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Original Article

SERUM AND ASCITIC FLUID HIGH SENSITIVE C REACTIVE PROTEIN AS PROGNOSTIC MARKER IN PATIENTS WITH SPONTANEOUS BACTERIAL PERITONITIS

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ABSTRACT

Background: Spontaneous Bacterial Peritonitis (SBP) is the most frequent bacterial infection in cirrhotic patients with ascites. The mortality rate in those patients ranges from 40-70%. Aim: to assess level of serum and ascetic fluid polymorph nuclear leucocytes (PMN), high sensitive C reactive protein (hs-CRP) in patients with SBP before and after treatment. **Methods**: A cohort study was done on 114 patients SBP admitted in the Internal Medicine, Faculty of Medicine, Zagazig University during the period from December 2017 to September 2018. All patients were subjected to full history taking, thorough clinical examination, routine laboratory investigation, ultrasonography and ascitic fluid sampling. They was followed up for 5 days from starting treatment by parenteral third generation cephalosporin and peripheral blood (PMN), serum (hs-CRP), ascitic fluid PMN and hs-CRP were measured again.

Results: the largest percentage of the patients were male, had posthepatitic C cirrhosis and child C score. There was statistically non-significant difference between antibiotic responders and non-responders regarding peripheral blood PMN before or five days after antibiotic use. There was statistically non-significant difference in ascitic fluid PMN, serum and ascitic fluid hs-CRP before treatment while the difference is significant between both groups regarding them five days after treatment. Percent change in serum hs-CRP was equal to that of ascitic fluid PMN. Percent change in ascitic fluid hs-CRP was comparable to that of ascitic fluid PMN. **Conclusion:** Serum and ascitic fluid hs-CRP level can be considered as alternative prognostic markers in cirrhotic patients with SBP.

Keywords: Spontaneous Bacterial Peritonitis**,** Ascitic fluid, hs-CRP

INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is the development of a bacterial infection in the peritoneum leading to peritonitis, in spite of the absence of an obvious cause for the infection. It occurs almost wholly in patients with portal hypertension; frequently due to liver cirrhosis [1].Gram-negative bacteria is the most common organism that causes SBP. The most commonly isolated species ascitic fluids are E.coli and klebsiella. Gram-positive cocci species such as streptococci and staphylococci have traditionally been responsible for less than 25% of SBP cases though the incidence of such

cases has been increasing. Anaerobic and fungal infections of the ascitic fluid are uncommon but have been reported [2].

In people with ascites, the incidence may be as high as 18%. No compete predilection is known for SBP [3].

Patients, at elevated risk for developing SBP, are those with decompensated liver cirrhosis, low complement levels[4], low ascitic fluid protein level (< 1 g/dL), high serum bilirubin level and serum albumin level less than 2.85 g/dL [5], variceal hemorrhage [2] using proton pump inhibitors (PPI) [6] or beta-adrenergic antagonists [7].

Hs-CRP is the same gracefully sensitive and totally nonspecific marker for systemic infection, inflammation, tissue damage and/or almost any form of poor non-physiological stress [8].

The high-sensitivity CRP assay can detect much lower levels of CRP than the traditional methods, so it was reported that serum levels of hs-CRP were significantly higher in patients with SBP than in those with sterile ascitic fluid [9].

This study aims to establish the role of hs-CRP in serum and ascitic fluid as a prognostic marker for eradication of SBP.

SUBJECTS AND METHODS

A clinical based Prospective cohort study was adopted. The study was carried out in collaboration between the Internal Medicine and Clinical Pathology Departments, Faculty of Medicine, Zagazig University, during the period from December 2017 to September 2018.

Study population:

Assuming that ascetic fluid level of hs-CRP in SBP patients before treatment is 77.2±45.0, after treatment 56.0±35.0, confidence level 95%, power 80%, so total sample size is 114 patients calculated by open Epi.

Inclusion criteria

- Male and female patients with decompensated cirrhosis with ascites and diagnosed as having SBP

Exclusion criteria

- Patient with Coronary artery diseases
- Patient with Collagen vascular disorders or any form of acute arthritis.
- Patient with Ascites who did not have the criteria of SBP
- Patient with other causes of elevated hs-CRP as acute infections or septicemia.
- Patient refused to participate in the study.

Diagnosis of liver cirrhosis: was done by physical signs, laboratory and ultrasound findings and severity of the liver disease was scored according to Child–Pugh's classification.

Case definition of SBP: patients had PMN≥ 250 in ascitic fluid sample.

Methods:

All subjects of the study were subjected to the following:-

A- Full history taking:

This included history of abdominal pain, fever, deterioration of conscious level, paracentesis or abdominal operation.

B- Clinical examination: including

The presences of stigmata of liver cirrhosis, jaundice, ascites, lower limb edema or hepatic encephalopathy…etc.

C-Routine investigations:

They were done according to the methods applied in the laboratories of zagazig university hospitals and included:

1- Complete blood picture (by automated blood counter).

2- Liver function tests: serum bilirubin (total and direct), serum albumin, serum ALT and AST measured by kinetic method

3- Renal function tests: serum creatinine, urea.

4- Coagulation profile: PT, PTT and INR.

D-Radiology investigations:

Ultrasonography for diagnosis of cirrhosis as a shrunken liver (small and nodular), enlarged spleen (splenomegaly) and portal hypertension (dilated portal vein, hilarvarices).

E- Special investigation: included

* 3cm blood was taken; serum was isolated and used for measuring serum high sensitive CRP

* Ascitic fluid sample containing 10cm by paracentesis with all aseptic precautions for

1. Diagnostic tests of SBP: white blood cell counts (PMN), protein, LDH
2. Ascitic fluid high sensitive CRP The hs-CRP ELISA is based on the principle of a solid phase enzyme- linked immunosorbent assay [11].

Follow up: After 5 days from starting treatment of SBP by ceftriaxone 2g/24h or cefotaxime 2g/8h, peripheral blood total leucocytic count, serum hs-CRP, ascitic fluid PMN and hs-CRP were measured again.

Administrative and ethical design:

- The study protocol was approved from the ethical committee at faculty of medicine, Zagazig University and institutional review board.
- The necessary official permissions to carry out the study were obtained from the managers of the Internal Medicine and Clinical Pathology Departments, faculty of Medicine, Zagazig University. The objectives of this study were explained to them to ensure their cooperation.
- An informed consent was obtained from all participants in this study.
- The work should be carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis

All data were collected, tabulated and statistically analyzed using SPSS 20.0 for windows (SPSS Inc., Chicago, IL, USA) and MedCalc 13 for windows (MedCalc Software bvba, Ostend, Belgium). Quantitative data were expressed as the mean ± SD & median (range), and qualitative data were expressed as absolute frequencies (number) & relative frequencies (percentage). Continuous data were checked for normality by using Shapiro Walk test. Mann-Whitney U was used to compare two groups of non-normally distributed data. Wilcoxon signed rank test was used to compare paired data in responders and non-responders. Spearman's rank correlation coefficient was calculated to assess correlations between study parameters. All tests were two sided. P-value < 0.05 was considered statistically significant (S), p-value < 0.001 was considered highly statistically significant (HS).

RESULTS

The highest percentage of studied patients are males (52.6%) with mean age 58.8 years old (±SD 5.12) ranging from 48 to 68 years old. The highest percentage of studied patients had post hepatitis C cirrhosis and belonged to Child C class (table 2).

The highest percentage of studied patients showed improvement in response to treatment on the fifth day (table 3).

Regarding TLC, there are statistically non-significant differences between responders and non-responders before and five days after treatment. On studying change over time in each group, non-responders showed statistically significant increase in TLC after treatment (table4)

PMN in peripheral blood and ascitic fluid before and after treatment

There are statistically non-significant differences between responders and non-responders before and five days after treatment in peripheral blood PMN. On pair wise comparison of PMN levels in each group, there is no significant change over time (table 5).

Regarding ascitic fluid PMN, there is statistically non-significant difference between responders and non-responders before treatment, while there is statistically significant difference between them five days after treatment. On studying change over time in each group, responders showed statistically significant decline in ascitic fluid PMN after treatment while non-responders showed statistically significant increase in ascitic fluid PMN (table 5).

Hs-CRP in peripheral blood and ascitic fluid before and after treatment

Regarding serum hs-CRP, there is statistically non-significant difference between responders and non-responders before treatment while there is statistically significant difference between them five days after treatment. On studying change over time in each group,

responders showed statistically significant decline in serum Hs-CRP after treatment while non-responders showed statistically significant increase in serum Hs-CRP (table 6).

Concerning ascitic fluid Hs-CRP, there are statistically non-significant differences between responders and non-responders before treatment, while there is statistically significant difference between them five days after treatment. On studying change over time in each group, responders showed statistically significant decline in ascitic fluid hs-CRP after treatment while non-responders showed statistically significant increase in ascitic fluid Hs-CRP (table 6).

Percent change in peripheral blood and ascitic fluid PMN and hs-CRP in the studied patients:

Regarding serum, ascitic fluid HS-CRP and PMN, there are statistically significant differences in percent change between responders and non-responders. All of these parameters significantly decreased in responder group making them reliable as prognostic parameters in contrast with peripheral blood PMN, which doesn't significantly differ between both groups (table 7).

Table 1 Child Pugh score parameters**:**

Parameters	1 point	2 points	3 points
Serum bilirubin total (mg/dL)	<2	2-3	> 3
Serum albumin (mg/dL)	>3.5	2.8-3.5	<2.8
INR*	<1.7	1.71-2.30	>2.30
Ascites	None	Suppressed with medication	Refractory
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

*INR: International Normalized Ratio; Child-Pugh A=5-6 points, Child-Pugh B=7-9 points, Child-Pugh C=10 or more points [10].

Table 2 Distributions of studied patients according to demographic **Characteristics, cause of cirrhosis and Child classification:**

	N (%)
Gender:	
Male	60 (52.6)
Female	54 (47.4)
Cause:	
Hepatitis B	3 (2.6)
Hepatitis C	108 (94.7)
Combined B and C	2 (1.8)
Unknown etiology	1 (0.9)
Child Pugh classification:	
A	0 (0)
B	19 (16.7)
C	95 (83.3)
Age (years):	
Mean ± SD	58.8 ± 5.12
Range	48 - 68

Table 3 Response to treatment in studied patients:

	N (%)
Response to treatment: Yes No	 102 (89.5) 12 (10.5)

Table 4 Change in TLC in before and after treatment in the studied patients:

	Responder		**Non responder**		**Z**	p
	Mean ± SD	**Median**	**Mean ± SD**	**Median**		
Peripheral blood: Before After	 5808.33± **2005.2** **8366.67±5020.2**	 4500 4950	 5776.77 ± **4069.8** **5843.14 ± 353.47**	 7000 8050	 -0.582 -1.608	 0.560 0.108
Wx	-1.654		-2.112			
p	0.098		0.035			

Table 5 Change in PMN in peripheral blood and ascitic fluid before and after treatment in the studied patients:

	Non responder		**Responder**		**Test**	p
	Mean ± SD	**Median**	**Mean ± SD**	Median		
peripheral blood: Before After %change	 3541.67±**1258.58** **5051.67±3857.76** **78.54%**	 4200 4200	 3592.55±**2460.32** **3975.78±2584.98** **18.58%**	 2650 3100	 -0.55 -0.22	 0.579 .0.825
Wx	-0.157		-1.058			
p	0.875		0.132			
Ascitic fluid: Before After % change	 2701.67±**4071.23** **4403.33±4310.8** **341.72%**	 540 2900	 3613.24±**357.76** **764.67±1017.43** **-77.82%**	 3250 210	 -1.45 -4.21	 0.144 <0.001**
Wx	-3.072		-8.769			
p	0.002		<0.001			

Table 6 Change in Hs-CRP in serum and ascitic fluid before and after treatment in the studied patients:

	Non responder		**Responder**		**Test**	p
	Mean ± SD	**Median**	**Mean ± SD**	Median		
Serum: Before After %change	 41.17 ±**25.23** **139.22±148.67** **341.72%**	 30.7 80.5	 73.73 ± **69.61** **19.34 ± 28** **-77.82%**	 55.62 9.91	 -1.718 -4.627	 0.086 <0.001**
Wx	-3.072		-8.745			
p	0.002		<0.001			
Ascitic fluid: Before After % change	 12.9 ± **5.1** **35.3 ± 14.08** **200.81%**	 10.75 30.54	 16.34 ± **23.73** **2.43±2.34** **-69.66%**	 9.45 1.435	 -1.219 -5.653	 0.223 <0.001**
Wx	-3.072		-8.608			
p	0.002		<0.001			

Table 7 Percent Change in PMN and Hs-CRP in serum and ascitic fluid before and after treatment in studied patients:

	Non responder		**Responder**		**MW Test**	p
	Mean ± SD	**Median**	**Mean ± SD**	Median		
PMN						
Serum PMN:	78.54±**183.45**	43.04	18.58 ± **139.48**	0.74	-0.923	0.356
Ascitic fluid	**341.71±480.18**	85.19	-77.82 ± **10.26**	-78.44	-5.562	<0.001**
HS-CRP						
Serum	341.71 ±**480.18**	85.19	-77.82 ± **10.26**	-78.44	-5.562	<0.001**
Ascitic fluid	200.81 ±**148.96**	113.27	-69.66 ± **41.89**	-84.45	-5.486	<0.001**

DISCUSSION

Ascites is the most common complication of liver cirrhosis. About 50% of the patients will develop ascites within ten years from the first diagnosis [12]. Cirrhotic ascites forms as the result of a particular sequence of events. Development of portal hypertension is the first abnormality to occur. Hypoalbuminemia and decreased plasma oncotic pressure direct fluid to extravasate from the plasma to the peritoneal fluid and thus ascites is infrequent unless both hypoalbuminemia and portal hypertension co-exist [4].

Spontaneous bacterial peritonitis (SBP) is the most common infection in patients with cirrhosis [13]. It is also the most common infection responsible for sepsis-induced acute-on-chronic liver failure [14].

The diagnosis of SBP is based on a PMN leukocyte count (PMN >250/mm3) in ascitic fluid. The diagnosis of SBP (based on a PMN >250/mm3) does not take into account bacterial ascites, which is a variant of SBP where a single bacterial organism grows in ascitic fluid but the number of PMN is <250/mm^3 [14].

C-reactive protein (CRP) proved to be the most reliable marker in the identification of bacterial infection, but their diagnostic accuracy and the cut-off values were highly variable and sometimes unexpectedly high cut-off values were reported [15].

Role of hs-CRP as a marker of inflammation has been extensively studied in Coronary Artery Diseases (CAD). Apart from CAD, hs-CRP is also being studied in other conditions like chronic liver diseases, collagen vascular diseases and inflammatory arthritis. As far as liver diseases are concerned CRP and hs-CRP has been studied as an inflammatory marker in infective hepatitis, alcoholic liver diseases, cirrhosis and SBP. CRP levels increases in decompensated cirrhosis and infections in cirrhosis [16]. Abdel-Razik et al. [17] found that CRP is increased in cirrhotic patients with ascitic fluid infection (AFI).

So, in this work, we tried to establish the role of hs-CRP in serum and ascitic fluid as a prognostic marker for eradication of SBP. This clinical-based prospective cohort study involved 114 patients with liver cirrhotic ascites and spontaneous bacterial peritonitis referred to the Internal Medicine and Clinical pathology Departments, Faculty of Medicine, Zagazig University during the period from December 2017 to September 2018.

The study objectives were to assess level of serum and ascetic fluid PMN in patients with SBP before and after treatment and also, to assess level of serum and ascitic fluid of high sensitive c reactive protein in cirrhotic patient with SBP before and after treatment.

By the end of this study, we concluded that serum and ascitic fluid hs-CRP significantly changed after starting antibiotic therapy. They can be used as an alternative to ascitic fluid PMN to diagnose antibiotic response.

In this study, the highest percentage of studied patients was males with mean age 58.8 years old (table 2).

In the current study, patients suffered from liver cirrhosis with different etiologies mainly post hepatitis C cirrhosis and had child C (table 2).

This comes in harmony with the highest incidence and prevalence of hepatitis C in

Egypt making it the most common cause of cirrhosis among Egyptian patients.

In agreement with our findings, **Rizk et al. [18]** in Mansoura University, found that out of their patients, 96% had post hepatitis C and B infection. Yet, in disharmony with ours, 71% of the patients were classified as stage B.

In disagreement with this study, **Kadam et al. [19] in India,** found that about three quarters of their patients had post alcoholic cirrhosis followed by post hepatitis B (8%) then post hepatitis C (4%)

Preto-Zamperlini et al. [20] reported a significant elevation of CRP in serum in patients with SBP, leading to the conclusion that CRP was an independent variable in the prediction of SBP.

Also, in study by **Yildirim et al. [21], Rizk et al. [18]**, it was found that CRP was increased in the serum of SBP patients.

Based on this point, we started to investigate the role of change of hs-CRP in diagnosis of drug response.

In our study, regarding total leucocytic count (TLC) in peripheral blood, there were statistically non-significant differences between responders and non-responders before and five days after treatment making TLC a less sensitive follow up marker for diagnosis and prognosis of SBP (table 4).

Regarding peripheral blood PMN, there were statistically non-significant differences between responders and non-responders before and five days after treatment.

Concerning ascitic fluid PMN, there is statistically non-significant difference between responders and non-responders before treatment. Five days after treatment, the responders showed statistically significant decline in ascitic fluid PMN after treatment while non-responders showed statistically significant increase in ascitic fluid PMN (table 5).

On measuring serum hs-CRP, there was statistically non-significant difference between responders and non-responders before treatment while five days after treatment, responders showed statistically significant decline in serum hs-CRP after treatment and non-responders showed statistically significant increase in serum hs-CRP (table 6).

There was statistically significant decrease in the mean serum hs-CRP level two days after antibiotic therapy in responders (table 6)

Regarding asascitic fluid hs-CRP, there were statistically non-significant differences between responders and non-responders before treatment. Five days after treatment, responders showed statistically significant decline in ascitic fluid hs-CRP after treatment (while non-responders showed statistically significant increase in ascitic fluid hs-CRP (table6).

On measuring percent change in peripheral blood PMN, it was found to be increasing in non-responders and also increasing yet to a less extent in responders. Concerning serum hs-CRP, ascitic fluid PMN, both had been decreasing in responders to the same levels making serum hs-CRP an alternative to ascitic fluid PMN in diagnosis of drug response. Also ascitic fluid CRP had decreased to a level comparable to ascitic fluid PMN which made it a reasonable alternative in diagnosis as well (table 7)

Our results came in agreement with **Guler et al. [22]** who studied serum hs-CRP level in cases of SBP and compared serum hs-CRP levels two days after standard antibiotic treatment.

Our results were near to results of **Kadam et al. [19]** who found that the mean level of ascitic fluid hs-CRP before antibiotic therapy of the patients with SBP was significantly higher than the mean level of hs-CRP of the cirrhotic patients without spontaneous bacterial peritonitis. The mean level of ascitic fluid hs-CRP at 5th day after initiation of antibiotic therapy was significantly lower than that of level of hs-CRP before initiation of antibiotic therapy. Thus, significant reduction in level of hs-CRP was observed. The mean ascitic fluid hs-CRP level in the patient, who died and in the patient who had prolong hospital stay more than two weeks was also significantly higher than the mean ascitic fluid hs-CRP level of the

controls, again emphasizing the prognostic significance of hs-CRP.

All of these parameters significantly decreased in responder group making them reliable as prognostic parameters

In old study by **Runyon et al. [23]** who tested ascitic fluid and serum specimens for C-reactive protein (CRP) concentrations. The ascitic fluid CRP concentrations of patients with sterile portal hypertension-related ascites were not significantly different from those of infected specimens. However, the serum CRP values were significantly higher in patients with peritonitis than in patients with sterile portal-hypertension-related ascites. Ascitic fluid CRP did not appear to be a useful indicator of ascitic fluid infection; this may be due to the use of laser nephelometry in measuring the level of CRP (less accurate than hs-CRP).

So, in this study, we prove the prognostic role of serum hs-CRP which can be used as an alternative to ascitic fluid PMN, which is by far less invasive and painful. This study differ from other previous studies in (CRP not hs-CRP which is more accurate in little elevation, some study discussed hs-CRP in ascitic fluid only).

This study had some strength points. The first that good randomizations led to statistically non-significant difference between responders and non-responders concerning study parameters making drug used is the only responsible factor for any change and removing possible confounders. The second, the nature of the study as prospective ones exclude any possible recording or recalling bias.

Yet, it had some limitations; it is performed in a single center and relatively small sample size. We recommend further large scale multicentric prospective studies to validate our findings.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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