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Scientific Research

Role of Portal Hypertension in Prediction of Bacterial Infection in Decompensated Cirrhosis

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Abstract

Background: Bacterial infection in cirrhotic patients is a fatal complication. The high incidence of bacterial infections in those patients may be related to several alterations in the defensive mechanisms against infections and increased intestinal permeability with bacterial translocation. Aim: To evaluate the role of portal hypertension (PH) in predicting the occurrence of bacterial infections in decompensated cirrhosis. Patients and Methods: In this retrospective cohort study, 99 patients—56 males and 43 females, with decompensated liver cirrhosis were included. Diagnosis of liver cirrhosis was based on clinical, laboratory and ultrasonographic examinations. Patients were classified according to the presence of bacterial infection into patients with infection—Group 1, and those without infection—Group 2. Laboratory, abdominal US and upper endoscopic data for all patients were collected. Logistic regression analysis was done to detect the independent factors for prediction of bacterial infection. Results: The mean age of patients was 50.5 ± 14.2 years. Bacterial infection was found in 41 patients (41.4%) and no infection in 58 patients (58.6%). Infected patients showed statistically significant higher values in the level of bilirubin, PT and Child-Pugh score (P value = 0.000) and lower values in the level of albumin, total serum protein and PC than those without infection (P value = 0.006, 0.000 and 0.000 respectively). Portal vein diameter (PVD) and splenic diameter (SD) showed statistically significant higher values in infected patients than in those without infection (P value = 0.028 and 0.000 respectively), also infection was more significantly prevalent in patients with varices than those without varices (P value = 0.000). The independent predictors for bacterial infection were: the age, total serum bilirubin, serum albumin, PT, PC, child score, PVD, SD and the presence of varices. Conclusion: Presence of varices (as a complication of PH) is an independent risk factor for the development of bacterial infection in decompensated cirrhotic patients and reduction of PH by any way could decrease this fatal complication.

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Keywords

Portal Hypertension; Bacterial Infection; Liver Cirrhosis

1. Introduction

Bacterial infections are a known complication of cirrhosis, with a reported incidence that ranges between 15% and 47% [1] [2].

Hospitalized patients with cirrhosis are at increased risk of developing bacterial infections and the most common causes are spontaneous bacterial peritonitis [SBP] and urinary tract infections. The independent predictors for the development of bacterial infections in those patients are poor liver synthetic function and gastrointestinal hemorrhage [3].

Cirrhotic patients who develop an infection have a significantly higher mortality than uninfected patients [4] [5]. Current evidence also suggests that infection predisposes to recurrent variceal hemorrhage [6] and is associated with failure to control variceal hemorrhage [7] [8]. Antibiotic prophylaxis in the setting of variceal hemorrhage significantly decreases the incidence of bacterial infections and improves survival [9].

Studies assessing the aetiology and types of bacterial infections in cirrhotic patients showed that the most common infections were community-acquired, mainly urinary-tract infections, SBP and pneumonia, 70% - 80% of which were caused by gram negative bacilli (GNB), mainly *Escherichia coli*, suggesting that the gut was the main source of bacteria. The spectrum of bacteria causing infection in cirrhosis in more recent series showed a significantly higher rate of Gram-positive cocci infections, probably due to an increase in the number of therapeutic invasive procedures [10] and the use of chronic antibiotic prophylaxis [11] [12]. However, the most common infections, SBP and urinary-tract infection, are still caused mainly by GNB [10]. Recent investigations suggest that the prevalence of infections caused by multiresistant bacteria is increasing in cirrhosis [13].

Bacterial translocation (BT), which increases by portal hypertension, is defined as the migration of viable microorganisms from the intestinal lumen to mesenteric lymph nodes (MLN) and other extra-intestinal organs and sites. BT in cirrhotic patients increases in conditions associated with a high risk of infections by GNB and multiple organ failure such as hemorrhagic shock, intestinal obstruction, major burn injury and serious trauma [14]. BT has been postulated as the main mechanism in the pathogenesis of SBP [15].

1.1. Aim of the Work

To assess the possible role of PH in the development of bacterial infections in decompensated cirrhotic patients.

1.2. Patients and Methods

99 patients with decompensated liver cirrhosis admitted to Qena University Hospital from April to October 2013; with Child-Pugh classes B or C were included in this retrospective cohort study. Diagnosis of liver cirrhosis was based on clinical, laboratory and ultrasonographic examinations. Patients with other immune-compromised diseases or receiving immune-suppressive drugs were excluded. Patients with autoimmune hepatitis were diagnosed at the hospital on admission for their first time and they were included before starting corticosteroid therapy but others under corticosteroid therapy were excluded.

2. Methods

Clinical and laboratory data for all patients including: complete blood count, liver function tests (ALT, AST, serum bilirubin, albumin and total protein, prothrombin time (PT) and concentration (PC), INR and serum alkaline phosphatase), serum electrolytes, glucose and serum creatinine were recorded. Abdominal US data were recorded including the following: the size of the liver and the spleen, the size of the portal and splenic vein and the presence and the degree of ascites. The presence or absences of bacterial infections including their sites were detected. Patients were classified into: Group 1; patients without bacterial infections and Group 2; patients with bacterial infections. The types of infections were defined according to the following standard criteria: Pneumo-

nia was diagnosed in the presence of infiltrates on chest x-ray with concurrent fever, cough, and neutrophilic leukocytosis; spontaneous bacterial peritonitis was diagnosed in the presence of a neutrophil leukocyte count in the ascitic fluid >250 cells/mm^3 without any evidence of surgically treatable sources of infections; urinary tract infection was diagnosed when fever and urinary symptoms were associated with bacteriuria, leukocyturia, and positive urine culture; GI tract infection was diagnosed when vomiting, diarrhea, fever, and abdominal pain were associated with neutrophilic leukocytosis and positive stool culture; skin and soft tissue infections were diagnosed when fever and cellulitis were associated with neutrophilic leukocytosis. Data of upper endoscopy (using Olympus, GIF-XQ260 instrument) for all patients including presence or absence of varices (esophageal or gastric) and/or portal hypertensive gastropathy (PHG) were recorded. The size of esophageal varices was graded as described by Beppu *et al*. (1981) into Grade 1: enlarged but straight varices, Grade 2: enlarged tortuous varices and Grade 3: coiled shaped markedly enlarged varices [16]. If PHG was present, it was described as either mild or severe as described by Mc Cormack *et al*., (1985) [17].

Statistical Analysis

Data entry and analysis were done using statistical package of social science (SPSS) version 16. The data are presented as means ± SD. Statistical methods included independent-t-tests; used for comparison between the two groups in case of continuous variables and the Chi-square test for comparison between categorical variables. Logistic regression analysis was done to detect the independent predictors for statistically significant variables. P value < 0.05 was considered statistically significant.

3. Results

3.1. Patients

99 patients with liver cirrhosis; 56 male (56.6%) and 43 female (43.4%), with their mean age was 50.5 ± 14.2 years were included in the current study. The aetiology of liver cirrhosis was due to chronic HCV in 78 (78.8%), HBV in 13 (13.2%), autoimmune hepatitis in 2 (2%) and cryptogenic cause in 6 (6%) patients.

3.1.1. Clinical Data for All Patients

History of hematemesis was encountered in 20 patients (20.2%). Ascites was found in 90 patients (91%); 49 of them were mild degree, 24 moderate and 17 patients presented by marked ascites. Hepatic encephalopathy as a manifestation of decompensated cirrhosis was found in 78 patients (78.8%); 58 of them were Grade I-II and 20 patients were Grade III-IV. Hepato-renal syndrome was detected in 4 patients (4%). As regard Child-Pugh score; 58 were in class B (58.6%) and 41 were in class C (41.4%). This is illustrated in **Table 1**.

3.1.2. Laboratory Data for All Patients

The mean values of the laboratory data for all patients are illustrated in **Table 2** and the mean value for child-Pugh score were 11.71 ± 2.05.

3.1.3. Sonographic Data of All Patients

Showed that the mean liver span was 10.5 ± 2.5 cm, PVD was 1.29 ± 0.25 cm and SD was 16.09 ± 2.45 cm; this is illustrated in **Table 3**.

3.1.4. Endoscopic Data for All Patients

No varices detected were in 40 (40.5%) patients and esophageal varices were found in 59 (59.5%) patients; 17 were Grade 1, 20 were Grade 2 and 22 were Grade 3. Gastric varices (G.V) were found in 6 (6.1%) patients and PHG was found in 78 (78.8%) patients; this is illustrated in **Table 3**.

3.2. Bacterial Infection

It was not found in 58 patients (58.6%); (Group 1) and was found in 41 patients (41.4%); (Group 2). The most common type of infection was SBP which was found in 16 (39% of infected patients), followed by respiratory tract infection in 12 patients (29.3%) then urinary tract infection in 8 (19.5%), soft tissue infection in 3 (7.3%) and GIT infection in 2 patients (4.9%).

Table 1. Clinical data for all patients.

Parameter	Value
Age	50.5 ± 14.2
Gender	
Male	56 (56.6%)
Female	43 (43.4%)
Hematemesis	20 (20.2%)
Ascites	
No	9 (9.1%)
Mild	49 (49.5%)
Moderate	24 (24.2%)
marked	17 (17.2%)
HE	
No	21 (21.2%)
Grade I-II	58 (58.6%)
Grade II-IV	20 (20.2%)
HRS	4 (4%)
Child class	
B	58 (58.6%)
C	41 (41.4%)

All data are expressed as number (%) or mean ± SD. HE: hepatic encephalopathy, HRS: hepato-renal syndrome.

Table 2. Laboratory data for all patients.

Parameter	Value
Bilirubin (mg/dl)	2.57 ± 1.34
ALT (U/L)	87.7 ± 153.5
AST (U/L)	54.2 ± 74
Albumin (g/dl)	2.55 ± 0.89
Protein (g/dl)	6.42 ± 1.04
PT (sec)	16.81 ± 2.99
PC (%)	56.15 ± 17.85
INR	1.66 ± 0.74
ALP	105.6 ± 72.9
Child score	11.71 ± 2.05
Hemoglobin (g/dl)	10.3 ± 2.47
WBCs (10^3/µl)	10.2 ± 3.05
PLT (10^3/µl)	122.5 ± 92.1
Creatinine (mg/dl)	0.90 ± 0.86

All data are expressed as mean ± SD or Number (%).

Table 3. Sonographic and endoscopic data for all patients.

Parameter	Value
Liver span	10.5 ± 2.5
PVD (cm)	1.29 ± 0.25
SD (cm)	16.09 ± 2.45
Endoscopy	
O.V (%)	59 (59.5%)
G.V (%)	6 (6.1%)
PHG (%)	78 (78.8%)
Esophageal V.	
G1	17 (29%)
G2	20 (34%)
G3	22 (37%)

All data are expressed as mean ± SD or number (%).

3.3. Comparison between Both Groups

As regard parameters of liver function; patients with infection showed statistically significant higher values in the level of bilirubin, PT and Child-Pugh score (P value = 0.000) and a lower values in the level of albumin, total serum protein and PC than those without infection (P value = 0.006, 0.000 and 0.000 respectively). As regard sonographic findings; PVD and SD showed statistically significant higher values in patients with infection than in those without infection (P value = 0.028 and 0.000 respectively), also infection was more significantly prevalent in patients with esophageal & gastric varices than those without varices (P value = 0.000); this is shown in **Figure 1**. Total leucocytic count was significantly higher in patients with infection than in those without infection (P value = 0.04), this is illustrated in **Table 4**.

Logistic regression analysis for the significant parameters between both groups, which was done to detect the independent factors predicting the presence of infection, showed that the independent factors were: the age, total serum bilirubin, serum albumin, PT, PC, Child score, PVD, SD and presence of varices; this is illustrated in **Table 5**.

4. Discussion

Bacterial infection is a common complication in cirrhotic patients with high incidence of mortality. Liver dysfunction and PH are the two major sequels of this disease, so the current study aimed to define the possible risk factors for developing bacterial infection for possible avoidance of this fatal complication.

The independent factors predicting the occurrence of bacterial infection in the current study were the age, parameters of liver dysfunction including Child-Pugh score; bilirubin, albumin, PT, PC, INR and parameters of portal hypertension including presence of varices, PVD and SD. This result coincide with that obtained with Garsia-Tsao *et al*., (1993), who suggested that PH alone may not be a major factor in the development of spontaneous infections in cirrhosis and that other mechanisms, such as a defective immune system, may be more important [18].

The high incidence of bacterial infections in cirrhotic patients may be explained by the presence of several alterations in the defensive mechanisms against infections, small intestinal bacterial overgrowth, depression of hepatic monocyte macrophage functions and reduction of serum and ascitic fluid complement levels [19].

Advanced liver disease may contribute to the observed increase in BT by different mechanisms. PH is associated with characteristic structural changes in the small intestinal wall [20] and functional abnormalities such as protein-losing enteropathy [21], reduced small bowel motility [22] and small intestinal bacterial overgrowth [23]. Clearance of translocated organisms from MLN may also be impaired, given the impaired chemotaxis, phago-

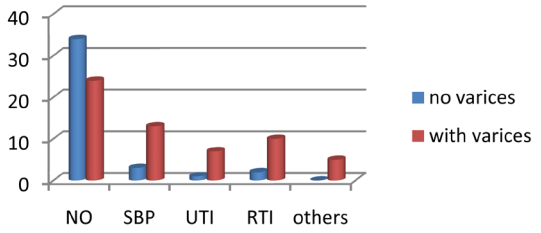

Figure 1. Types of bacterial infections in patients with and without varices.

Table 4. Laboratory, sonographic and endoscopic data for patients with and without bacterial infection.

Parameter	No infection 58 (58.6%)	Infection 41 (41.4%)	P value
Bilirubin (mg/dl)	1.68 ± 1.46	3.47 ± 1.22	0.000
Albumin (g/dl)	2.77 ± 0.96	2.33 ± 0.83	0.006
Protein (g/dl)	6.96 ± 0.88	5.88 ± 1.2	0.000
P.T (sec)	15.01 ± 1.7	18.6 ± 4.28	0.000
P.C (%)	63.4 ± 14.9	48.9 ± 20.8	0.000
Child score	10.40 ± 2.2	13.03 ± 1.9	0.000
WBCs (10^3/µl)	8.5 ± 3.4	11.9 ± 2.7	0.04
PLT (10^3/µl)	118.57 ± 78.8	127.88 ± 105.4	0.61
PVD (cm)	1.25 ± 0.27	1.34 ± 0.24	0.028
SD (cm)	14.35 ± 2.77	17.84 ± 2.14	0.000
Varices			
Yes (%)	24 (41.4%)	35 (85.4%)	
No (%)	34 (58.6%)	6 (14.6%)	0.000*

All data are expressed as mean ± SD and number (%). Independent t test were used, *Chi^2 test was used.

Table 5. Logistic regression analysis for the presence of infection.

Independent variables	P value	Odds ratio
Age	0.003	0.951
Bilirubin	0.001	1.39
Albumin	0.008	0.463
PT	0.000	1.5
PC	0.000	0.955
Child score	0.004	1.45
PVD	0.032	1.8
S.D	0.000	1.77
varices	0.039	1.67

P value < 0.05 = significant. CI = 95%.

cytosis and intracellular killing by polymorphonuclear leukocytes and monocytes associated with advanced liver disease [19].

Cirera *et al*., [2001] also in their study postulated that the degree of PH was not associated with a higher prevalence of BT and suggested that, in addition to PH, the simultaneous occurrence of other factors favoring BT and the presence of several abnormalities in the defense mechanisms against the infection are probably required to allow enteric bacteria to translocate to MLN and to cause systemic infection in cirrhosis [24].

So, from this current study, we can postulate that reduction of PH by any way could reduce the translocation of bacteria through porto-systemic shunts by passing the liver and so could decrease the incidence of bacterial infection in those patients. In accordance with our results, Giannelli *et al*., (2014) study; which is the most recent one, postulated that carvidolol as a β-blocker, in addition to reducing portal pressure, it can also reduce bacterial translocation and so reduce bacterial infections in those patients adding more beneficial effect to the usefulness of these agents [25].

5. Conclusion

Presence of varices (as a complication of PH) is an independent risk factor for the development of bacterial infection in decompensated cirrhotic patients and reduction of PH by any way could decrease this fatal complication. Further studies on larger sample size are needed.

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