	0,863
CRP	-0,229	0,114	-0,245	0,090	-0,217	0,135	0,024	0,869	0,253	0,080
WBC count of ascites	-0,666	<0,001*	-0,615	<0,001*	-0,444	0,001*	-0,322	0,024*	0,539	<0,001*
Neutrophils count of ascites	-0,598	<0,001*	-0,564	<0,001*	-0,355	0,012*	-0,470	0,001*	0,604	<0,001*
Ascites LDH	-0,154	0,318	-0,129	0,405	-0,044	0,774	-0,219	0,153	0,390	0,009*
Ascites glucose	0,187	0,220	0,101	0,509	0,178	0,242	-0,108	0,479	0,040	0,792

*p<0,05. Abbreviations : WBC : White blood cell count ; INR: International normalized ratio ; LDH : Lactate dehydrogenase ; CRP : C-reactive protein ; PON : Paraoxanase ; SPON : Soluble paraoxanase ; ARES : Arylesterase.



	AUC	SE	95% CI
PON	0.875	0.05	0.749 to 0.952
SPON	0.871	0.05	0.744 to 0.949
ARES	0.745	0.07	0.600 to 0.859
Catalase	0.752	0.07	0.608 to 0.864
Myeloperoxidase	0.847	0.05	0.716 to 0.934

Pairwise comparison of ROC curves

PON ~ SPON	
ΔAUC	0.004
p	0.798
PON ~ ARES	
ΔAUC	0.130
p	0.001
PON ~ Catalase	
ΔAUC	0.123
p	0.165
PON ~ Myeloperoxidase	
ΔAUC	0.027
p	0.728
SPON ~ ARES	
ΔAUC	0.126
p	0.003
SPON ~ Catalase	
ΔAUC	0.119
p	0.178
SPON ~ Myeloperoxidase	
ΔAUC	0.023
p	0.770
ARES ~ Catalase	
ΔAUC	0.006
p	0.948
ARES ~ Myeloperoxidase	
ΔAUC	0.102
p	0.307
Catalase ~ Myeloperoxidase	
ΔAUC	0.095
p	0.270

Abbreviations : AUC: Area under the curve, SE: Standart error, CI: Confidence interval, PON: Paraoxonase, SPON: Stimulated paraoxonase, ARES: Arylesterase, ΔAUC: Difference Area under the curve

Figure 1. — Comprasions of ROC curves of paraoxonase, stimulated paraoxonase, arylesterase, catalese and myeloperoksidase.

catalase levels 11.8 and lower predicted the the presence of SBP with a specificity of 60.0% and a specificity of 87.5% (AUC ± SE : 0.752 ± 0.07 ; + PV : 98.9% ; -PV : 10.3% ; p <0.001). The myeloperoxidase levels 2.7 and more predicted the the presence of SBP with a specificity of 84.0% and a sensitivity of 75.0% (AUC ± SE : 0.847 ± 0.05 ; + PV : 98.5% ; -PV : 19.8%. ; p <0.001).

The superior diagnostic performance evaluation of PON, SPON, ARES, catalase and myeloperoxidase levels in predicting the presence of SBP is shown in Figure 1.

According to this ; PON and SPON levels were found to have superior performance in predicting the presence of SBP compared to ARES levels ($p < 0.05$), there was no superiority in predicting the presence of SBP in terms of other paired comparisons ($p > 0.05$).

Discussion

Although spontaneous bacterial peritonitis is a disease with high mortality and morbidity, its diagnosis can be difficult. Therefore, many methods, including ultrasonography, are used to predict infection in the ascites (19). In this study, the diagnostic discrimination of oxidative and non-oxidative markers in patients with ascites was investigated for the same reason and in patients with SBP compared to patients without SBP, MPO level was found higher ; ARES, PON, SPON and CAT levels were found lower. In this study it has been shown that SPON, ARES and MPO levels with high sensitivity ; PON and CAT levels with high specificity predict presence of SBP. To the best of our knowledge, this study is the first study to investigate the availability of oxidative and non-oxidative markers in the diagnosis of SBP.

Cellular damage and consequently oxidative imbalance develop as a result of the increase of free radicals in infectious diseases (20). PON and SPON are the enzymes synthesized primarily from the liver and have beneficial effects against many diseases and exposures and contribute to the improvement of the above mentioned oxidative imbalance. ARES is an esterase enzyme that is encoded by the same gene and has similar effects (21). Previous studies have shown that these substances with anti-inflammatory properties have decreased especially in infective conditions. Bojic et al. showed that PON levels were significantly lower in patients with sepsis compared to the control group (22). In addition, Esen et al. showed a significant decrease in PON1 levels in patients with acute brucellosis (22). PON and ARES levels were studied in patients with sepsis and lower levels were found in the study group compared to the control group (24). Furthermore, this study showed that decreased PON and ARES levels were associated with poor prognosis. Similarly in our study, PON levels were found to be lower when ascites was infected. The negative correlation of PON and ARES levels with ascites neutrophil count suggests that these parameters may be related to disease severity.

Catalase is a well-known antioxidant molecule and in previous studies it is shown that CAT levels are correlated with disease severity (25). In addition, catalase activity decreases in the presence of infection. Kumar et al. stated that the mismatch between oxidant and antioxidant status plays a significant role in the severity of sepsis (26). In this study, especially the decrease in CAT level and increase of MPO level are emphasized. CAT activity in our study showed a significant decrease in the presence of infection of ascites.

In our study, myeloperoxidase was found to be higher in patients with SBP in contrast to all other parameters. MPO is an enzyme secreted by neutrophils and plays a pivotal role in the formation of oxidative stress in many infectious diseases (27). In fact, elevation in MPO levels, which has a protective role in bacterial infections, is important for host defense (29). However, as in many diseases, uncontrolled increase of MPO in SBP aggravates the diseases. Although MPO has been shown to play a role in the pathogenesis of many diseases (29-31), no studies have been conducted in patients with ascites. In our study, myeloperoxidase was studied in ascites and shown to have high sensitivity and specificity for prediction of SBP.

In our study, PON and SPON levels showed superior diagnostic performance in predicting the presence of SBP compared to ARES levels ($p < 0.05$), but no superiority was found in predicting the presence of SBP in terms of other bilateral comparisons. When the literature is examined, it is seen that especially the first three parameters are used more frequently to show oxidative stress. CAT and MPO are less commonly used to show oxidative imbalance because these two parameters are studied in tissue rather than body fluids or serum.

The most important limitation of our study is the small number of patients. However, since these parameters have been studied for the first time in ascites, we think that the number of patients is sufficient. Another important limitation of our study is that only patients with spontaneous bacterial peritonitis confirmed with the culture results were taken to study. We know that patients with culture-negative spontaneous bacterial peritonitis account for approximately 50% of all patients. More detailed and randomized studies are needed to overcome this deficiency. Another limitation of our study was lack of patient follow-up. Unfortunately, some of these patients had their follow-up outside after the study. In addition, some patients died of severe illness. Therefore, we could not perform ascites examination after SBP recovery.

In conclusion, in this study it was shown that PON, SPON, ARES, CAT and MPO activities can be used for the diagnosis and severity of spontaneous bacterial peritonitis. Just like the neutrophile count, these markers can be easily measured at the patient's bedside after entering clinical practice. Since we provide high specificity and sensitivity for these parameters in our study, we think that these studies can be used in the clinical practise with the support of future studies.

Conflict of Interest

The authors declare there are no conflicts of interest.
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