Acute Phase Inflammatory Markers and Clinical Parameters in Chronic Liver Disease Egyptian Patients

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Abstract: Introduction: Significant proportion of cirrhotic patients even without infection show elevated levels of several acute phase proteins (APPs). Bacterial infections especially spontaneous bacterial peritonitis (SBP) is a common cause for hospitalization in patients with liver cirrhosis. A hypothetic relationship between APPs and infection in liver cirrhosis needs further validation. **Aims/Methods**: To evaluate inflammatory response markers (APPs) in chronic liver diseases with emphasis on their correlation with bacterial infections such as SBP. This study was conducted on 100 subjects at National Liver Institute, Menoufia University, Egypt. Subjects were recruited in the study according to pre-defined selection criteria and were divided into 4 groups: A (25 normal subjects or Controls), B (25 patients with chronic liver diseases ± liver cirrhosis), C (25 patients with liver cirrhosis and ascites), D (25 patients with liver cirrhosis, ascites and SBP). Subjects were subjected to thorough history taking, complete clinical examination and to laboratory tests: complete blood count, urine analysis, stool analysis, bilirubin (total and direct), total protein, albumin, AST, ALT, alkaline phosphatase, gamma glutamyltranspeptidase (GGT), prothrombin time, prothrombin concentration, international normalized ratio (INR), urea, creatinine, random blood glucose, viral markers: Hepatitis B Surface Antigen (HBs-Ag), Hepatitis C Virus Anti-body (HCV-Ab), sodium, potassium, erythrocyte sedimentation rate (ESR), C-reactive protein level (CRP), fibrinogen, ferritin, haptoglobin, ascetic fluid analyses. Abdominal ultrasound and chest x-ray. Child-Turcotte-Pugh (CTP), APACHE II (Acute Physiology and Chronic Health Evaluation), MELD (Model for End-Stage Liver Disease), Glasgow Coma Scale (GCS) were calculated. **Results**: CRP among the examined APPs seems to be the best test to discriminate bacterial infection in cirrhotic patients. However, a new threshold of >1.3 mg/dl should be applied (AUC 0.86). Ferritin is increased in cirrhotic patients even without infection but significantly rise with infection (AUC 0.85). Haptoglobin and fibrinogen levels declined according to the progression of cirrhosis. There is high significant difference of plasma APPs during infection and after resolution of SBP. Ascetic fluid culture and sensitivity in group D showed 13 (52%) culture negative and 12 (48%) culture positive cases. Escherichia coli were the most common isolated organism (24%) in culture positive group. MELD, APACHE II, CTP scores were more severe in ascetic fluid culture positive than negative group. **Conclusions**: Culture positive ascetic fluid is a more severe variant than culture negative ascetic fluid as higher levels of APPs, and severe MELD, APACHE II, CTP scores were found. APPs; especially CRP are effective and reproducible markers of infection which can be used safely and repeatedly for diagnosis and follow-up of infection in cirrhotic patients.

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1.Introduction

Natural history of cirrhosis can be divided into a pre-clinical and a subsequent clinical phase. The pre-clinical phase is usually prolonged over several years; once clinical events occur, such as the development of portal hypertension, ascites, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy, variceal bleeding or hepatocellular carcinoma; the remaining course of the disease is much shorter and usually fatal ***(Durand and Valla, 2005)***.

Bacterial infections are common causes for hospitalization of patients with cirrhosis. SBP***(Terg et al., 2009)***, urinary tract infections, respiratory infections and bacteraemia are the most frequent infective complications in cirrhosis ***(Navasa and Rodés, 2004)***. The particular susceptibility of cirrhotic patients to such infections is related to the concomitant presence of various facilitating mechanisms, such as changes in the intestinal flora and intestinal barrier, reticuloendothelialdysfunction, decreased opsonic activity of the ascitic fluid and neutrophil leucocyte dysfunction. The above mechanisms are postulated to favour bacterial translocation in cirrhosis ***(Guarner and Soriano, 2005)***. Early and accurate diagnosis of infection is crucial in patients with liver impairment. One of the earliest signs of infection is the acute-phase response. Acute-phase responses may be divided into changes in the concentration of acute phase proteins (APPs)and a large number of behavioural, physiological and biochemical changes ***(Gabay and***

Kushner, 1999). APPsare synthesized exclusively in the liver almost glycosylated ***(Moshage, 1997)*** and can be divided into 2 subgroups. Type I proteins include: CRP, complement 3 (C3), serum amyloid A and are induced by interleukin-1-like cytokines. Type II proteins include: fibrinogen, haptoglobin, and α1-antitrypsin and are induced by interleukin-6-like cytokines ***(Baumann and Gauldie, 1994)***.A significant proportion of cirrhotic patients without infection show elevated levels of several APPs such as CRP, ferritin, haptoglobin even without infection. CRP, ferritin and β2-microglobulin significantly increase when cirrhotic patients are affected by bacterial infections, irrespective of the underlying cause of cirrhosis ***(Tsiakalos et al., 2009)***.

CRP was first described by *Tillet and Francis* in the early 1930s as an acute-phase protein that was thought to be produced exclusively by hepatocytes as part of the acute-phase response, but later studies suggest other sites of production, including coronary artery smooth muscle cells,inflamed kidneys, human neurons, and alveolar macrophages ***(Bota et al., 2005)***.

Haptoglobin (Hp) is an APP synthesized primarily by hepatocytes, and to a lesser extent in other tissues including lung, skin, spleen, and kidney under inflammatory conditions ***(Quaye, 2008)***. Hp modulates both innate and adaptive immune responses and has been demonstrated to bind activated neutrophils and to inhibit several of their functions ***(Rossbacher et al., 1999)***.Hp is haemoglobin (Hb)-binding serum protein. It is an acute phase protein synthesized mainly in the liver. Hp serum levels are increased during the acute phase reaction and in response to injury ***(Asleh and Levy, 2005)***. Hp plays an essential role in capturing free Hb, thus preventing its deposition in the glomeruli and proximal tubule cells of the kidney. Moreover, Hp functions as an anti-oxidant through its ability to bind Hb and thereby preventing oxidative tissue damage mediated by free Hb***(Miller et al., 1997)***.

Fibrinogen is an acute phase reactant, synthesized in the liver by hepatocytes and megakaryocytes. This protein helps to stop bleeding by helping blood clots to form as it is converted by thrombin into fibrin during blood coagulation. Fibrinogen concentrations may rise sharply in any condition that causes inflammation or tissue damage. Elevated concentrations of fibrinogen are not specific and do not tell about the cause or location of the disturbance. Usually these elevations in the fibrinogen blood level are temporary, returning to normal after the underlying condition has been resolved ***(Muszbek et al., 2008)***.

Ferritin concentrations increase drastically in the presence of an infection or cancer; this is necessary to counter the infective agent's attempt to bind iron from the host's tissue. Infective agents may cause ferritin to migrate from the plasma to within cells, in order to deny iron to the infective agent ***(Ong et al., 2005)***.

2. Methods

This prospective case-controlled study was conducted on 75 cases with chronic liver disease and liver cirrhosis at the National Liver Institute, Menoufia Universityin Egypt over 20 months period. 25 apparently healthy individuals served as a control group. Patients were recruitedaccording to pre-defined selection criteria. Inclusion criteria were established diagnosis of chronic liver disease±liver cirrhosis based on liver biopsy or on obvious clinical, endoscopic, biochemical or imaging features. Exclusion criteria were age <18 and >70 years old, ongoing cardiac failure, organic kidney disease, treatment for chronic obstructive pulmonary disease, Diabetes Mellitus, Hepatocellular carcinoma or extra-hepatic malignancy, use of nephrotoxic (e.g. Aminoglycosides) or hepatotoxic drugs, presence of infections other than SBP.

Cases were divided into 4 groups: A (25 normal subjects/Controls), B (25 patients who have chronic liver diseases ± liver cirrhosis), C (25 patients with cirrhosis and ascites), D (25 patients with cirrhosis, ascites and SBP).Patients in group D were assessed at the start and those who were diagnosed with SBP received standard treatment and re-evaluated after resolution of SBP.Patients were givenstandard anti-bacterial treatment for SBP in case of presence ofascitic fluid absolute polymorph-nuclear cells (PMNC)>250/mm^3.

After signing an informed consent; all participants (cases + controls) weresubjected to: thorough history taking, complete clinical examination, laboratory investigations (Complete Blood Count, Complete urine analysis, Stool analysis), liver function tests(Serum bilirubin (total and direct, Total protein, Serum albumin, AST and ALT, alkaline phosphatase, gamma glutamyltranspeptidase, prothrombin time and concentration and International normalized ratio [INR]), kidney function tests (urea, creatinine), randomblood glucose, viral markers: HBs Ag, HCV Ab., serum sodium and potassium, inflammatory markers (Erythrocyte Sedimentation Rate [ESR], CRP, Fibrinogen, Ferritin, Haptoglobin), Ascitic Fluid Analysis[Cytology] [PMNC], complete aseptic bed-side culture and sensitivity using blood culture technique was done using Hi Media Blood Culturing System), Radiological investigations (Real-Time Pelvi-Abdominal Ultrasound, Plain Chest X-Ray), Child-Turcotte-Pugh (CTP) ***(Pugh et al.,1973)***, APACHE II(Acute Physiology and Chronic Health Evaluation)***(Knaus et al.,1985)***, MELD (Model for

End-Stage Liver Disease)***(Kamath and Kim, 2007)***, Glasgow Coma Scale***(Weissenborn et al., 2001)***.

Statistical Procedures

Data was statistically analyzed using SPSS (statistical package for social science) program version 17 for windows and Epi-Data info program version; for all the analysis a *p* value <0.05 was considered statistically significant. Data were shown as mean, standard deviation (SD), range or value, 95% confidence interval (95% CI), frequency and percent. All data were tested with Kolmogorov-Smirnov Z test and most of them were found normally distributed and so presented with mean± SD using parametric tests on doing association or correlation.

3.Results

StudyBase-Line Characteristics (Table 1):

Group A:

25 normal subjects (Control). 12 (48%) were males and 13 (52%) were females. Their ages ranged from 22 to 55 years (38.9±10.12). Body mass index (BMI) ranged from 20 to 34 kg/m^2 (28.12±3.8).**Group B**: 25 patients who have chronic liver diseases±liver cirrhosis. 10 (40%) were males and 15 (60%) were females. Their ages ranged from 40 to 58 years (49.2±5.11). BMI ranged from 23to 33 kg/m^2(27.5±4.9).**Group C**: 25 patients with cirrhosis andascites. 14 (56%) were males and 11 (44%) were females. Their ages ranged from 27 to 63 years (50.9±9.3). BMI ranged from 21to 39 kg/m^2 (29.2±4.12). **Group D**: 25 patients with cirrhosis, ascites and SBP. 20(80%) were males and 5 (20%) were females. Their ages ranged from 41 to 63 years (53.1±7.2). BMI ranged from 20 to 36 kg/m^2 (28.5±3.19).

Table (1):**Demographic Characteristics**

Variable			*Group A (N=25)* Mean ± SD	*Group B (N=25)* Mean ± SD	*Group C (N=25)* Mean ± SD	*Group D (N=25)* Mean ± SD
Age (year)			38.9±10.12	49.2 ± 5.11	50.9 ± 9.3	53.1± 7.2
BMI			28.12±3.8	27.5 ± 4.9	29.2 ± 4.12	28.5± 3.19
Gender	Male	Number	12	10	14	20
		%	48	40	56	80
	Female	Number	13	15	11	5
		%	52	60	44	20

***Clinical Scores (Table 2)**:

CTPscore increased significantly in groups B, C and D (5.68±0.69, 11.8±2 and 13±1.41).

Similarly, there was an incremental value in MELD score (8.8±1.53, 16.64±7.62 and 20.64±5.65) in groups B, C, D respectively; with high statistically significant difference between groups BversusC, B and D (p-value <0.01); but there was no significant difference between groups CversusD (p-value >0.05).

Table (2): **Clinical Scores**

Score	*GroupB (N=25)*	*GroupC (N=25)*	*Group D (N=25)*	ANOVA test	p-Value	Post Hoc test
CTP	5.68±0.69	11.8±2	13±1.41	557.1	<0.01**	**p4= <0.01**** **p5= <0.01**** **p6= <0.01****
MELD	8.8±1.53	16.64±7.62	20.64±5.65	82.14	<0.01**	**p4= <0.01**** **p5= <0.01**** **p6= >0.05**

***Significant.** ** **Highly significant.**

p1= correlation between groupsA and B. **p2=** correlation between groups A and C.

p3= correlation between groups A and D. **p4**= correlation between groups B and C.

p5= correlation between groups B and D.**p6**= correlation between groups C and D.

Liver functions (Table 3):

Serum albumin was 4.92±0.47, 3.81±0.47, 2.31±0.56and1.94±0.28 gm/dLin groups A, B, C, Drespectively; while prothrombin concentration was 94.2±4.84, 75.88±9.87, 51.84±18.29 and 39.16±15.34% respectively.

There was a significant decrease in serum albumin and prothrombin concentration in decompensated cirrhosis groups (C and D) compared to controls (group A) and compensated cirrhotic patients (group B) (p-value <0.01).

Table (3): Liver functions

Variable	*GroupA (N=25)*	*GroupB (N=25)*	*Group C (N=25)*	*Group D (N=25)*	ANOVA test	p-Value	Post Hoc test
Serum Albumin (g/dl)	4.92±0.47	3.81±0.47	2.31±0.56	1.94±0.28	226.4	<0.01**	**p1= >0.05 p2= <0.01** p3= <0.01** p4= <0.01** p5= <0.01** p6= >0.05**
Serum Total Bilirubin (mg/dl)	0.89±0.19	1.07±0.33	4.18±4.51	5.45±4.31	49.39	<0.01**	**p1= >0.05 p2= <0.01** p3= <0.01** p4= <0.01** p5= <0.01** p6= >0.05**
Serum Direct Bilirubin (mg/dl)	0.45±0.23	0.46±0.29	2.77±3.68	3.69±3.49	43.82	<0.01**	**p1= >0.05 p2= <0.01** p3= <0.01** p4= <0.01** p5= <0.01** p6= >0.05**
Prothrombin Time (sec)	12.56±0.65	14.04±1.13	19.48±6.32	21.68±5.32	26.93	<0.01**	**p1= >0.05 p2= <0.01** p3= <0.01** p4= <0.01** p5= <0.01** p6= >0.05**
Prothrombin Conc. (%)	94.2±4.84	75.88±9.87	51.84±18.29	39.16±15.34	70.46	<0.01**	**p1= >0.05 p2= <0.01** p3= <0.01** p4= <0.01** p5= <0.01** p6= >0.05**
INR	1.12±0.06	1.24±0.1	1.57±0.58	1.83±0.44	21.17	<0.01**	**p1= >0.05 p2= <0.01** p3= <0.01** p4= <0.01** p5= <0.01** p6= >0.05**
AST (10- 34 U/l)	32.44± 6.90	79.44± 67.49	78.04± 76.58	78.80 ± 62.90	24.85	<0.01**	**p1= >0.05 p2= <0.01** p3= <0.01** p4= <0.01** p5= <0.01** p6= >0.05**
ALT (10- 44 U/l)	30.84± 10.06	58.92± 59.82	49.20± 36.88	38.40± 34.00	7.91	<0.05*	**p1= >0.05 p2= <0.01** p3= <0.01** p4= <0.01** p5= <0.01** p6= >0.05**
Alkaline Phosphatase (45-122 U/l)	115.84± 20.57	123.80± 30.39	85.44± 38.31	96.04± 42	23.36	<0.01**	**p1= >0.05 p2= <0.01** p3= <0.01** p4= <0.01** p5= <0.01** p6= >0.05**
GGT (11-55 U/l)	27.36± 13.04	34.4 ± 6.43	36.28± 22.94	38.36± 40.26	8.87	< 0.05*	**p1= >0.5 p2= >0.05 p3= <0.05* p4= >0.05 p5= >0.05 p6= >0.05**

***significant.** ** Highly significant.**

p1= correlation between groups A and B. **p2=** correlation between groups A and C.
p3= correlation between groups A and D. **p4**= correlation between groups B and C.
p5= correlation between groups B and D.**p6**= correlation between groups C and D.

On the contrary, there was a significant increase in serum total anddirect bilirubin, prothrombin time, INR, ALT, AST and alkaline phosphatase in groups C and D compared to groups A and B (p-value <0.01). Serum total bilirubin was 0.89±0.19, 1.07±0.33, 4.18±4.51 and 5.45±4.31 mg/dL respectively.Serum direct bilirubin was 0.45±0.23, 0.46±0.29, 2.77±3.68 and 3.69±3.49 mg/dL respectively.Prothrombin time was 12.56±0.65, 14.04±1.13, 19.48±6.32 and 21.68±5.32 seconds respectively. INR was 1.12±0.06, 1.24±0.1, 1.57±0.58 and 1.83±0.44 respectively. ALT was 30.84±10.06, 58.92±59.82, 49.20±36.88 and 38.40±34 U/L respectively. AST was 32.44±6.90, 79.44±67.49, 78.04±76.58 and 78.80±62.90 U/L respectively. Alkaline phosphatase was 115.84±20.57, 123.80±30.39, 85.44±38.31 and 96.04±42 U/L respectively. GGT was significantly higher in group D compared to group A(p-value <0.01).GGT was 27.36±13.04, 34.4±6.43, 36.28±22.94 and 38.36±40.26 IU/L respectively.

Renal functions and serum electrolytes (Table 4):

Blood urea showed a significant increase with mean±SD of 40.36±5.65, 42.04±12.67, 86.08±58.47 and 97.40±67.56mg/dLin groups A, B, C and Drespectively. The increase was statistically significant in groupsCand D compared to groups A and B(p-value <0.01).

Moreover; serumcreatinine showed mean±SD of 0.87±0.18, 0.66±0.21, 1.25±0.74 and 1.26±1.025 mg/dLin groups A, B, C, Drespectively; with high statistically significant increase in groups C and D when compared to group B(p-value <0.01).

Serum sodium was 141.60±2.52, 135.32±3.46, 128.44±5.57 and 125.20±7.09mmol/l among all groups. It was significantly reduced in group B and C versus groups A and B (p-value <0.01) as well as in groupsC and D (p-value<0.05).

Serum potassium was 4.53±0.58, 4.65±0.50, 4.46±0.61 and 4.39±0.67mmol/l, random blood glucose was 148.20±35.9, 133.92±31.00, 139.72±46.12 and 139.20±51.02 mg/dLin groups A, B, C, Drespectively, with no significant difference between groups (p-value >0.05).

***Ascetic fluid total leucocyte count (Groups C&D)**:

Ascetic fluid TLC was significantly higher in group D compared togroup C (340±70.71 versus 936±293.83 cells/mm^3) (p-value <0.01).

Table (4): **Renal functions and Electrolytes**

Normal Levels	*Group A (N=25)*	*Group B (N=25)*	*Group C (N=25)*	*Group D (N=25)*	Kruskal-Wallis test	p-Value	Post Hoc test
Urea (15-45 mg/dl)	40.36±5.65	42.04±12.67	86.08±58.47	97.4±67.56	20.65	<0.01**	**p1= >0.05 p2= <0.01** p3= <0.01** p4= <0.01** p5= <0.01** p6= >0.05**
Creatinine (0.6-1.4 mg/dl)	0.87±0.18	0.66±0.21	1.25±0.74	1.26±1.025	19.01	<0.01**	**p1= <0.01** p2= >0.05 p3= >0.05 p4= <0.01** p5= <0.01** p6= >0.05**
Serum Sodium (135-146 mmol/l)	141.6±2.52	135.32±3.46	128.44±5.57	125.2±7.09	53.7	<0.01**	**p1= <0.01** p2= <0.01** p3= <0.01** p4= <0.01** p5= <0.01** P6= <0.05**
Serum Potassium (3.5-5 mmol/l)	4.53±0.58	4.65±0.5	4.46±0.61	4.39±0.67	0.86	>0.05	-

***Significant.** ** **Highly significant.**

p1= correlation between groups A and B. **p2**= correlation between groups A and C

p3= correlation between groups A and D. **p4**= correlation between groups B and C.

p5= correlation between groups B and D.**p6**= correlation between groups C and D.

Inflammatory markers (Table 5):

CRP was 0.4±0.00, 0.88±0.59, 3.54±4.93 and 9.02±6.42 mg/l respectively. There was a statistically significant incremental value.ESR did not change significantly between studied groups (40±5.51, 49.04±17.52, 41.96±12.32 and 54.68±27). Similarly; fibrinogen (241.12±32.9, 218.96±108.43, 198.12±102.44 and 243.52±159.36 mg/dL) showed no significant difference among different groups.

Serum ferritinwas 46.52±22.59, 134.74±153.56, 383.20±426.62 and 906.84±851.83 ng/mL in groups A,

B, C, and Drespectively. It washigher in groups C and D compared to control and compensated groups.

On the contrary; haptoglobin decreased significantly in diseased groups compared to control with values of 1.08±0.44, 0.59±0.49, 0.44±0.35 and 0.57±0.39 g/l respectively (p<0.01).

Regarding fibrinogen; there was no statistical significant difference between all the studied groups (241.12±32.9, 218.96±108.43, 198.12±102.44, 243.52±159.36 mg/dL respectively).

Table (5): **Inflammatory Markers**

Normal Levels	*Group A (N=25)*	*Group B (N=25)*	*Group C (N=25)*	*Group D (N=25)*	Kruskal-Wallis test	p-Value	Post Hoc test
ESR	40±5.51	49.04±17.52	41.96±12.32	54.68±27	**5.46**	**> 0.05**	-
CRP (<0.6 mg/l)	0.4±0.00	0.88±0.59	3.54±4.93	9.02±6.42	**77.41**	**<0.01****	**p1= < 0.01** p2= < 0.05* p3= < 0.01** p4= > 0.05 p5= < 0.01** p6= < 0.01**
Ferritin (2.2-178 ng//ml)	46.52 ± 22.59	134.74 ± 153.56	383.2 ± 426.62	906.84 ± 851.83	**61.48**	**<0.01****	**p1= > 0.05 p2= < 0.01** p3= < 0.01** p4= > 0.05 p5= < 0.01** p6= > 0.05**
Haptoglobin (0.3-2.0 g/l)	1.08±0.44	0.59±0.49	0.44±0.35	0.57±0.39	**23.25**	**<0.01****	**p1= < 0.01** p2= < 0.01** p3= < 0.01** p4= > 0.05 p5= > 0.05 p6= > 0.05**
Fibrinogen (200-300 mg/dl)	241.12± 32.9	218.96± 108.43	198.12± 102.44	243.52± 159.36	**7.06**	**> 0.05**	-

***Significant.** ** **Highly significant.**

p1= correlation between groups A and B. **p2=** correlation between groups A and C.

p3= correlation between groups A and D. **p4**= correlation between groups B and C.

p5= correlation between groups B and D.**p6**= correlation between groups C and D.

Ascitic fluid culture and sensitivity in Group D:

Culture results revealedno growth in 13 patients (52%), *Staphylococcus aureus* in 2 patients (8%) (Amoxicillin and Clavulanic acidsensitive), *Staphylococcus epidermidis* in 2 patients (8%) (Vancomycinsensitive), *Escherichia coli*in 6 patients (24%) (Imipenemsensitive), *Pseudomonas aeruginosa*in 1 patient (4%) (Amikacinsensitive) and Streptococciin 1 patient (4%) (Ciprofloxacin sensitive).

Group D was further subdivided into culture positive group (Number=12) and culture negative group (Number=13). There was no statistical significant difference between both groups regarding studied inflammatory markers ESR (34.75±20.04 versus 26.62±10.45), CRP (4.88±6.79 versus 2.31±1.66), Ferritin (398.58±460.95 versus 271.08±195.07), haptoglobin (0.44±0.35 versus 0.44±0.36), fibrinogen (188.50±175.65 versus 131.85±119.48) in culture positive versus culture negative groups. There was no statistical significant difference between both sub-groups regarding studied clinical scores CTP(12.42±1.55 versus 13.54±1.13), MELD (19.08±4.62 versus 22.08±6.29)in culture positive and culture negative groups respectively.

***Inflammatory Markers in Group D during infection and after resolution of SBP(Table 6)**:

Concerning ESR, CRP, Ferritin, Fibrinogen; mean±SD was 54.68±27.02, 9.02±6.42, 906.84±851.83, 243.52±159.36) before treatment and 30.32±16.17, 3.54±4.93, 332.28±347.33, 159.04±148.7 after treatment respectively, with statistically significant difference before and after treatment of SBP in group D (p-value <0.01) denoting that all studied inflammatory markers decreased significantly after treatment (Table 6). CRP at acute level of 1.3 mg/Lshowed sensitivity 80.0%, specificity 82.0% in diagnosis of infection in group D with accuracy 87.4% and AUC 0.86**(Figure 1)**. Haptoglobin at acute level of 0.45 g/L showed sensitivity 60.0%, specificity 32.7% in diagnosis of infection in group D with accuracy 33.7% and AUC 0.34.However fibrinogen at acute level of 152 mg/dl showed sensitivity 60%, specificity 16% in diagnosis of infection in group D with accuracy 36.9% and AUC 0.38.

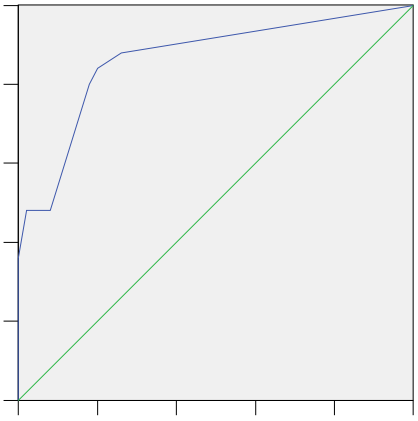

Figure (1): Sensitivity, specificity and accuracy of CRP in diagnosis of infection in group D.

CRP	Sensitivity	Specificity	AUC	Accuracy	p-value	95 % CI
Cut level 1.3	80.0 %	82.0 %	0.86	87.4 %	< 0.01**	0.77 – 0.96

Ferritinat acute level of 88.5 ng/mL showed sensitivity 88%, specificity 70% in diagnosis of infection in group D with accuracy 85.7% and AUC 0.85**(Figure 2)**.

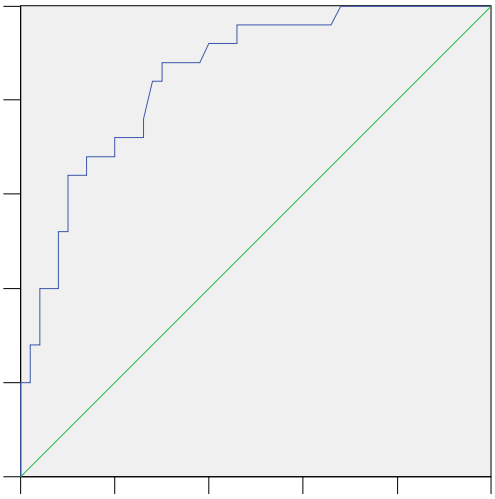

Figure (2): Sensitivity, specificity and accuracy of ferritin in diagnosis of infection in group D.

Ferritin	Sensitivity	Specificity	AUC	Accuracy	p-value	95 % CI
Cut level 88.5	88.0 %	70.0 %	0.85	85.7 %	< 0.01**	0.77 – 0.94

Table (6): Inflammatory Markers in Group D during infection and after resolution of SBP

Value	Before Treatment	AfterTreatment	Wilcoxon Test	p-value
ESR	54.68±27.02	30.32±16.17	3.58	< 0.01**
CRP	9.02±6.42	3.54±4.93	4.29	< 0.01**
Ferritin	906.84±851.83	332.28±347.33	4.09	< 0.01**
Fibrinogen	243.52±159.36	159.04±148.70	3.97	< 0.01**

**** Highly significant**

4.Discussion

In this study it was found that ESRdid not change significantly among studied groups as it is a non-specific test that is increased by any cause or focus of inflammation. In a study that was conducted by ***Das et al., (2011)*** it was concluded that ESR was significantly elevated in alcoholic liver disease patients compared to normal participants and non-alcoholic fatty liver disease patients. As it is a marker of inflammation, so it indicates that chronic alcohol consumption is associated with inflammatory response.

In the present study, a highly significant incremental difference was found in CRP level between normal subjeclts and patient with liver disease even in the absence of infection. This difference was also observed by ***Tilg et al., (1992)*** in their study of serum CRP level in normal subjects and chronic liver disease patients (CRP in control was 0.4±0.1 vs. 1.2±0.2 mg/dL in cirrhotic patients). The increase in CRP was partly attributed to higher levels of interleukin-6, which is a key cytokine in the control of CRP production.

Dalianaet al., (2005) Found that serum level of CRP is not lower in patients with cirrhosis than in other patients; although the liver is considered the main source of CRP. A study done by ***Shima et al.,(1996)*** reported that CRP rises in patients with chronic HCV and HBV as it is regulated by several cytokines which mediate liver inflammation through activating cytotoxic t-cell response in chronic viral hepatitis. It was also observed that CRP rises in patients with acute viral hepatitis and decline in convalescent phase.

In another point of view; one study examined a cohort of decompensated liver disease patients with worsening grades of hepatic encephalopathy and increased serum ammonia levels and revealed that CTP score, total leucocytic count, neutrophilsand CRP showed obvious criteria of increased values related to worsening of hepatic condition. This study confirms the importance of inflammation in the pathogenesis of hepatic encephalopathy. The patients in this study did not show overt signs of infection and were clinically stable at the time of enrollment. Despite this, several patients had raised inflammatory markers ***(Shawcross et al., 2007)***.

Another study evaluated the value of acute phase proteins as indicators of bacterial infection in 88 patients with liver cirrhosis. CRP and ferritin were significantly elevated inbacterial infection. No significant differences were noted in haptoglobin, and fibrinogen levels. Diagnostic performance of APPs values was analyzed, using the ROC analysis where curves were fitted for all APPs. CRP yielded as the best test for the detection of bacterial infection (area under the ROC curve = 0.91) followed by ferritin. They demonstrated that serum levels of several APPs (like CRP and ferritin) were increased in cirrhotic patients even without infection (***Tsiakalos et al., 2009)***. Those findings comply with the results of the present study and of those of a study that was conducted by ***Meliconi et al. (1988)***, who described that APPs are elevated in the sera of cirrhotic chronic liver disease patients with different aetiologies. On the contrary, the levels of haptoglobin and fibrinogen, declined according to the progression of cirrhosis, as it is indicated by CTP staging and these are similar findings to the present study.

A study was undertaken to determine whether host factors of obesity and fatty liver potentiate hepatic inflammation and the expression of inflammatory mediators among patients with chronic HCV. Its findings demonstrated that patients with chronic HCV who are overweight and obese have increased circulating and hepatic CRP levels. CRP expressionwas not influenced by the presence of steatosis or the extent of hepatic inflammation and was not associated with the severity of hepatic fibrosis. The highly significant correlation between circulating high sensitive-CRP and hepatic CRP mRNA levels is consistent with hepatocytes as the primary source of CRP production ***(Jonsson et al., 2008)***. These results pointed to the same findings that were found in the present study which is the relationship between inflammation irrespective of its type and serum levels of CRP.

Patients with simple steatosis and steatohepatitis had significantly raised serum levels of IL-6 which is a potent stimulator for CRP synthesis compared with healthy controls (***Haukeland et al., 2006)***. In the present study high significant differences in serum CRP level, serum ferritin between group C (cirrhotic patients without bacterial infection) and group D (cirrhotic patients with bacterial infection) were found. CRP seems to be the best test to identify bacterial infection among cirrhotic patients with and without bacterial infections (p-Value < 0.001); these results are consonant with several studies like***Bota et al., (2005)*** and ***Park et al., (2005)***; who also described elevated CRP serum concentrations in infected patients with cirrhosis. Increased CRP levels can be partially attributed to its independent production regulation by interleukin-6 and its insensitivity to Hepatocyte Growth Factor (HGF) as described by ***Guillénet al., (1996)***.

Another explanation is that CRP is synthesized not only by the hepatocytes, but as it has been described, by other cell types such as alveolar macrophages ***(Dong and Wright, 1996)*** and renal cells ***(Jabs et al., 2003)***. However in the present study, because of cirrhotic patients without infection exhibit serum CRP levels above the threshold of 0.6 mg/dl, the normal upper limit of CRP value should not be applied as a cut-off value for the detection of bacterial infection in cirrhotics. Therefore, it is necessary to find a new cut-off value to discriminate infection which was found to be>1.3 mg/dl with a high diagnostic specificity (82 %), sensitivity (80 %) and accuracy (87.4%). This in agreement with ***Lin et al., (2002)*** who suggested that a CRP value >2 mg/dl with sensitivity (80.39%), specificity (80.77%) and accuracy (80.62%); is acceptable to differentiate patients with infection from those without. While ***Tsiakalos et al., (2009)*** suggested that CRP threshold should be moved to 5.5 mg/dL, because above these levels, it has almost the same sensitivity (79%), but much better specificity (96%) and diagnostic accuracy (92%). In contrast, ***Le Moine et al., (1994)*** found CRP to have weak predictive power for infection in patients with decompensated cirrhosis and also ***Spahr et al., (2001)*** suggested that the diagnostic value of CRP is limited by the extensive overlap of values between infected and un-infected patients.

A study that was conducted to detect the relation between the levels of some biological markers with disease severity in patients with liver cirrhosis and end stage liver disease progressing to hepatic encephalopathy demonstrated that CRPlevels were significantly increased with the severity of liver disease. Serum bilirubin increased proportionally with the progression of liver disease. Furthermore, values of serum albumin and platelets count decreased significantly with disease worsening. All previous findings present a strong correlation with the present study and support its idea precisely ***(Papadopoulos et al., 2010)***.

In agreement with the present study; a similar study made high emphasis on the importance of increased levels of CRP in patients with liver cirrhosis compared to healthy people. This study also stressed upon the directly proportional increase of CRP with advancement of liver disease ***(Montagnese et al., 2011)***.

In a recent study conducted on patients with fulminant hepatic failure (FHF) in septic shock;it was found that there was marked decrease in the level of factor V activity as well as significant decrease of CRP level despite the presence of septic shock. In view of their findingsthey proposed that in FHF; CRP is a

marker of severity of the liver dysfunction rather than a marker of infection. In addition, they also proposed that in patients with a very high suspicion of infection and an abnormally low CRP level, the presence of FHF should be ruled out, namely, assessing factor V activity ***(Silvestre et al., 2010)***.

Another research group studied the acute phase response in 50 FHF patients. They demonstrated that CRP concentrations were markedly lower than expected for such a severe inflammatory stimulus. Some mechanisms, alone or in combination, may explain these findings; CRP is exclusively produced by the liver, and their production in FHF may already be at maximal rate, being limited by the severe loss of hepatic synthetic function as part of the inflammatory response to the liver cell injury ***(Izumi et al., 1994)***.

Concerning the use of CRP in patients with liver disease, there are studies with conflicting results. However, the study of ***Bota et al al., (2005)***, demonstrated that in critically ill patients with and without cirrhosis, CRP and procalcitonin were good markers of documented infection. Moreover, the predictive power for infection of CRP and Procalcitonin was the same in patients with and without cirrhosis.

In another study; 138 patients were submitted to major liver resection. 48 patients had a CRP level of ≤3.2 mg/dLand 11 patients of them developed septic complications. It was observed that serum CRP levels were significantly lower in patients who developed persistent hyperbilirubinemia, ascites, encephalopathy, and coagulopathy ***(Rahman et al., 2008)***.

Also, in the present study, it was noticed that serum levels of ferritin is increased in cirrhotic patients even without infection; this findings may comply with the results of the study conducted by ***Meliconi et al., (1988)*** and also in agreement with ***Tsiakalos et al., (2009)***.

However, in the present study it was found that serum level of (haptoglobin, fibrinogen) declined according to the progression of cirrhosis and this should be considered a reflection of the underlying hepatic impairment, the severity of which affects their levels in serum. One possible explanation is the mitogenic role of the human hepatocyte growth factor (HGF). Cirrhosis stimulates the production of HGF, as it protects against stellate cell activation, prevents collagen deposition, activates collagenase enzyme to cause matrix degradation and has noticeable decremental effects on the synthesis of several plasma APPs, such as haptoglobin and fibrinogen whose production is down regulated. This is in agreement with ***Tsiakalos et al., (2009)*** who found the same results.

In agreement with the present study; a study was performed on patients with Non-Alcoholic Fatty Liver Diseaseand showed that the severity of hepatic portal and lobular inflammation correlated positively with ferritin level. Interestingly, serum ferritin at a cut-off value of ≥240 ng/ml in a multivariate logistic regression; was significantly associated with stage of fibrosis (p = 0.034), lobular inflammation (p = 0.009) and portal inflammation (p = 0.043). In this study, the authors showed that increased concentration of serum ferritin is an independent predictor of fibrosis (78% sensitivity, 50% specificity) and inflammation, both portal (78% sensitivity, 60% specificity) and lobular (85% sensitivity, 67% specificity) ***(Manousou et al., 2011)***.

A study to determine physiological and biochemical predictors of development of bacteraemia and mortality in patients with acute liver failure (ALF) showed a worsening of Systemic Inflammatory Response Syndrome (SIRS) score and bilirubin especially in patients who had an evidence of bacteraemia in relation to ALF***(Karvellas et al., 2009)***.The present study showed similar hypothesis which is the predictive response of clinical and biochemical markers in predicting inflammation and sepsis in relation to decompensated liver disease.

There was asignificant incremental value of Child-Pugh score (CTP)score among the diseased groups (B, C, D) (5.68±0.69, 11.80±2.00and 13.00±1.41) with p-value <0.001. This difference can be attributed to the severity of their liver function impairment, which predisposes to bacterial infections. Similar results were reported by ***Tsiakalos et al., (2009)*** and***Thabut et al., (2007)***. The latter found comparable results as the present study regarding MELD score.

In the present study there was a high significant difference of plasma APPs and its correlation during infection and after resolution of SBP in Group D with p-value <0.001. These results are also in agreement with ***Lin et al., (2002)***.

In the present study;ascitic fluid culture and sensitivity in group D showed that 13 (52%) were culture negative, while 12 (48%) were culture positive. This finding is in agreement with ***Saleh et al., (1994)*** and ***Pelletier et al., (1990)*** as their results ranged from (50-71%) for culture positive group and also with ***Riggio and Angeloni, (2009)*** who found the ascitic fluid culture may be negative in up to 60% of patients with SBP. This is in contrast to the study done by ***Kamani et al., (2008)*** on 187 patients where 44 (23.5%) had culture positive, while 143 (76.4%) had culture negative. Also, it was found that patients with culture positive ascitic fluid had high CTP score compared to culture negative patients (13.54±1.13 versus 12.42±1.55) respectively, and this is in agreement with ***Kamani et al., (2008)*** who found CTP

score 12.52±1.45 vs. 11.44±1.66 for culture positive and culture negative respectively.

The results of the present study together with reports of***Kamani et al., (2008)*** and ***Pelletier et al., (1990)*** suggest that culture positive is a more severe variant than culture negative patients as it was found that they have higher levels of APPs, as well as higher MELD and CTP scores than culture negative group.

In the present study, Escherichia Coli was the most common organism (24%) that was isolated in culture positive group. While Staphylococcus Aureasand Staphylococcus Epidermidis were found in 16% (8% per each); Pseudomonas Auregenosawas found in (4%), Streptococci was found in (4%) of culture positive cases. Almost the same result were obtained in***Kamani et al., (2008)***who found that E. coli was the most common organism found in two thirds of patients with SBP. Escherichia Coli is the main gut flora. Under normal conditions, even if bacteria cross through the intestinal epithelia they should be destroyed by phagocytes before reaching the blood circulation. Gut-associated lymphoid tissue (GALT), considered the largest immunological organ of the body, is organized very similarly to lymph nodes and plays a key role in controlling bacterial translocation (BT). But cirrhotic patients have decreased small bowel motility, reduced acidity and a reduced secretion of IgA into the intestinal lumen. These factors could be responsible for the occurrence of intestinal bacterial overgrowth, increased mucosal permeability due to portal hypertension and impaired host immune defenses mechanisms.Consequently all are implicated in BT in cirrhotic patients ***(Balzan et al., 2007)***.

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