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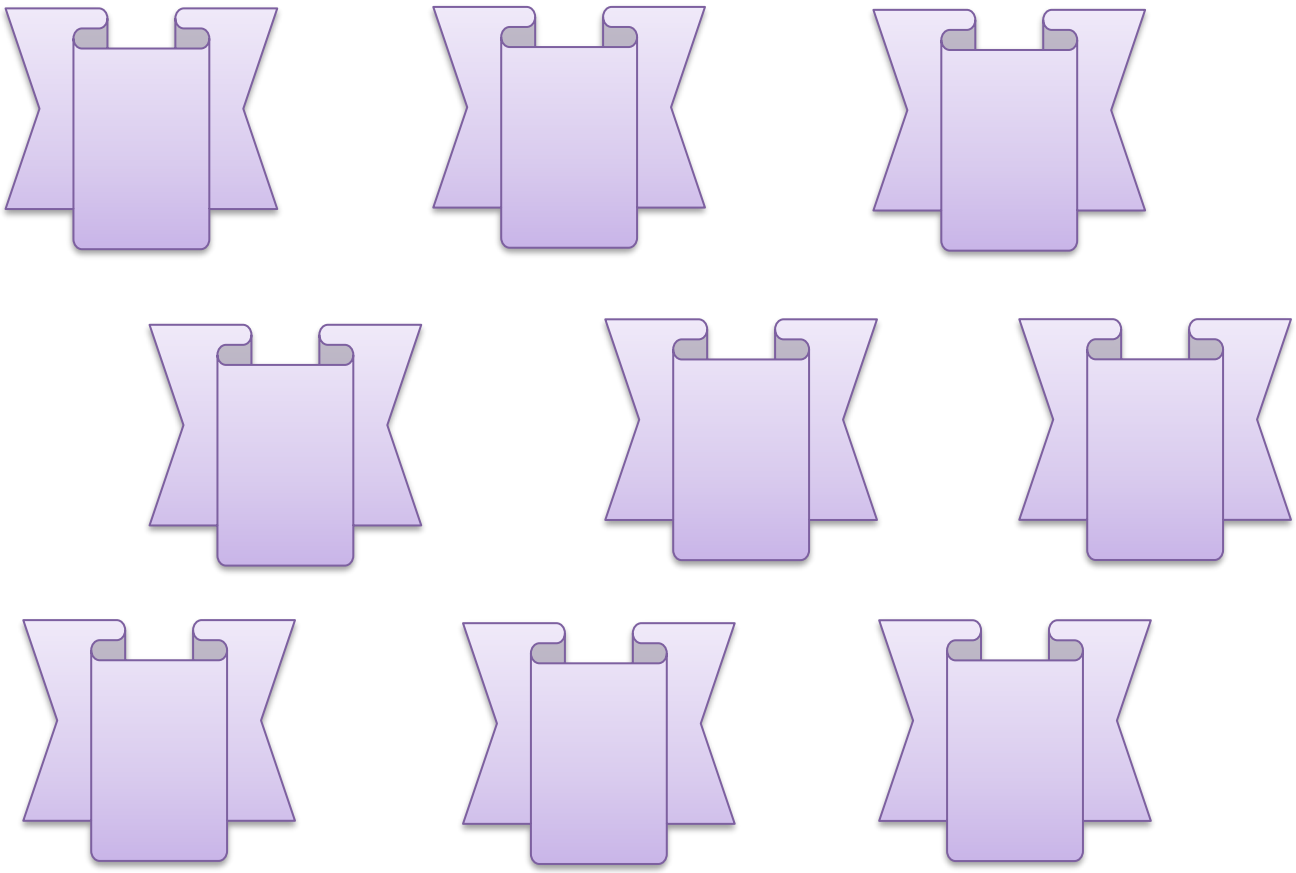

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Original Article

Diagnostic Value of Ascitic Endocan in Spontaneous Bacterial Peritonitis

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ABSTRACT

Background: Endocan is a potential marker of many immune-inflammatory conditions. It may be linked to liver cirrhosis. Increased endocan levels is linked to liver diseases [e.g., chronic hepatitis] which could be developed to liver decompensation and may be elevated in ascetic fluid.

Aim of the work: The current work aimed to evaluate the role of ascetic endocan in the diagnosis of Spontaneous Bacterial Peritonitis [SBP] among patients with decompensated cirrhosis.

Patients and Methods: In this cross-sectional study, 100 patients with cirrhotic ascites were selected from patients who were admitted to Nasser institute and Al-Azhar University Hospitals during the period from April 2022 to April 2023. All patients were assessed on a clinical basis, and laboratory investigations were performed. The ascetic levels of endocan were measured and compared between groups.

Results: Both groups were comparable regarding patient demographics. All patients in non-SBP had negative culture, while 12 patients in SBP group had positive results [10 of E-Coli, one Klebsiella and one Streptococcus viridans]. The major cause of cirrhosis in both groups was the HCV [76% of SBP compared to 80% of the non-SBP group]. The endocan levels showed a significant increase in the SBP than the non-SBP groups [5.20±1.80 vs 2.96±1.80 ng/ml]. Endocan significantly and positively correlated with each of TLC, AST, ALT, creatinine, albumin, bilirubin, INR, CRP, HBsAg and HCV antibodies. The hazardous ratio [HR] for endocan was 1.644 [95% CI: 1.011 – 2.707]. The endocan is also predictive of SBP development with an HR 1.673 [95% CI:1.031 – 2.806].

Conclusion: Ascetic Endocan is increased in ascitic fluid and represents an independent risk factor for SBP, with a significant diagnostic value in patients with decompensated cirrhosis.

Keywords: Ascites; Endocan; Spontaneous Bacterial Peritonitis.

INTRODUCTION

Cirrhosis is the end stage of chronic liver damage due to different conditions. It is characterized by fibrosis, with consequent distortion and destruction of the normal architecture of the liver [1]. Spontaneous bacterial peritonitis [SBP] leads to a high mortality. In patients with cirrhotic liver, associated infections are responsible for a 4-fold increase in mortality [2]. SBP is the most common infection in patients with decompensated liver cirrhosis and ascites. It accounts for 10%–30% of overall bacterial infections in hospitalized patients with liver cirrhosis. Early detection of SBP is of crucial importance for management and outcome of the condition [3].

Endocan is a known endothelial cell-specific molecule1 [ESM-1], soluble, 50-kDa proteoglycan. It is produced by the activated endothelial cells. It plays a pivotal role in regulation of cell adhesion, inflammation, and tumor progression [4].

In patients with bacteremia, serum levels of endocan are significantly higher than healthy control subjects. Moreover, higher serum levels of endocan were reported in sepsis, suggesting that it is involved in the body's natural anti-inflammatory response. Thus, it may be a new biomarker for the severity and prognosis of sepsis [5]. In addition, serum endocan may be considered as a biomarker of infection in patients with decompensated liver cirrhosis. However, the endocan status in ascites remains unclear [6]. Thus, this study aimed to assess the role of ascetic endocan in the diagnosis of SBP among patients with de-compensated cirrhosis.

PATIENTS AND METHODS

In this cross-sectional study, 100 patients with cirrhotic ascites were selected from ascites patients who were admitted to Nasser institute and Al-Azhar University Hospitals during the period from April 2022 to April 2023. Two group of patients were selected; group [1] consisted of 50 patients with SBP diagnosed after ascetic fluid analysis to have polymorpho-nuclear leucocyte [PMNL] cells more than 250 as the SBP group and group [2] consists of 50 ascetic patients with free ascetic fluid of PMNL as the non-SBP group.

Patients are 18-80 years old and patients with cirrhotic ascetics only were included. Patients diagnosed with infection other than SBP, non-cirrhotic ascites, patients who refused to be enrolled in the study and patients of SBP managed with antimicrobial drugs within the last two weeks were excluded.

The protocol was seeking approval from the Ethical Committee of Al-Azhar University, Faculty of Medicine. A written informed consent from the caregivers and an assent from patient was taken before starting the study.

Laboratory investigations included complete blood count [CBC], erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], urine analysis, liver function tests, prothrombin time [PT], International normalization ratio [INR], partial thromboplastin time [PTT], serum creatinine, blood urea, Hepatitis C virus antibodies, [HCVab], Hepatitis B virus Antigens [HBsAg] and Alpha-fetoprotein.

Ascetic fluid samples were collected in serum separator tubes and were allowed to clot for 30 minutes before centrifugation for 10 minutes at 3000×g. Serum was removed and samples were stored at -20 °C. Endocan levels were determined by reagents for human Endocan ELISA Kit Cat.No.ESM1 [USCN, Wuhan, China].

Statistical methods: Collected data were coded, fed to computer and statistically analyzed using statistical package for social science [SPSS] version 27 [IBM Inc., USA]. All numeric data were expressed in the form of range [minimum to maximum], mean and standard deviation [SD], and student -t test was used to compare between groups. On the other side, categorical data were presented by the relative frequency and percentages and groups compared by Chi square test or Fisher-Exact test. $P < 0.05$ was set as the margin of significance.

RESULTS

Table [1] represented the distribution of the study groups according to patient age and gender. Males represented 50% of the SBP group, compared to 46% of the non-SBP group, with no significant differences between groups regarding age or sex distribution.

The results of ascitic fluid culture revealed that all patients in Non-SBP group were negative compared to 76% of the SBP group.

The positive 12 patients in the SBP groups were 10 of E-Coli, one with Klebsiella and one patient with Streptococcus viridans, and there was significant difference between groups [Table 2].

The major cause of cirrhosis in both groups was the HCV [76% of SBP compared to 80% of the non-SBP group]. Other minor causes were HBV, AIH and the causes could not be detected in 12% in SBP compared to 8.0% of the non-SBP, with non-significant difference between groups [Table 2].

The endocan levels ranged between 0.7 to 6.7 ng/ml and there was a significant increase of endocan in SBP than the non-SBP groups [5.20±1.80 vs 2.96±1.80 ng/ml, respectively] [Table 3].

The correlation analysis revealed significantly proportional [positive] correlation between endocan from one side and each of TLC, AST, ALT, creatinine, albumin, bilirubin, INR, CRP, HBsAg and HCV antibodies [Table 4].

Serum levels of INR, HBV, HCV and CRP were not associated with the development of SBP. However, serum levels of endocan were correlated with markers of liver function. We do a Cox proportional regression analysis. The hazard ratio [HR] for endocan was 1.644 [95% CI: 1.011 – 2.707]. The endocan was also a predictive marker of the development of SBP with HR of 1.673 [95% CI: 1.031 – 2.806] P = 0.007 in univariate analysis. In multivariate analysis, the HR of the endocan was 1.634 [95% CI: 1.012 – 2.638; P = 0.047] [Table 5].

Table [1]: Distribution of study groups according to patient age and gender

	Demographic Data	SBP Group [n=50]	Non-SBP Group [n=50]	T test	P value
Age [years]	Mean ± SD	56.10±8.60	53.18±7.79	1.828	0.07
	Min. – Max.	25 - 82	28 - 67		
Sex [n, %]	Male	25 [50%]	23 [46%]	0.160	0.42
	Female	25[50.0%]	27[54.0%]		

Table [2]: Distribution of study groups according to the results of the culture and cause of cirrhosis

		SBP Group [n=50]	Non-SBP Group [n=50]	Test	p
Culture [n, %]	Negative	38 [76%]	0 [0%]	13.63	**0.003***
	Escherichia Coli	10 [20%]	0 [0%]		
	Klebsiella	1 [2%]	0 [0%]		
	Staphylococcus aureus	0 [0%]	0 [0%]		
	Streptococcus viridans	1 [2%]	0 [0%]		
Cause of Cirrhosis [n, %]	HCV	38 [76%]	40 [80%]	0.451	0.929
	HBV	5 [10%]	5 [10%]		
	AIH	1 [2%]	1 [2%]		
	Undetected	6 [12%]	4 [8%]		

Table [3]: Distribution of the study groups regarding levels of endocan

Endocan Level	SBP Group [n=50]	Non-SBP Group [n=50]	T test	P value
Mean ± SD.	5.20±1.80	2.96±1.80	6.90	<0.001*
Min. - Max	0.7 - 6.7	0.9 – 6.0		
Median	2.88	2.2		

Table [4]: Correlation between inflammatory indicators and Endocan level

	Endocan Level	
	r	**P value**
TLC	0.471	0.0001*
AST	0.602	0.0001*
ALT	0.541	0.0001*
Creatinine	0.226	0.0001*
Albumin	0.250	0.003
Bilirubin	0.440	0.0001*
INR	0.210	0.0001*
CRP	0.320	0.0001*
HBs	0.520	0.0001*
HCV	0.430	0.0001*

Table [5]: Univariate and Multivariate of SBP group

	Univariate			Multivariate		
	HR	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Age	0.835	0.482 – 1.446	0.519	–	–	–
TLC %	2.807	1.619 – 4.865	0.001	2.527	1.452 – 4.398	0.01
AST	2.525	1.179 – 5.504	0.001	2.471	1.154 – 5.290	0.01
ALT	2.093	1.072 – 4.112	0.002	2.482	1.134 – 5.412	0.023
Endocan	1.703	1.467 – 1.976	0.001	1.634	1.012 – 2.638	0.047
Platelet count	0.785	0.903 – 1.045	0.446	–	–	–
INR	1.878	0.580 – 6.077	0.293	–	–	–
HCV	1.632	0.670 – 3.932	0.294	–	–	–
HBV	1.021	0.582 – 1.816	0.934	–	–	–
CRP [mg/L]	1.025	0.951 – 1.092	0.584	–	–	–

DISCUSSION

Endocan is a new biomarker of sepsis, and it reflects the magnitude of endothelial cell activation and injury. It is involved in the body's natural anti-inflammatory response [7]. Hence, this study assessed the role of ascetic endocan in the diagnosis of SBP among patients with decompensated cirrhosis. We found no differences between SBP group and Non-SBP group regarding demographic data, clinical findings, laboratory investigations. However, Endocan ascetic levels was high in SBP patients.

Kartik *et al.* [8] study included 330 patients with liver cirrhosis and there was 181 with SBP and 149 non-SBP; with male to female ratio 82:99, respectively. The average age was 57 [49 - 69] years for SBP and 65 [57 - 70] for Non-SBP. In addition,

Sigirici *et al.* [9] concluded that there were no significant differences in age, gender, and cause of cirrhosis between the SBP and Non-SBP groups.

Furthermore, **Zhang *et al.*** [10]**,** as in the current work, found no significant differences between SBP and non-SBP groups regarding results of the laboratory investigations. However, **Sun *et al.*** [11] reported contradictory result regarding laboratory investigations, where there was a significant difference between the SBP and the non-SBP group. The values of ascitic endocan fluid level and liver function tests were significantly higher in the SBP group than in the non-SBP group. This could be attributed to different inclusion and exclusion criteria.

As in the current study and regarding endocan levels, **Zuwala-Jagiello *et al.*** [6] reported that, the level of ascitic endocan levels in the SBP group was significantly higher than in the non-SBP group [$p < 0.001$]. **Sigirici *et al.*** [9] indicated that ascitic endocan levels are highly accurate and sensitive for the diagnosis of SBP in patients with decompensated cirrhosis.

In the study of **Kartik *et al.*** [8] reported that ascitic TNF-α, IL-6, and endocan were significantly positively correlated with ascitic total leucocytic count [TLC]. **Sigirici *et al.*** [9] also showed a significant positive correlation of ascitic endocan with ascitic IL-6, ascitic AST [$p < 0.001$, $r = 0.385$], serum TLC [$p < 0.001$, $r = 0.230$], and serum CRP [p 0.011, $r = 0.250$]. **Boaretti *et al.*** [12] run a multivariate analysis by binary logistic regression model and showed that endocan levels in ascitic fluid were independent risk factors for SBP and that the higher the concentration, the greater the likelihood of SBP occurrence. In another study, **Zhang *et al.*** [10] run a uni- and multi-variate analysis and observed that endocan levels are elevated in liver dysfunction. Endocan ascetic fluid levels may be an independent prognostic biomarker of infection and mortality in patients with liver cirrhosis and liver cancer.

On the other side, **Boaretti *et al.*** [12] reported that the endocan ascetic fluid levels of SBP was lower in comparison to control healthy group. This could be attributed to the different inclusion criteria.

In conclusion, the current work showed that ascitic endocan level is an independent risk factor for SBP and has a high diagnostic value for detection of SBP in patients with decompensated cirrhosis. We found that

cirrhotic patients with high endocan ascetic fluid levels had a higher risk of developing SBP. However, the small sample size represented a limiting step of the current work. Thus, the results must be treated with caution and future studies are recommended.

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