Ascitic Fluid High Sensitive C-Reactive Protein. A Prognostic Marker in Spontaneous Bacterial Peritonitis

Thesis Submitted for Fulfillment of Master Degree in Internal Medicine

By

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First and foremost, thanks to (ALLAH), the Most Gracious and the Most Merciful, who granted me to finish this work.

Prayer and peace be upon the most honorable of Messengers (MOHAMAD).

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<tr>
<td>ALT</td>
<td>Serum Alanine Aminotransferase</td>
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<td>ARDS</td>
<td>Acute Respiratory Distress Syndrome</td>
</tr>
<tr>
<td>AST</td>
<td>Serum Aspartate Aminotransferase</td>
</tr>
<tr>
<td>BT</td>
<td>Bacterial Translocation</td>
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<tr>
<td>CBC</td>
<td>Complete Blood Count</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>CTP</td>
<td>Child–Turcotte–Pugh</td>
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<tr>
<td>EEG</td>
<td>Electroencephalography</td>
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<tr>
<td>ELISA</td>
<td>Enzyme-Linked Immunosorbent Assay</td>
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<tr>
<td>GIT</td>
<td>Gastrointestinal Tract</td>
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<tr>
<td>HE</td>
<td>Hepatic Encephalopathy</td>
</tr>
<tr>
<td>HPS</td>
<td>Hepatopulmonary Syndrome</td>
</tr>
<tr>
<td>HRS</td>
<td>Hepatorenal Syndrome</td>
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<tr>
<td>hs-CRP</td>
<td>High sensitive CRP</td>
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<tr>
<td>HVPG</td>
<td>Hepatic Venous Pressure Gradient</td>
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<tr>
<td>INR</td>
<td>International Normalized Ratio</td>
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<tr>
<td>IP-10</td>
<td>Interferon-γ-induced protein</td>
</tr>
<tr>
<td>JGA</td>
<td>Juxtaglomerular Apparatus</td>
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<tr>
<td>MELD</td>
<td>Model For End-Stage Liver Disease</td>
</tr>
<tr>
<td>MIP-1β</td>
<td>Macrophage Inflammatory Protein Type 1 Beta</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td><strong>NAFLD</strong></td>
<td>Nonalcoholic Fatty Liver Disease</td>
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<tr>
<td><strong>NASH</strong></td>
<td>Nonalcoholic Steatohepatitis</td>
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<tr>
<td><strong>NK</strong></td>
<td>Natural killer cells</td>
</tr>
<tr>
<td><strong>NO</strong></td>
<td>Nitric Oxide</td>
</tr>
<tr>
<td><strong>PBC</strong></td>
<td>Primary Biliary Cirrhosis</td>
</tr>
<tr>
<td><strong>PCT</strong></td>
<td>Procalcitonin</td>
</tr>
<tr>
<td><strong>PMN</strong></td>
<td>Polymorphonuclear Leukocyte</td>
</tr>
<tr>
<td><strong>PPH</strong></td>
<td>Portopulmonary Hypertension</td>
</tr>
<tr>
<td><strong>PT</strong></td>
<td>Prothrombin Time</td>
</tr>
<tr>
<td><strong>RAAS</strong></td>
<td>Renin Angiotensin- Aldosterone System</td>
</tr>
<tr>
<td><strong>RES</strong></td>
<td>Reticuloendothelial System</td>
</tr>
<tr>
<td><strong>SAAG</strong></td>
<td>Serum Ascites Albumin Gradient</td>
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<td><strong>SBC</strong></td>
<td>Secondary Biliary Cirrhosis</td>
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<tr>
<td><strong>SBP</strong></td>
<td>Spontaneous Bacterial Peritonitis</td>
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<td><strong>TIPS</strong></td>
<td>Transjugular Intrahepatic Portosystemic Shunt</td>
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<tr>
<td><strong>TLC</strong></td>
<td>Total Leukocytic Count</td>
</tr>
<tr>
<td><strong>TNF</strong></td>
<td>Tumor necrosis factor</td>
</tr>
<tr>
<td><strong>UNOS</strong></td>
<td>United Network For Organ Sharing</td>
</tr>
<tr>
<td><strong>US</strong></td>
<td>Ultrasound</td>
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<tr>
<td><strong>VH</strong></td>
<td>Variceal Hemorrhage</td>
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Introduction

Patients with liver cirrhosis (LC) are at high risk for bacterial infections. It has been reported that 30% to 60% of inpatients with LC develop a bacterial infection (Strauss E (2014), and the incidence of bacterial infections in patients with LC is 4-5-fold higher than that in the general population (Jalan R, et al. 2014).

Among patients with LC accompanied by bacterial infections, spontaneous bacterial peritonitis (SBP) is the most common complication (10% to 30% cases) and often life-threatening, with mortality among ranging from 10% to 46% (Dever JB and Sheikh MY, 2015).

The gold standard method for the diagnosis of SBP is a polymorphonuclear cell (PMN) count of ≥250 cells/mm3 in the ascitic fluid, regardless of bacterial isolation [Solà E, et al ,2016]. However, paracentesis is not always possible and can sometimes be too time-consuming for an early diagnosis of SBP (Gaya DR, et al.2007).

Therefore, novel and useful biomarkers for early diagnosis of SBP are desirable. Laboratory methods for early prediction of response to the first treatment are also desirable because nonresponse to the first treatment is a predictor of mortality accompanied with SBP (Piano S, et al. 2016).

C-Reactive Protein (CRP) was discovered by Tillet and Francis in 1930 and they proposed the hepatic synthesis of CRP. It is an acute phase protein found in the blood stream the levels of which rise in response to inflammation. High sensitivity CRP (hs- CRP) test measures low levels of CRP using Laser nephelometry. This test gives immediate results
within 25 minutes and also with sensitivity down to 0.04 mg/l. It is a more sensitive inflammatory marker. *(Ramamoorthy RD, et al. 2012)*

Studies have supported the view that CRP levels increases in decompensated cirrhosis and infections in cirrhosis. *(Cervoni JP, et al. 2012)*
Aim of the work

The aim of the study is to clarify the role of high sensitive CRP as a prognostic factor in patient with spontaneous bacterial peritonitis
Patients and Methods

Selection of patients

30 cases of cirrhosis with ascites who satisfied the criteria of SBP. The definitive diagnosis of SBP was made by an elevated ascitic fluid absolute Polymorph Nuclear (PMN) leukocyte count of ≥250 cells/mm³ in absence of any intra abdominal source of infection.

There will be a control group of 20 cirrhotic patient with ascitis & without SBP.

Exclusion criteria

Coronary artery diseases, Diabetes mellitus, Collagen vascular disorders, Any form of acute arthritis, Acute infections, Septicemia.

Methods

Highly sensitive CRP levels will be estimated after diagnosis of SBP and on 5th day after treatment with standard recommended antibiotic therapy (inj. cefotaxim 2 g 12 hourly for 5 days)

Haemoglobin, TLC, Serum bilirubin, AST, ALT serum creatinine, INR, will be estimated in all cases.

Test principle

The kit uses a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) to assay the level of Human high sensitivity C-Reactive Protein (hs-CRP) in samples.

Add high sensitivity C-Reactive Protein (hs-CRP) to monoclonal antibody Enzyme well which is pre-coated with human high sensitivity
Patients and Methods

C-Reactive Protein (hs-CRP) monoclonal antibody, incubation; then, add hs-CRP antibodies labeled with biotin, and combined with Streptavidin-HRP to form immune complex; then carry out incubation and washing again to remove the uncombined enzyme. Then add Chromogen Solution A, B, the color of the liquid changes into the blue, And at the effect of acid, the color finally becomes yellow. The chroma of color and the concentration of the human Substance high sensitivity C-Reactive Protein (hs-CRP) of sample were positively correlated.

Materials supplied in the Test Kit

1. Standard (48mg/L) 0.5ml
2. Standard diluent 3ml
3. Microelisa Stripplate 12well×8strips
4. Str- HRP-Conjugate Reagent 6ml
5. 30×wash solution 20ml
6. Biotin-hs-CRP Ab 1ml
7. Chromogen Solution A 6ml
8. Chromogen Solution B 6ml
9. Stop Solution 6ml
10. Instruction one
11. Closure plate membrane two
12. Sealed bags one

Washing method

Manually washing method: shake away the remain liquid in the enzyme plates; place some bibulous papers on the test-bed, and flap the plates on the upside down strongly. Inject at least 0.35ml after-dilution washing solution into the well, and marinate 1~2 minutes. Repeat this process according to your requirements.
Specimen requirements

1. Can’t detect the sample which contain nan3, because nan3 inhibits HRP active.
2. Extract as soon as possible after Specimen collection, and according to the relevant literature, and should be experiment as soon as possible after the extraction. If it can’t, specimen can be kept in -20 ºC to preserve, Avoid repeated freeze-thaw cycles.
3. Serum- coagulation at room temperature 10-20 mins, centrifugation 20-min at the speed of 2000-3000 r.p.m. Remove supernatant, If precipitation appeared, Centrifugal again.
4. Plasma-use suited EDTA or citrate plasma as an anticoagulant, mix 10-20 mins, centrifugation 20-min at the speed of 2000-3000 r.p.m. Remove supernatant, If precipitation appeared, Centrifugal again.
5. Urine- collect sue a sterile container, centrifugation 20-min at the speed of 2000-3000 r.p.m. Remove supernatant, If precipitation appeared, Centrifugal again. The Operation of Hydrothorax and cerebrospinal fluid Reference to it.
6. Cell culture supernatant- detect secretory components, collect sue a sterile container, centrifugation 20-min at the speed of 2000-3000 r.p.m. remove supernatant, detect the composition of cells, Dilute cell suspension with PBS（PH7.2-7.4）, Cell concentration reached 1 million / ml, repeated freeze-thaw cycles, damage cells and release of intracellular components, centrifugation 20-min at the speed of 2000-3000 r.p.m. remove supernatant, If precipitation appeared, Centrifugal again.
7. Tissue samples- After cutting samples, check the weight, add PBS （PH7.2-7.4）, Rapidly frozen with liquid nitrogen, maintain samples at 2-8ºC after melting, add PBS（PH7.4）, Homogenized
by hand or Grinders, centrifugation 20-min at the speed of 2000-3000 r.p.m. remove supernatant.

Note: Grossly hemolyzed samples are not suitable for use in this assay.

**Assay procedure**

1. Standard dilution: this test kit will supply one original Standard reagent, please dilute it by yourself according to the instruction.

2. The quantity of the plates depends on the quantities of to-be-tested samples and the standards. It is suggested to duplicate each standard and blank well. Every sample shall be made according to your required quantity, and try to use the duplicated well as possible.

3. Inject samples:
   - Blank well: don’t add samples and hs-CRP-antibody labeled with biotin, Streptavidin-HRP, only Chromogen solution A andB, and stop.
   - 240 mg/dL Standard No.5 120μl Original Standard + 120μl Standard diluents
   - 120 mg/dL Standard No.4 120μl Standard No.5 + 120μl Standard diluents
   - 60 mg/dL Standard No.3 120μl Standard No.4 + 120μl Standard diluent
   - 30 mg/dL Standard No.2 120μl Standard No.3 + 120μl Standard diluent
   - 15 mg/dL Standard No.1 120μl Standard No.2 + 120μl Standard diluent solution are allowed; other operations are the same.
   - Standard wells: add standard 50μl, Streptavidin-HRP 50μl(since the standard already has combined biotin antibody, it is not necessary to add the antibody);
Patients and Methods

- To be test wells: add sample 40μl, and then add both hs-CRP-antibody 10μl and Streptavidin-HRP 50μl. Then seal the sealing memberance, and gently shaking, incubated 60 minutes at 37 ℃.

4. Confection: dilute 30 times the 30×washing concentrate with distilled water as standby.

5. Washing: remove the memberance carefully, and drain the liquid, shake away the remaining water.

6. Add chromogen solution A 50μl, then chromogen solution B 50μl to each well. Gently mixed, incubate for 10 min at 37℃ away from light.

7. Stop: Add Stop Solution 50μl into each well to stop the reaction(the blue changes into yellow immediately).

8. Final measurement: Take blank well as zero , measure the optical densit(OD) under 450 nm wavelength which should be carried out within 15min after adding the stop solution.

9. According to standards’ concentration and the corresponding OD values, calculate out the standard curve linear regression equation, and then apply the OD values of the sample on the regression equation to calculate the corresponding sample’s concentration. It is acceptable to use kinds of software to make calculations.

Summary procedures

1. Preparing reagents, samples and standards
2. Add prepared samples and standards, antibodies labeled with enzyme, reacting 60 minutes at 37 ℃
3. Plate washed five times, adding Chromogen solution A, B, reacting 10 minutes at 37℃
4. Add stop solution
5. measure the OD value within 10min
Patients and Methods

6. Calculate

**Calculation**

Take the standard density as the horizontal, the OD value for the vertical draw the standard curve on graph paper, find out the corresponding density according to the sample OD value by the Sample curve (the result is the sample density) or calculate the straight line regression equation of the standard curve with the standard density and the OD value, with the sample OD value in the equation, calculate the sample density.

**Specificity**

This assay has high sensitivity and excellent specificity for detection of hs-CRP. No significant cross-reactivity or interference between hs-CRP and analogues was observed.

Limited by current skills and knowledge, it is impossible for us to complete the cross-reactivity detection between hs-CRP and all the analogues, therefore, cross reaction may still exist.

Sample linear regression with the expected concentration of the correlation coefficient R is over 0.95.
Chapter 1
Liver cirrhosis

The word "cirrhosis" derived from Greek word, meaning tawny (the orange-yellow colour of the diseased liver). While the clinical entity was known before, it was René Laennec who gave it the name "cirrhosis" in 1819. Liver cirrhosis represents the final common histologic pathway of chronic liver diseases. Many forms of liver injury are marked by fibrosis. Fibrosis is defined as an excess deposition of the components of extracellular matrix (i.e. collagens, glycoproteins and proteoglycans) within the liver (Wong et al., 2015).

Cirrhosis results from different mechanisms of liver injury that lead to necrotic inflammation and fibrogenesis; histologically it is characterised by diffuse nodular regeneration surrounded by dense fibrotic septa and collapse of liver structures, together causing distortion of hepatic vascular architecture (Zhou et al., 2014; Murray et al., 2015).

This distortion results in increase the resistance to portal blood flow leading to portal hypertension and in hepatic synthetic dysfunction. Clinically, cirrhosis has been regarded as an end-stage disease that invariably leads to death, unless liver transplantation is done, and the only preventive strategies have been screening for oesophageal varices and hepatocellular carcinoma (Tsochatzis et al., 2014).

Epidemiology:

Cirrhosis is late-stage liver disease which occurs when fibrosis replaces healthy tissue (Byass, 2014). Globally, liver cirrhosis was estimated to be responsible for over one million deaths in 2010, which
equates to approximately 2% of all deaths worldwide (Mokdad et al., 2014). It is estimated that in 2013, liver cirrhosis resulted in 170,000 deaths in Europe (Zatonski et al., 2010). Cirrhosis is the leading cause of adult liver transplants in Europe 58,357 carried out between 1988 and 2013 (ELTR, 2015).

Cirrhosis is an increasing cause of morbidity and mortality in more developed countries. It is the 14th most common cause of death in adults worldwide but the fourth in central Europe; it results in 1.03 million deaths per year worldwide (Lozano et al., 2012), 170 000 per year in Europe (Blachier et al., 2013), and 33 539 per year in the USA (Hoyert and Xu, 2012). Cirrhosis is the main indication for 5500 liver transplants each year in Europe. The main causes in more developed countries are infection with hepatitis C virus, alcohol misuse, and, increasingly, non-alcoholic liver disease; infection with hepatitis B virus is the most common cause in subsaharan Africa and most parts of Asia (Blachier et al., 2013).

The prevalence of cirrhosis is difficult to assess and probably higher than reported, because the initial stages are asymptomatic so the disorder is undiagnosed. Prevalence was estimated at 0.3% in a French screening programme, and the annual incidence was 15.3–132.6 per 100000 people in studies in the UK and Sweden (Blachier et al., 2013).

Pathogenesis and pathology:

Following hepatic injury, hepatic stellate cells are activated with expression of smooth muscle specific actin. Different aetiological factors were suggested in activation of hepatic stellate cells: transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), acetaldehyde from alcohol metabolism may be involved and thrombin may also
stimulate stellate cell proliferation. Other growth factors and cytokines affect stellate cells include fibroblast growth factor, interleukin-1, epithelial growth factor (EGF) and tumor necrosis factor-(TNF-) (Friedman et al.,2008).

Following hepatic injury, the early changes in matrix in the space of Disse are important with formation of collagens (type I,II and V) and fibronectin. Sinusoids are converted to capillaries and there is loss of endothelial fenestra. The fibrous septa are formed, separating hepatocyte nodules which eventually replace the entire liver architecture, leading to decreased blood flow throughout (Friedman et al.,2008).

Etiology:

There are numerous causes of liver diseases that end with cirrhosis, either by causing chronic hepatic inflammation or cholestasis. The most common causes of cirrhosis in the United States are hepatitis C, alcoholic liver disease, and nonalcoholic liver disease, which together accounted for approximately 80 percent of patients on the liver transplantation waitlist between 2004 and 2013 (Wong et al., 2015).

Hepatitis C virus (HCV) is considered the most common etiology of chronic liver disease (CLD) in Egypt, where prevalence of antibodies to HCV (anti-HCV) is approximately 10-fold greater than in the United States and Europe. Reported are results that show HCV is the most common cause of liver cirrhosis in Egypt (Strickland et al. 2002).

In developed countries, common causes of cirrhosis include

- Chronic viral hepatitis (hepatitis B, C)
- Alcoholic liver disease
- Hemochromatosis
• Nonalcoholic fatty liver disease

**Less common causes include:**

• Autoimmune hepatitis
• Wilson disease
• Alpha-1 antitrypsin deficiency
• Primary and secondary biliary cirrhosis
• Primary sclerosing cholangitis
• Medications (eg, methotrexate, isoniazid)
• Idiopathic adulthood ductopenia
• Granulomatous liver disease
• Idiopathic portal fibrosis
• Polycystic liver disease
• Hereditary hemorrhagic telangiectasia
• Veno-occlusive disease
• Infection (eg, brucellosis, syphilis, echinococcosis)
• Right-sided heart failure

*(Heidelbaugh and Bruderly, 2006)*

**General Causes:**

**Alcoholism**

Chronic alcoholism cause alcoholic liver disease (also called alcohol-induced liver disease). Alcoholic liver disease includes fatty liver (build-up of fat cells in the liver), alcoholic hepatitis (inflammation of the liver caused by chronic drinking), and alcoholic cirrhosis. Alcoholic cirrhosis is the primary type of cirrhosis in the U.S. It develops in 10 -
20% of heavy drinkers, usually after 10 - 15 years of heavy alcohol consumption (Wong et al., 2015).

**Chronic Hepatitis**

Chronic hepatitis, both hepatitis B and hepatitis C, is another primary cause of cirrhosis. Chronic hepatitis C is a more common cause of cirrhosis in developed countries, while hepatitis B is a more common cause of cirrhosis worldwide, especially in Africa and parts of Asia. People with chronic hepatitis B who are co-infected with hepatitis D are especially at risk for cirrhosis. The longer a patient has had chronic hepatitis, the greater the risk for eventually developing cirrhosis (Safaei et al., 2016).

**Autoimmune Hepatitis**

Autoimmune hepatitis develops when the immune system attacks the body's own cells and organs. People who have autoimmune hepatitis also often have other autoimmune conditions, including systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, scleroderma, inflammatory bowel disease, glomerulonephritis, and hemolytic anemia. Autoimmune hepatitis typically occurs in women ages 15 – 40 (Chang et al., 2015).

**Bile Ducts Disorders**

Disorders that block or damage the bile ducts can cause bile to back up in the liver, leading to inflammation and cirrhosis. These diseases include primary biliary cirrhosis and primary sclerosing chlorangitis (Toshikuni et al., 2014).

**Primary Biliary Cirrhosis.**
Up to 95% of primary biliary cirrhosis (PBC) cases occur in women, usually around age 50. In people with PBC, the immune system attacks and destroys cells in the liver’s bile ducts (Toshikuni et al., 2014).

**Primary Sclerosing Cholangitis.**

Primary sclerosing cholangitis (PSC) is a chronic disease that mostly affects men, usually around age 40. The cause is unknown, but immune system defects, genetics, and infections may play a role (Zhou et al., 2014).

**Nonalcoholic Fatty Liver Disease (NAFLD) And Nonalcoholic Steatohepatitis (NASH)**

Nonalcoholic fatty liver disease (NAFLD) occurs in people who do not drink a lot of alcohol. In fact, NAFLD is now the most common liver disease in American children (Nusrat et al., 2014).

Nonalcoholic fatty liver disease can lead to nonalcoholic steatohepatitis (NASH). NASH is characterized by liver inflammation and injury, as well as a fatty liver. NASH occurs in about half of people with diabetes and up to 75% of obese people (Nishikawa and Osaki, 2015).

**Hereditary Disorders**

**Hemochromatosis.**

Hemochromatosis is a disorder of iron metabolism. This disease interferes with the way the body normally handles iron. The iron overload accumulates in organs in the body. When excess iron deposits accumulate in the liver, they can cause cirrhosis (Nishikawa and Osaki, 2015).
Other Hereditary Disorders:

Other inherited diseases that can cause cirrhosis include Wilson’s disease (which causes an accumulation of copper in the body), alpha-1 antitrypsin deficiency (a genetic disorder caused by defective production of a particular enzyme), and glycogen storage diseases (a group of disorders that cause abnormal amounts of glycogen to be stored in the liver) (Zhou et al., 2014).

Classification of cirrhosis:

(I) Morphological classification:

1. Micronodular cirrhosis:

   It is characterized by regenerating small nodules (2ml) separated by thin fibrous septa. It is characterized by involvement of every lobule. It represents impaired capacity for regrowth usually due to chemical agent as in alcoholism which diffuse uniformly through the liver. (Huang et al., 2011).

2. Macronodular cirrhosis:

   This type is characterized by septa and nodules of variable size; larger nodules separated by wider scars and irregularly distributed throughout the liver, usually due to an infectious agent such as viral hepatitis which does not diffuse uniformly throughout the liver (Huang et al., 2011).

3. Mixed cirrhosis:
It occurs when both macro and micronodules are present with equal frequency. There is however, no aetiological, functional, or prognostic value to nodule size. (Ahmed, 2015).

(II) Histological or pathological classification:

(A) **Portal cirrhosis:** It is the commonest form. It is so called because the pathological changes are mainly in the portal tract. It may be macronodular or micronodular type (Kim et al., 2011).

The causes of portal cirrhosis include (Rastogi et al., 2013):

1. Idiopathic.
2. Post-hepatitic.
3. Nutritional and alcoholic cirrhosis.
4. Metabolic cirrhosis.
5. Autoimmune hepatitis.

(B) **Biliary cirrhosis:** Biliary cirrhosis refers to nodular fibrosis due to bile duct obstruction, which may be intrahepatic or extra hepatic. It may be 1<sup>st</sup> or 2<sup>nd</sup> (Kim et al., 2011).

**1-Primary Biliary Cirrhosis (PBC):**

Primary biliary cirrhosis is a chronic cholestatic liver disease with a variable clinical course. It has been called chronic non suppurative destructive cholangitis. It is an autoimmune liver disease characterized by destruction of intrahepatic bile ducts, and high titers of antimitochondrial antibodies in serum (Kim et al., 2011).
2-Secondary biliary cirrhosis:

It is a sequel of long standing obstruction of the biliary tract for more than one year before cirrhosis develops, sclerosing cholangitis and genetic or developmental diseases in which cholestasis is prominent (e.g. cystic fibrosis, biliary atresia) (Rastogi et al., 2013).

(c) Cardiac cirrhosis: A rare form of cirrhosis resulting from chronic hepatic congestion.

(III) Aetiological classification:


2- Alcohol (Huang et al., 2011).

3- Metabolic; hemochromatosis, Wilson’s disease, alpha-1 antitrypsin deficiency, type IV glycogenosis, galactosemia, congenital tyrosinosis, non-alcoholic steatohepatitis and intestinal bypass (Pinto et al., 2015).

4- Prolonged intra- and extra-hepatic cholestasis (Sari et al., 2012).

5- Hepatic venous outflow obstruction as in Budd-Chiari syndrome, veno-occlusive disease and constrictive pericarditis (Sari et al., 2012).

6- Disturbed immunity (autoimmune hepatitis) (Roberts, 2011)

7- Toxins and therapeutic agents e.g. methotrexate and amiodarone (Pinto et al., 2015).

8- Other possible factors to be considered include the following:

   a) Malnutrition, infection (e.g. syphilis and malaria)

   b) Cryptogenic cirrhosis (Pinto et al., 2015)

(IV) Functional classification:
Compensated Cirrhosis

Compensated cirrhosis means that the liver is heavily scarred but can still perform many important bodily functions. Many people with compensated cirrhosis experience few or no symptoms and can live for many years without serious complications (D’Amico et al., 2006).

Decompensated Cirrhosis

Decompensated cirrhosis means that the liver is extensively scarred and unable to function properly. People with decompensated cirrhosis eventually develop many symptoms and complications that can be life threatening (Garcia-Tsao et al., 2010).

Clinical presentation and Diagnosis

Cirrhosis is often asymptomatic until complications of liver disease develop. Undiagnosed cirrhosis is a common finding at autopsy. Diagnosis of asymptomatic cirrhosis usually occurs when incidental screening tests as, liver transaminases or clotting function tests or radiological findings suggest liver disease (Chen et al., 2011).

CLINICAL FEATURES

Patients with cirrhosis may come to clinical attention in numerous ways:

- Stigmata of chronic liver disease on physical examination (e.g., palmar erythema, spider telangiectasias)
- Abnormal serum chemistry test results and hematologic indices (e.g., serum aminotransferases, bilirubin, alkaline phosphatase, albumin, prothrombin time, and platelet count).
- Radiographic abnormalities (e.g., small, shrunken, nodular liver on ultrasound or computed tomographic [CT] examination)
- Complications of decompensated liver disease (e.g., ascites, variceal hemorrhage)

(Friedman and Keeffe, 2011)

A patient with cirrhosis may present with none, some, or all of the following findings (Table. 1).

Table. 1: Cirrhosis findings (Friedman and Keeffe, 2011):

<table>
<thead>
<tr>
<th>General features:</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Fatigue</td>
</tr>
<tr>
<td>✓ Anorexia</td>
</tr>
<tr>
<td>✓ Malaise</td>
</tr>
<tr>
<td>✓ Weight loss</td>
</tr>
<tr>
<td>✓ Muscle wasting</td>
</tr>
<tr>
<td>✓ Fever</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Parotid enlargement</td>
</tr>
<tr>
<td>▪ Diarrhea</td>
</tr>
<tr>
<td>▪ Cholelithiasis</td>
</tr>
<tr>
<td>▪ Gastrointestinal bleeding</td>
</tr>
<tr>
<td>✓ Esophageal/gastric/duodenal/rectal/stomalvarices</td>
</tr>
<tr>
<td>✓ Portal hypertensive gastropathy/enteropathy/colopathy</td>
</tr>
</tbody>
</table>
**Hematologic**
- Anemia
  - Spur cell anemia (hemolytic anemia seen in severe alcoholic liver disease)
  - Splenomegaly with resulting pancytopenia
- Thrombocytopenia
- Leukopenia
- Impaired coagulation
- Disseminated intravascular coagulation
- Hemosiderosis

**Pulmonary**
- Decreased oxygen saturation
- Altered ventilation–perfusion relationships
- Portopulmonary hypertension
- Hyperventilation
- Reduced pulmonary diffusion capacity
- Hepatic hydrothorax

**Cardiac: hyperdynamic circulation**

**Renal**
- Secondary hyperaldosteronism leading to sodium and water retention
- Renal tubular acidosis (more frequent in alcoholic cirrhosis, Wilson disease, and primary biliary cirrhosis)
- Hepatorenal syndrome

**Endocrinologic**
- Hypogonadism
- Feminization (acquisition of estrogen-induced characteristics)
- Diabetes

**Neurologic**
- Hepatic encephalopathy
- Peripheral neuropathy
- Asterixis
### Musculoskeletal

- Reduction in lean muscle mass
- Hypertrophic osteoarthropathy: synovitis, clubbing, and periostitis
- Hepatic osteodystrophy
- Muscle cramps
- Umbilical herniation

### Dermatologic

- Spider telangiectases
- Palmar erythema
- Nail changes
- Pruritus
- Clubbing
- Jaundice

### Laboratory findings (Nagasako et al., 2009; Jalan et al., 2014).

Several laboratory abnormalities may be seen in patients with cirrhosis. In addition, because it is common for panels of serum chemistries to be sent for screening or evaluation of specific complaints, laboratory abnormalities may be the first indication that a patient has cirrhosis. Common abnormalities include elevated serum bilirubin, abnormal aminotransferases, elevated alkaline phosphatase/gamma-glutamyl transpeptidase, a prolonged prothrombin time/ elevated international normalized ratio (INR), hyponatremia, and thrombocytopenia (Nagasako et al., 2009; Jalan et al., 2014).

### Serum chemistries

Hyponatremia is common in patients with cirrhosis and ascites and is related to an inability to excrete free water hypervolemic type. This results primarily from high levels of anti-diuretic hormone secretion (Shaikh et al., 2010). Hyponatremia often becomes severe as cirrhosis progresses to end-stage liver disease (Ennaifer et al., 2016). As cirrhosis
progresses, patients may develop hepatorenal syndrome, with a progressive rise in serum creatinine (Anavi et al., 2015).

- Imaging studies

**Ultrasonography**

One of the noninvasive, well tolerated imaging studies. In advanced cirrhosis, the liver may appear small and nodular. Surface nodularity and increased echogenicity with irregular appearing areas are consistent with cirrhosis, but can also be seen with hepatic steatosis. There is typically atrophy of the right lobe and hypertrophy of the caudate or left lobes. Investigators have attempted to use the ratio of the width of the caudate lobe to the width of the right lobe as an ultrasonographic criterion for the diagnosis of cirrhosis. However, the sensitivity is poor (Yeom et al., 2015).

**Computed tomography**

Triphasic CT study is not routinely used in the diagnosis and evaluation of cirrhosis & its only useful when hepatic focal lesion is suspected. CT findings of hepatic nodularity, atrophy of the right lobe and hypertrophy of the caudate or left lobes, ascites, or varices suggest the presence of cirrhosis & also detect hepatic focal lesions (Huber et al., 2014; Yeom et al., 2015; Merli et al., 2016).

**Liver biopsy**

The gold standard for diagnosing cirrhosis is examination of an explanted liver, either at autopsy or following liver transplantation, because the architecture of the entire liver can be appreciated. In clinical practice, cirrhosis is diagnosed with a liver biopsy during which a sample of the liver is obtained by either a percutaneous, transjugular, laparoscopic, or radiographically-guided fine-needle approach (Sanada
et al., 2014). The method for obtaining the biopsy will depend on the clinical setting. The sensitivity of a liver biopsy for cirrhosis is in the range of 80 to 100 percent, depending on the method used, and the size and number of specimens obtained (Sanada et al., 2014; Jain et al., 2016).

Assessing the severity of cirrhosis:

A. Child–Turcotte–Pugh (CTP) score

Child and Turcotte published a classification system as a tool to determine the pre-operative risk of portosystemic shunt surgery for patients with variceal bleeding. It took into account five factors, including ascites, encephalopathy, nutritional status, and serum levels of bilirubin and albumin. Pugh et al modified this system and replaced nutritional status with prothrombin time (PT) and assigned a score ranging from 1 to 3 for each variable. This modified score was eventually expanded to predict outcomes in cirrhotic patients undergoing surgery (Table. 3) (Wayne et al., 2002; Zhao et al., 2012).

Table.2: Child–Turcotte–Pugh (CTP) score for cirrhosis patients (Wayne et al., 2002)

<table>
<thead>
<tr>
<th>Child-Turcotte-Pugh Classification for Severity of Cirrhosis</th>
<th>Points*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt; 3.5</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
</tr>
</tbody>
</table>

*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)

Class A = 5 to 6 points (least severe liver disease)
Class B = 7 to 9 points (moderately severe liver disease)
Class C = 10 to 15 points (most severe liver disease)
B. Model for End-stage Liver Disease (MELD)

The Model for End-stage Liver Disease (MELD) is a prospectively developed and validated chronic liver disease severity scoring system that uses a patient's laboratory values for serum bilirubin, serum creatinine, and the international normalized ratio (INR) for prothrombin time to predict three-month survival. In patients with cirrhosis, an increasing MELD score is associated with increasing severity of hepatic dysfunction and increased three-month mortality risk. Given its accuracy in predicting short-term survival among patients with cirrhosis, MELD was adopted by the United Network for Organ Sharing (UNOS) in 2002 for prioritization of patients awaiting liver transplantation in the United States. For example, a patient with a MELD score less than or equal to 15 has a predicted 3-month survival of 95% while a patient with a MELD score of 30 has a predicted 3-month survival of only 65% (Delis et al., 2009).

Calculation of MELD Score: The MELD score, which estimates the survival probability of a patient with end-stage liver disease, is based on three commonly obtained laboratory parameters: serum bilirubin, serum creatinine, and international normalized ratio (INR) (Figure. 2) (Freeman et al., 2002).

<table>
<thead>
<tr>
<th>Model for End Stage Liver Disease (MELD) Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MELD</strong> = 3.78 x ( \log_e ) serum bilirubin (mg/dL) + 11.20 x ( \log_e ) INR + 9.57 x ( \log_e ) serum creatinine (mg/dL) + 6.43 (constant for liver disease etiology)</td>
</tr>
</tbody>
</table>

**NOTES:**
- If the patient has been dialyzed twice within the last 7 days, then the value for serum creatinine used should be 4.0
- Any value less than one is given a value of 1 (i.e. if bilirubin is 0.8, a value of 1.0 is used) to prevent the occurrence of scores below 0 (the natural logarithm of 1 is 0, and any value below 1 would yield a negative result)
Management

Generally, liver damage from cirrhosis cannot be reversed, but treatment could stop or delay further progression and reduce complications. A healthy diet is encouraged, as cirrhosis may be an energy-consuming process. Close follow-up is often necessary. Antibiotics are prescribed for infections, and various medications can help with itching. Laxatives, such as lactulose, decrease risk of constipation; their role in preventing encephalopathy is limited (Lee et al., 2015).

Alcoholic cirrhosis caused by alcohol abuse is treated by abstaining from alcohol. Treatment for hepatitis–related cirrhosis involves medications used to treat the different types of hepatitis, such as interferon for viral hepatitis and corticosteroids for autoimmune hepatitis. Cirrhosis caused by Wilson's disease, in which copper builds up in organs, is treated with chelation therapy (for example, penicillamine) to remove the copper (Liou, 2014; Angeli et al., 2015).

- Preventing further liver damage

Regardless of underlying cause of cirrhosis, alcohol and paracetamol, as well as other potentially damaging substances, are discouraged. Vaccination of susceptible patients should be considered for hepatitis A and hepatitis B (Menachery and Duseja, 2011).

- Liver Transplantation
If complications cannot be controlled or when the liver ceases functioning, liver transplantation is necessary. Survival from liver transplantation has been improving and the five-year survival rate is now around 80%. The survival rate depends largely on the severity of disease and other medical problems in the recipient. In the United States, the MELD score is used to prioritize patients for transplantation (Kamath and Kim, 2007). Transplantation necessitates the use of immune suppressants (cyclosporine or tacrolimus).

- **Management of compensated cirrhosis**

  Patients with compensated cirrhosis are not jaundiced and have not yet developed ascites, encephalopathy, or variceal hemorrhage. The median survival of patients with compensated cirrhosis is ~ 9 years, but it is as long as 12 years when patients are censored at the time of decompensation (D'Amico et al., 2006). The two goals in the management of compensated cirrhosis are (i) treatment of the underlying liver disease (e.g., hepatitis C or B, alcohol, non-alcoholic steatohepatitis), and (ii) prevention/early diagnosis of the complications of cirrhosis. The treatment of the underlying liver disease is beyond the scope of these recommendations. The main recommendations specific to patients with newly diagnosed cirrhosis are screening for varices and HCC (Garcia-Tsao and Lim, 2009).

- **Decompensated cirrhosis**

  In patients with previously stable cirrhosis, decompensation may occur due to various causes, such as constipation, infection (of any source), increased alcohol intake, medication, bleeding from esophageal varices or dehydration. It may take the form of any of the complications of cirrhosis (Angeli et al., 2015).
Patients with decompensated cirrhosis generally require admission to hospital, with close monitoring of the fluid balance, mental status, and emphasis on adequate nutrition and medical treatment - often with diuretics, antibiotics, laxatives and/or enemas, thiamine and occasionally steroids, acetylcysteine and pentoxifylline. Administration of saline is avoided as it would add to the already high total body sodium content that typically occurs in cirrhosis (Harrison, 2015).

- **Palliative care**

  Palliative care is specialized medical care that focuses on providing patients with relief from the symptoms, pain, and stress of a serious illness, such as cirrhosis. The goal of palliative care is to improve quality of life for both the patient and the patient's family and it is appropriate at any stage and for any type of cirrhosis (Ferrell et al., 2007).

  Especially in the later stages, people with cirrhosis experience significant symptoms such as abdominal swelling, itching, leg edema, and chronic abdominal pain which would be amenable for treatment through palliative care (Sanchez and Talwalkar, 2006). People with cirrhosis are rarely referred to palliative care (Poonja et al., 2014).

**Complications of cirrhosis**

- **Variceal haemorrhage**

  Patients with cirrhosis who present with upper gastrointestinal hemorrhage should have a diagnostic endoscopy performed to investigate the possibility of variceal hemorrhage, as indicated by the presence of: active bleeding from a varix, a “white nipple” overlying a varix, clots overlying a varix, or varices with no other potential source of bleeding (Fortune and Garcia-Tsao, 2014). As portal blood pressure increases,
blood is forced through anatomical venous anastomoses between portal and systemic circulations. These dilated varices are thin walled and prone to spontaneous bleeding. The majority of varices occur within the lower oesophagus (90%) but can also occur in the stomach or elsewhere in the GIT. Despite the improvements in management, the mortality from variceal haemorrhage remains high. In those with advanced cirrhosis and active variceal bleeding the mortality is 30%. For many patients variceal haemorrhage may be the initial presentation of their chronic liver disease (Fortune and Garcia-Tsao, 2014).

- **Ascites**

  Ascites is the most common complication of cirrhosis and is associated with a poor prognosis and quality of life. It is primarily caused by increased renal sodium retention in response to the splanchnic vasodilation which occurs in portal hypertension (EASL, 2012).

- **Sepsis**

  Patients with cirrhosis are prone to a variety of bacterial and other infectious complications. Most common infections include urinary tract and lower respiratory infection together with bacteraemia and spontaneous bacterial peritonitis. Sepsis is estimated to cause up to a quarter of all deaths in cirrhotic patients (Lee et al., 2015).

  Furthermore, patients with cirrhosis show a greater systemic response to infection than non-cirrhotic patients, resulting in an increased incidence of septic shock, multiorgan failure and death. Early recognition and empirical broad-spectrum antimicrobial therapy is key to the
successful management of this complication (Sulpice et al., 2014; Lee et al., 2015).

- Spontaneous bacterial peritonitis

  Approximately 10% of in-patients with ascites will develop spontaneous bacterial peritonitis (SBP). Early recognition and treatment can reduce mortality from >90% to approximately 20%. Ascitic fluid neutrophil count >250/mm3 is diagnostic. Culture of ascitic fluid may be negative. Albumin infusion 1.5 g/kg at diagnosis and 1 g/kg on day 3 reduces the risk of developing renal impairment and improves survival (EASL, 2010).

- Renal dysfunction

  Renal impairment is frequently seen in cirrhotic patients and is a poor prognostic sign. Up to 60% of those admitted to ICU with cirrhosis will have renal dysfunction. Acute renal dysfunction may be due to sepsis, hypovolaemia, acute tubular necrosis, drug-induced renal failure, parenchymal renal disease or hepatorenal syndrome (HRS) (Demirtas et al., 2006).

  In hepatorenal syndrome portal hypertension induces splanchnic vasodilation leading to a reduction in effective arterial blood volume, subsequent activation of the sympathetic nervous system and renin-angiotensin-aldosterone system and consequently profound renal vasoconstriction. Two forms of HRS are described: type 1 HRS in which renal dysfunction is acute and rapidly progressive, and has extremely high mortality without liver transplantation; type 2 is more indolent in progression of HRS (Pinto et al., 2015).

- Hepatic encephalopathy
Hepatic encephalopathy (HE) is a frequent and debilitating complication of cirrhosis. Overt HE occurs in 30-40% of patients with cirrhosis and has a high rate of recurrence. It is a potentially reversible syndrome which produces a wide spectrum of neuropsychiatric manifestations. The pathophysiology is complex and incompletely understood but relates to elevated plasma and CNS ammonia levels resulting in neuronal oedema (Vilstrup et al., 2014). Diagnosis is usually clinical but a raised serum ammonia or slow wave activity on electroencephalography (EEG) may support the diagnosis of HE. Consideration should also be given to other causes of altered mental status, particularly in the presence of a focal neurological deficit or atypical features (Vilstrup et al., 2014).

- **Hepatopulmonary syndrome (HPS)**

  Hepatopulmonary syndrome (HPS) is a complication of liver disease in which there is marked dilation of the pulmonary vascular beds leading to abnormalities of perfusion/ventilation matching and profound hypoxaemia. The pathophysiology is incompletely understood but thought due to the increase in circulating vasodilator substances (Suceveanu et al., 2013).

- **Hepatocellular Carcinoma**

  Cirrhosis is a major risk factor for the development of hepatocellular carcinoma. Its pathogenesis results from the development of regenerative nodules with small-cell dysplasia that leads to cellular carcinoma (Faber et al., 2014; Xin et al., 2014).
Chapter (2)

Spontaneous bacterial peritonitis

Definition:

Spontaneous bacterial peritonitis (SBP) is an acute bacterial infection of ascitic fluid. SBP was defined by presence of a polymorphonuclear leukocyte (PMN) count of >250 cells/mm$^3$ in ascitic fluid sample and culture-positive SBP implied a positive culture result in ascitic fluid among SBP (Kim et al., 2016).

Epidemiology:

SBP is one of the most frequent bacterial infections in patients with cirrhosis and ascites, occurring in 10% to 25% of these patients (Lutz et al., 2015). In addition, SBP is associated with high mortality rates (20%–40%) in these patients (Tandon and Garcia-Tsao, 2008; Cheong et al., 2009).

SBP in patients with cirrhosis is typically caused by gram-negative bacteria that are part of the intestinal microbial flora (mainly species in the family Enterobacteriaceae) (Caruntu and Benea, 2006). Thus, 3rd-generation cephalosporins are the initial empirical therapy for SBP according to current guidelines (Runyon, 2009; EASL, 2010). However, in recent years there has been an increase in invasive procedures, antibiotic prophylaxis, and widespread antibiotic use in patients with cirrhosis, which has changed the bacterial spectrum and lead to an increase in SBP by gram-positive bacteria (Reuken et al., 2012; Alexopoulou et al., 2013).
Chapter 2  
Spontaneous bacterial peritonitis

Variants of spontaneous bacterial peritoneal infection:

Multiple variants of this infection have been described; each has a slightly different clinical setting and outcome (Mowat and Stanley, 2001).

- **Classical SBP**: PMNs > 250 cells/mm³ with positive ascitic culture for single organism.

- **Culture-negative SBP**: PMNs > 250 cells/mm³ with negative ascitic culture.

- **Mono-microbial non-neutrocytic bacteriascites**: PMNs < 250 cells/mm³ with positive ascitic culture for single organism.

- **Poly-microbial bacteriascites**: PMNs < 250 cells/mm³ and culture with multiple organisms.

- **Secondary bacterial peritonitis**: PMNs > 250 cells/mm³ and culture with multiple organisms. The ascitic fluid must present two of the following characteristics: total protein > 1 g/dL, glucose < 50 mg/dL, and lactate dehydrogenase (LDH) > 225 U/l (Mowat and Stanley, 2001).

Pathophysiology of SBP in cirrhotic patients:

when Gram-negative microorganisms of intestinal origin migrate from the intestinal lumen to mesenteric lymph nodes or other extraintestinal organs and sites, this is known as bacterial translocation (BT) (Garcia-Tsao and Wiest, 2004; Anikina et al., 2014). This leads to disruption of the normal host/flora equilibrium that leads to a self-perpetuating inflammatory response and, ultimately, infection. BT becomes clinically relevant due to changes in intestinal flora, portal hypertension, and, mainly, impairment in local/systemic immune defense.
mechanisms, as occurs in advanced cirrhosis. Indeed, susceptibility to bacterial infections parallels the severity of the disease (Bauer et al., 2002) (Figure. 2).

**Figure (2):** Altered gut permeability and bacterial overgrowth in cirrhotic patients lead to translocation of intestinal bacteria to the systemic circulation and bacteremia. Seeding of bacteria to the ascitic fluid leads to spontaneous bacterial peritonitis. Leukocyte dysfunction and decreased ascitic fluid defense mechanisms facilitate this process (Bauer et al., 2002).

Several mechanisms account for an abnormal BT in cirrhosis. Among these, bacterial overgrowth with expansion of aerobic Gram-negative bacterial flora has been described, possibly due to impaired small-bowel motility and a decreased intraluminal concentration of bile salts (Zhang et al., 2003; Tandon and Garcia-Tsao, 2008; Bernardi, 2010). These microbial species translocate more readily than anaerobes. Namely, certain Escherichia coli strains possess a great ability to adhere to the intestinal mucosa and are highly resistant against host defense
mechanisms (Bellot et al., 2013). In addition, structural abnormalities in intestinal mucosa, including widening of intercellular spaces, edema, vascular congestion and inflammation, lead to an enhanced permeability (Assimakopoulos et al., 2013).

Once microorganisms have gained access to the mesenteric lymph nodes, their persistence and further dissemination to the blood stream via the lymphatic system is facilitated by an impairment in both innate and acquired immunity. Abnormalities in reticuloendothelial system function, and non-specific humoral and cell-mediated immunity have been described in cirrhotic patients (Fouts et al., 2012; Brenner et al., 2015; Vogt et al., 2016). Defective neutrophil granulocyte functions, such as chemotaxis, adherence, phagocytosis, and bacterial killing capacity also play a major role, and have long been recognized (Fukui, 2015). All these mechanisms also favor the occurrence and persistence of bacteremia, either due to invasive diagnostic or therapeutic procedures, or the presence of localized infections, thus promoting bacterial seeding in different organs and sites. In this respect, low ascitic complement levels correlate with decreased opsonic activity, impaired bacterial killing and an increased risk of developing spontaneous bacterial peritonitis (SBP) (Nakamura, 2014).

Other factors facilitating bacterial infections in patients with cirrhosis are portal hypertension and malnutrition. Portal hypertension likely plays an important role in favoring both BT, by altering the anatomo-functional gut barrier, and the failure to clear portal or systemic bacteria and bacterial products which bypass the liver’s reticuloendothelial system through portosystemic shunting (Anikina et al., 2014). Whether increased portal pressure, demonstrated to be a risk factor for variceal bleeding, ascites, and hepatic encephalopathy in a large
cohort of compensated cirrhotic patients (Ripoll et al., 2007), is also associated with the risk of developing bacterial infections has not been ascertained. Poor nutritional status also plays a role, as both innate and acquired immunity are impaired in patients with severe malnutrition (Sam and Nguyen, 2009). In fact, innate and acquired immunity require immune cells activation and proliferation, which imply an increase in energy consumption. Malnutrition is commonly encountered in patients with advanced cirrhosis and is associated with increased prevalence of complications and mortality, especially when the protein compartment is involved (Nishikawa et al., 2017).

**Risk factors:**

1. A prior episode of SBP is the most important risk factor; two thirds of these patients will develop a recurrence of infection within the following year (Căruntu and Benea, 2006).

2. Gastrointestinal hemorrhage specifically variceal hemorrhage is a major risk factor for ascetic fluid infection. The cumulative probability of infection during a single hospitalization for bleeding is approximately 40% (Bernard et al., 1995).

3. Patients with fulminant hepatic failure are at risk of developing SBP (Guarner and Runyon, 1995).

4. An ascetic fluid total protein <1.0g/dl carries an increased risk of infection. SBP develops 10 times more frequently in hospitalized cirrhotics with low protein ascites than with high protein ascites (Tito et al., 1988).
Clinical presentation and diagnosis:

SBP is an ominous complication: its first descriptions, dating back to the first half of the last century, reported a mortality exceeding 90%. Such a figure did not substantially change up to the 1980s, when awareness and early recognition of the disease allowed prompt and appropriate antibiotic treatment thereby reducing the mortality rate to around 30% (Garcia-Tsao, 2004; Barreales and Fernandez, 2011). However, nosocomial SBP still carries a severe prognosis, with an overall 30-day mortality rate up to 58%, mainly due to infection by antibiotic-resistant bacterial strains (Cheong et al., 2009).

Early recognition of SBP is of paramount importance. However, signs of peritonitis are usually lacking up to the advanced stage of the disease, once the peritoneum is also involved by inflammation, and even non-specific signs of infection can be scarcely evident or even absent at presentation. At that time, up to 20% of patients are asymptomatic and the most frequent symptoms/signs (70–80%) are the appearance or worsening of hepatic encephalopathy and/or deterioration of renal function (Rimola et al., 2000; Shah et al., 2016). Thus, diagnostic paracentesis should be performed as soon as SBP is suspected, particularly in patients with fever and/or leukocytosis, and in any patient admitted to the hospital or emergency room, irrespective of SBP symptoms. Diagnosis relies on finding an ascites polymorphonuclear cell count greater than 250/μL, independent of ascites bacteriological culture results (Shah et al., 2016). Patients with hepatic hydrothorax should undergo diagnostic thoracentesis even when SBP has been ruled out, as spontaneous bacterial empyema can occur even when the ascitic fluid is not infected (Makhlouf et al., 2013).
Consequences of SBP

Advanced cirrhosis is characterized by a hyperdynamic circulatory syndrome, which results from the reduction of peripheral vascular resistance and represents the background of severe complications, such as hepatorenal syndrome (HRS) and increased susceptibility to shock (Domenicali et al., 2009).

Circulatory failure

Although an exact definition of the incidence of severe sepsis and septic shock in cirrhotic patients developing SBP or other bacterial infections is still lacking, it is conceivable that the effects of NO and other vasodilating systems on the smooth muscle, endothelial cells and cardiomyocytes promote further vasodilation and cardio-depression, eventually leading to refractory hypotension (Ren and Wu, 2006; Berk et al., 2015).

Renal failure

About a third of patients with SBP develop renal dysfunction, irrespective of the resolution of the infection. Interestingly, acute progressive renal failure can ensue even in the absence of shock. This kind of renal dysfunction is functional and does not improve with plasma volume expansion; such features are diagnostic of hepatic renal syndrome (HRS) type 1 (Salerno et al., 2007, 2008). HRS in the setting of SBP likely results from the worsening of splanchnic and systemic vasodilation leading to a further impairment in effective volemia. This results in activation of vasoconstrictor neurohumoral systems that leads to renal vasoconstriction. Cirrhotic cardiomyopathy also contributes as patients
with renal dysfunction have a lower baseline cardiac output which further declines with SBP (Lenz et al., 2004; Choi et al., 2008).

**Hepatic encephalopathy**

It is well known that SBP and other infections can worsen or precipitate hepatic encephalopathy, which often heralds such complications (Cordoba and Minguez, 2008). The mediators of systemic inflammatory response syndrome (SIRS), namely NO and pro-inflammatory cytokines, are likely responsible for such adverse effects, by modulating the cerebral effect of ammonia. The mechanisms underlying these abnormalities in cerebral function are far from being clarified, but production of reactive oxygen species, the direct effect of inflammatory cytokines on cerebral endothelial cells, astrocytes and vagal afferents, and reduced cerebral blood flow could all contribute (Blei, 2004; Cordoba, 2014).

**Coagulopathy**

The release of cytokines, such as tumor necrosis factor-α, interleukin 1 and 6, enhances coagulation abnormalities and the platelet dysfunction of cirrhosis. Hyperfibrinolysis, clotting factors consumption and production of endogenous heparin-like substances have been reported in cirrhotic patients with infection (Zambruni et al., 2004). These abnormalities, along with an increase in portal pressure, account for an increased incidence of variceal bleeding and consequent mortality (Triantos et al., 2014).

**Acute respiratory distress syndrome**

Cirrhosis seems to be an independent predicting factor of death in Acute respiratory distress syndrome (ARDS) patients (TenHoor et al.,
Chapter (2) Spontaneous bacterial peritonitis

2001). Again, infection-induced production and release of pro-inflammatory cytokines, NO and leukotrienes are thought to be involved in the development of ARDS in cirrhotic patients with sepsis (Rincon et al., 2012; Veeravagu et al., 2013).

Relative adrenal insufficiency

As in non-cirrhotic patients with sepsis, relative adrenal insufficiency, as defined by a blunted rise in cortisolemia after adrenocorticotropic hormone (ACTH) administration, has been reported in up to half of patients with cirrhosis. Relative adrenal insufficiency is associated with a greater need for vasopressors and increased in-hospital and 3-month mortality, up to 81 and 85%, respectively (Tsai et al., 2006).

Liver failure

Sepsis further impairs liver function, so that bacterial infections are a major cause of acute-on-chronic liver failure (Sen et al., 2002). The mechanisms leading to such a rapid deterioration have not been clarified. Studies in animal models of cirrhosis suggest lipopolysaccride challenge promotes hepatocyte death due to tumor necrosis factor-α-induced apoptosis. In addition, endoplasmic reticulum stress shuts down protein synthesis, thereby contributing to sepsis-induced liver dysfunction (Tazi et al., 2007).

Treatment

Intravenous antibiotics

If suspicion for SBP arises (i.e. fever, abdominal pain or tenderness, altered mental status, or otherwise unexplained decompensation in
patients with cirrhosis and ascites), then antibiotics should be started immediately to reduce complications and improve survival. Third-generation, broad-spectrum cephalosporins are the agents of choice for SBP treatment because of their superiority in randomised controlled trials and rare side effect profile with minimal risk of nephrotoxicity compared to other antibiotics (Cartier et al., 2010; Narula et al., 2011).

**Empiric treatment recommendations**

A. Cefotaxime 2 g IV q8h or

B. Ceftriaxone 1-2 g IV q24h or

C. Ticarcillin-clavulanate 3.1 g IV q6h or

D. Piperacillin-tazobactam 3.375 g IV q6h or 4.5 g IV q8h or

E. Ampicillin-sulbactam 3 g IV q6h or

F. Ertapenem 1 g IV q24h or

G. Levofloxacin 500 mg IV q24h or

H. Moxifloxacin 400 mg IV q24h

Duration of therapy is unclear; however, treatment for 5 days has shown success; 2 weeks is recommended if blood cultures are positive (Cartier et al., 2010).

**Antibiotics for multi-resistant bacteria**

Emergence of antibiotic resistance and changing profile to SBP-causing-bacteria have made standard treatment less reliable in some instances. In fact, 8–22% of Enterobacteriaceae have cephalosporin resistance (Papp et al., 2007; Strauss, 2013).
Albumin

Albumin is a single chain peptide protein, made in the liver, with a half-life of approximately 21 days. It regulates plasma oncotic pressure, buffers plasma, scavenges free radicals, and transports hormones, fatty acids, unconjugated bilirubin, metals, ions, and drugs. The structure and function of albumin is abnormal in advanced liver disease thereby impairing many key physiological processes (Jalan et al., 2009; Bernardi et al., 2014).

Prevention

The ominous fate of SBP warrants its prevention. First, general measures such as avoiding unnecessary hospitalization and invasive procedures, and counteracting malnutrition should be pursued. In addition, antibiotic prophylaxis can be instituted. As SBP usually results from BT of Gram-negative microorganisms of intestinal origin, an ideal prophylaxis would require safe and affordable agents able to decrease the bulk of these bacteria in the gut, but preserve the anaerobic flora. Such a selective intestinal decontamination is usually achieved by administering the poorly absorbed antibiotic norfloxacin (Fernandez et al., 2002; Papp et al., 2016).

Primary prophylaxis in acute gastrointestinal bleeding

Different antibiotic regimens have been employed, but oral norfloxacin 400 mg bid for 7 days is the most widely employed. As already reported (Papp et al., 2016), the epidemiology of bacterial infections in cirrhosis has changed in recent years, and the search for different approaches is warranted (Fernandez et al., 2006).
Primary prophylaxis in high risk patients

It has long been recognized that low ascitic fluid protein concentration (<10 g/L), and, therefore, reduced opsonic activity, and/or high serum bilirubin levels imply a high risk of developing a first episode of SBP (Terg et al., 2008).

Secondary prophylaxis in patients who have recovered from SBP

Patients surviving an episode of SBP have a 70% probability of recurrence at 1 year and a poor expected survival. It is uncertain whether prophylaxis should be continued until liver transplantation or death in all patients with prior SBP or could be discontinued in those showing an improvement of cirrhosis. The drug of choice has been norfloxacin 400 mg daily; however, there is increasing concern about the role of fluoroquinolones because of the potential for resistant pathogens (Chavez-Tapia et al., 2010).

Alternatives to antibiotic prophylaxis

Due to the risk of selecting antibiotic-resistant bacterial strains, alternative means of preventing SBP would be most welcomed. Prokinetics, such as cisapride, probiotics and bile salts have been employed. Although some studies showed a decrease of intestinal bacterial overgrowth in experimental cirrhosis, evidence for a reduced incidence of SBP or other bacterial infections in humans is still lacking (Bellot et al., 2010; Appenrodt et al., 2011).

Prognosis:

The mortality rate in patients with spontaneous bacterial peritonitis ranges from 40-70% in adult patients with cirrhosis. Patients with
concurrent renal insufficiency have been shown to be at a higher risk of mortality from spontaneous bacterial peritonitis than those without concurrent renal insufficiency. Mortality from spontaneous bacterial peritonitis may be decreasing among all subgroups of patients because of advances in its diagnosis and treatment (Mandorfer et al., 2014).
Cirrhosis represents the final stage of liver fibrosis. Patients with cirrhosis will eventually develop signs of portal hypertension including splenomegaly, esophageal varices, and ascites. Up to one-third of patients with cirrhosis and ascites will develop spontaneous bacterial peritonitis (SBP):

1. Mortality after an episode of SBP may be as high as 70% and increases with each subsequent episode

2. Current American

3. And European

4. guidelines recommend diagnostic paracentesis in all patients with decompensated liver disease and ascites in order to assess ascitic polymorphonuclear (PMN) cell count and exclude SBP.

The diagnosis rests upon an ascitic PMN cell count exceeding 250/ll. In most laboratories, PMN cell count is determined using manual or automated counting Cirrhosis represents the final stage of liver fibrosis. Patients with cirrhosis will eventually develop signs of portal hypertension including splenomegaly, esophageal varices, and ascites. Up to one-third of patients with cirrhosis and ascites will develop spontaneous bacterial peritonitis (SBP):

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The diagnosis rests upon an ascitic PMN cell count exceeding 250/ll. In most laboratories, PMN cell count is determined using manual or automated counting.

In the setting of cirrhosis, several abnormalities have been described in the humoral and cellular bactericidal systems including decreased serum levels of complement factors, impaired chemotaxis, poor function of phagocytes activity of neutrophils, and decreased function of Fc-g-receptors in macrophages (Wiest R, Garcia-Tsao G., 2005).

One of the earliest signs of infection is the acute-phase response. Acute-phase response may include the changes in the concentration of many plasma proteins, known as the acute-phase proteins that are synthesized almost exclusively in the liver; most are glycosylated (Strauss E and Gomes de Sá Ribeiro, 2003).

Inflammatory markers, such as C-reactive protein (CRP) and procalcitonin (PCT), and white blood cells (WBCs) could be used easily for the diagnosis and follow-up of several morbidities (Massaro KS et al., 2007).

**Possible Diagnostic Markers of SBP**

The possible serum or ascitic fluid markers of SBP reported in previous studies, except for the gold standard method of PMN count in the ascitic fluid, are as follows (Table 3).
Inflammatory markers in SBP

Table 3: The possible serum or ascitic fluid markers of spontaneous bacterial peritonitis reported in previous studies.

<table>
<thead>
<tr>
<th>Possible markers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In serum</strong></td>
</tr>
<tr>
<td>• Tumor necrosis factor-α</td>
</tr>
<tr>
<td>• Interleukin-6</td>
</tr>
<tr>
<td>• Procalcitonin</td>
</tr>
<tr>
<td>• High-sensitivity CRP</td>
</tr>
<tr>
<td><strong>In Ascitic fluid</strong></td>
</tr>
<tr>
<td>• Tumor necrosis factor-α</td>
</tr>
<tr>
<td>• Interleukin-6</td>
</tr>
<tr>
<td>• Lactoferrin</td>
</tr>
<tr>
<td>• Calprotectin</td>
</tr>
<tr>
<td>• Interferon-γ-induced protein 10kDa</td>
</tr>
<tr>
<td>• Macrophage inflammatory protein type 1 β</td>
</tr>
<tr>
<td>• High-sensitivity CRP</td>
</tr>
</tbody>
</table>

Proinflammatory Cytokines

Bacterial endotoxins are the main stimulus for the production of several proinflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6. In patients with SBP, TNF-α and IL-6 are released into the blood in response to hepatic injury (Abdel-Razik A. et al., 2016)

Lactoferrin

Lactoferrin is mainly produced by neutrophilic granulocytes and could therefore be a possible marker of PMN activity (Dever JB, Sheikh MY, 2015).

Previous studies showed that ascitic lactoferrin concentration was significantly increased in patients with SBP (Parsi MA et al., 2008)
Although lactoferrin detected in ascitic fluid has shown high sensitivity and specificity for the diagnosis of SBP (Dever JB, Sheikh MY, 2015), the timing of quantitative measurements remains to be clarified, and diagnostic test kits to measure lactoferrin are not yet commercially available.

**Procalcitonin**

A 116-amino acid prohormone of calcitonin, PCT, is normally synthesized in the C cells of the thyroid gland. Other sources of PCT include liver and inflammatory cells (Giamarellou H et al., 2004).

The serum PCT concentrations increase in patients with bacterial infections or sepsis (Simon L et al., 2004).

**Macrophage Inflammatory Protein Type 1 Beta**

Macrophage inflammatory protein type 1 beta (MIP-1β) is an acidic protein composed of 69 amino acids (Bode-Jänisch S et al., 2013).

It belongs to the family of chemokines, which are well known for their chemotactic and proinflammatory effects (Bode-Jänisch S et al., 2013).

The authors showed that ascitic MIP-1β levels were significantly higher in patients with SBP than in those without SBP, whereas there was no significant difference in serum MIP-1β levels between patients with and without SBP (Bode-Jänisch S et al., 2013). However, the number of studies on the diagnostic usefulness of MIP-1β is still limited.

**Interferon-γ-Induced Protein**

Interferon-γ-induced protein 10 kDa (IP-10) is one of the well-studied biomarkers of infection. It is involved in multiple biological functions, inducing chemotaxis, apoptosis, recruiting activated T-cells,
macrophages, and natural killer (NK) cells to sites of infection (Shiratori B. et al., 2014)

The possible usefulness of IP-10 in the serum and ascitic fluid for diagnosing SBP was reported by Abdel-razik et al. (Abdel-Razik A. et al., 2015)

The authors showed that serum and ascitic IP-10 levels were significantly higher in patients with SBP than in those without SBP. However, the number of studies on the diagnostic usefulness of IP-10 is still limited.

**High-Sensitivity (Sensitive) C-Reactive Protein**

The high-sensitivity C-reactive protein (hs-CRP) assay can detect much lower levels of CRP than the traditional methods (Guler K et al., 2009).

Guler et al. (Guler K et al., 2009) reported that serum levels of hs-CRP were significantly higher in patients with SBP than in those with sterile ascitic fluid.

The authors also reported that these levels promptly decreased after 2 days of administration of antimicrobial agents, indicating that the serum level of hs-CRP may be a useful marker for the prediction of response to the first treatment.

Kadam et al. (Kadam N et al., 2016) recently reported that the mean level of hs-CRP in ascitic fluid was significantly higher in patients with SBP than in those without SBP and was also higher in patients with SBP with poor outcomes.
Results

This study was conducted in internal medicine department, Banha University hospital. Patients were classified into two groups:

- **Group I:** 30 cases of cirrhosis with ascites with SBP
- **Group II:** 20 cirrhotic patient with ascitis & without SBP.

**General characteristics in study groups**

- There were no significant differences between both groups as regard age and gender. P values were 0.071 & 0.103 respectively. (Table 1 & Figure 3)

Table (1) Demographic characteristics in both groups

<table>
<thead>
<tr>
<th></th>
<th>Cases (n = 30)</th>
<th>Controls (n = 20)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean ±SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>54 ±9</td>
<td>49 ±9</td>
<td>0.071</td>
</tr>
<tr>
<td>Females</td>
<td>14 (46.7)</td>
<td>14 (70.0)</td>
<td>0.103</td>
</tr>
</tbody>
</table>

Mann Whitney U test was used for age. Chi-square test was used for gender.

**Figure (3)** Demographic characteristics in both groups

- **Hemoglobin and total leucocyte count in both groups**
Results

- There were no significant differences between both groups as regard hemoglobin and total leucocyte count. P values were 0.071 and 0.463 respectively.  

*(Table 2 & Figure 4)*

**Table (2) Hemoglobin and total leucocyte count in both groups**

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 30)</td>
<td>(n = 20)</td>
<td></td>
</tr>
<tr>
<td>HB</td>
<td>Mean ±SD</td>
<td>10.4 ±1.7</td>
<td>9.4 ±1.8</td>
</tr>
<tr>
<td>TLC</td>
<td>Mean ±SD</td>
<td>6.5 ±2.4</td>
<td>6 ±2.1</td>
</tr>
</tbody>
</table>

Mann Whitney U test was used  
HB = Hemoglobin  
TLC = Total Leucocyte Count

*Figure (4) Hemoglobin and total leucocyte count in both groups*
Liver and kidney functions in both groups

- Mean creatinine level was significantly higher in cases (3.15) compared to controls (1.19). P value was <0.001 (Table 3 & Figure 6)

- There were no significant differences between two groups as regard total bilirubin, AST and ALT. P values were 0.234, 0.620 and 0.276 respectively. (Table 3 & Figure 5)

Table (3) Liver and kidney functions in both groups

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 30)</td>
<td>(n = 20)</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>Median (range)</td>
<td>1.7 (0.8 - 25)</td>
<td>1.2 (0.6 - 5.8)</td>
</tr>
<tr>
<td>ALT</td>
<td>Mean ±SD</td>
<td>45 ±21</td>
<td>50 ±21</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Mean ±SD</td>
<td>3.15 ±0.77</td>
<td>1.19 ±0.48</td>
</tr>
</tbody>
</table>

Mann Whitney U test was used

Figure (5) AST & ALT in both groups
Results

**Figure (6)** serum creatinine in both groups

- **Child–Pugh score in both groups**
  - There was no significant difference between both groups as regard child Pugh score. P value was 0.759 (**Table 4 & Figure 7**)

<table>
<thead>
<tr>
<th>Table (4) Child Pugh score in both groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases</strong></td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td><strong>Child score</strong></td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
</tr>
</tbody>
</table>

Chi-square test was used
 '>' \textbf{INR in both groups}

>' Mean INR was significantly higher in cases (2.97) compared to controls (1.49). P value was <0.001\textit{(Table 5 & Figure 8)}

\textbf{Table (5) INR in both groups}

<table>
<thead>
<tr>
<th></th>
<th>Cases (n = 30)</th>
<th>Controls (n = 20)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR</td>
<td>Mean ±SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.97 ±0.67</td>
<td>1.49 ±0.63</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mann Whitney U test was used
Results

- Hepatic encephalopathy in both groups
  - There was no significant difference between both groups as regard hepatic encephalopathy. P value was 0.804 (Table 6 & Figure 9)

Table 6: Frequency distribution of hepatic encephalopathy in both groups

<table>
<thead>
<tr>
<th></th>
<th>Cases (n = 30)</th>
<th>Controls (n = 20)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic encephalopathy</td>
<td>Yes</td>
<td>10 (33.3)</td>
<td>6 (30.0)</td>
</tr>
</tbody>
</table>

Chi-square test was used
Results

Figure (9) Frequency distribution of hepatic encephalopathy in both groups

❖ CRP levels in both groups

➢ Mean CRP levels was significantly higher in cases (81.29 mg/dl) compared to controls (29.88 mg/dl). P value was <0.001 (Table 7 & Figure 10)

Table (7) CRP levels in both groups

<table>
<thead>
<tr>
<th></th>
<th>Cases (n = 30)</th>
<th>Controls (n = 20)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP baseline (mg/dl)</td>
<td>Mean ±SD</td>
<td>81.29 ±17.24</td>
<td>29.88 ±12.2</td>
</tr>
</tbody>
</table>

Mann Whitney U test was used
CRP levels pre and post treatment in cases group

- Mean CRP levels significantly decreased from 81.29 mg/dl pre-treatment to 51.9 mg/dl post-treatment. P value was <0.001 (*Table 8* & Figure 11)

**Table (8) CRP levels pre and post treatment**

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>±SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP pre(mg/dl)</td>
<td>81.29</td>
<td>17.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP post(mg/dl)</td>
<td>51.9</td>
<td>12.3</td>
<td></td>
</tr>
</tbody>
</table>

Paired t test was used.
Results

Figure (11) CRP levels pre and post treatment

- **Correlation between CRP pre-treatment and other parameters**
  - There was a significant negative correlation between CRP pre-treatment and age ($r = -0.365$ & $P$ value $= 0.047$).
  - There were no significant correlations between CRP pre-treatment and other parameters. *(Table 9 & Figure 12)*
Table 9: Correlation between CRP pre-treatment and other parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CRP pre-treatment (mg/dl)</th>
<th>r</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td>-.365-</td>
<td>0.047</td>
</tr>
<tr>
<td>HB</td>
<td></td>
<td>-.134-</td>
<td>0.479</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td></td>
<td>-0.195</td>
<td>0.302</td>
</tr>
<tr>
<td>TLC</td>
<td></td>
<td>-.160-</td>
<td>0.399</td>
</tr>
<tr>
<td>AST</td>
<td></td>
<td>0.308</td>
<td>0.098</td>
</tr>
<tr>
<td>ALT</td>
<td></td>
<td>0.194</td>
<td>0.303</td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
<td>0.239</td>
<td>0.203</td>
</tr>
<tr>
<td>INR</td>
<td></td>
<td>0.234</td>
<td>0.213</td>
</tr>
<tr>
<td>Serum albumin</td>
<td></td>
<td>0.231</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Pearson’s & Spearman correlation -when appropriate- were used

HB = Hemoglobin
TLC = Total Leucocyte Count

*Significant
Correlation between CRP post-treatment and other parameters

- There was a significant negative correlation between CRP post-treatment and age ($r = -0.422$ & P value = 0.02)
- There were no significant correlations between CRP post-treatment and other parameters. (*Table 10 & Figure 13*)
Table (10) Correlation between CRP post-treatment and other parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Correlation Coefficient (r)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.422*</td>
<td>0.02</td>
</tr>
<tr>
<td>HB</td>
<td>-0.178</td>
<td>0.346</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>-0.072</td>
<td>0.707</td>
</tr>
<tr>
<td>TLC</td>
<td>-0.173</td>
<td>0.361</td>
</tr>
<tr>
<td>AST</td>
<td>0.344</td>
<td>0.063</td>
</tr>
<tr>
<td>ALT</td>
<td>0.286</td>
<td>0.126</td>
</tr>
<tr>
<td>Creatinine</td>
<td>-0.088</td>
<td>0.645</td>
</tr>
<tr>
<td>INR</td>
<td>0.173</td>
<td>0.360</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>0.18</td>
<td></td>
</tr>
</tbody>
</table>

Pearson's & Spearman correlation - when appropriate - were used

HB = Hemoglobin
TLC = Total Leucocyte Count
*Significant
Results

ROC analysis of CRP in diagnosing SBP

- ROC analysis was done for diagnosing SBP. It revealed significant Area Under Curve of 0.99 with 95% confidence interval ranged from 0.972 to 1.0 and P value <0.001. Best cutoff point was 47.07 at which sensitivity and specificity were 100% and 90% respectively. *(Figure 14 & Table 11)*
**Figure (14) ROC analysis of CRP in diagnosing SBP**

**Table (11) ROC analysis of CRP in diagnosing SBP**

<table>
<thead>
<tr>
<th>AUC (95% CI)</th>
<th>SE</th>
<th>Cutoff</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.99 (0.972 - 1.0)</td>
<td>0.009</td>
<td>47.07</td>
<td>100.0%</td>
<td>90.0%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AUC = Area Under Curve  
95% CI = 95% Confidence interval  
SE = Standard Error
Statistical methods

Data management and statistical analysis were done using SPSS vs.25. (IBM, Armonk, New York, United states).

Numerical data was summarized as means and standard deviations. Categorical data was summarized as numbers and percentages.

Comparisons between two groups were done using Mann Whitney U test for numerical data. Categorical data was compared using Chi-square test. CRP pre and post treatment was compared using paired t test. CRP pre-treatment was compared between different Child Pugh scores using Kruskal Wallis test.

ROC analysis was done for CRP for diagnosing SBP. Area Under Curve with 95% confidence intervals were calculated. Best cutoff and diagnostic indices including sensitivity and specificity were calculated.

Correlation analysis was done between CRP and other parameters using Pearson's or Spearman's correlation when appropriate. “r” is the correlation coefficient. It ranges from -1 to +1. -1 indicates strong negative correlation. +1 indicates strong positive correlation while 0 indicates no correlation.

All P values were two sided. P values less than 0.05 were considered significant.
Discussion

Patients with liver cirrhosis (LC) are at high risk for bacterial infections. It has been reported that 30% to 60% of inpatients with LC develop a bacterial infection (Strauss E, 2014), and the incidence of bacterial infections in patients with LC is 4-5-fold higher than that in the general population (Jalan R, et al. 2014).

Among patients with LC accompanied by bacterial infections, spontaneous bacterial peritonitis (SBP) is the most common complication (10% to 30% cases) and often life-threatening, with mortality among ranging from 10% to 46% (Dever JB and Sheikh MY, 2015).

The gold standard method for the diagnosis of SBP is a polymorphonuclear cell (PMN) count of ≥250 cells/mm3 in the ascitic fluid, regardless of bacterial isolation (Solà E, et al., 2016). However, paracentesis is not always possible and can sometimes be too time-consuming for an early diagnosis of SBP (Gaya DR, et al. 2007).

One of the earliest signs of infection is the acute-phase response, Acute-phase response may include the changes in the concentration of many plasma proteins, known as the acute-phase proteins that are synthesized almost exclusively in the liver; most are glycosylated (Strauss E and Gomes de Sá Ribeiro, 2003).

Inflammatory markers, such as C-reactive protein (CRP) and procalcitonin (PCT), and white blood cells (WBCs) could be used easily for the diagnosis and follow-up of several morbidities (Massaro KS et al., 2007).
C-Reactive Protein (CRP) was discovered by Tillet and Francis in 1930 and they proposed the hepatic synthesis of CRP. It is an acute phase protein found in the blood stream the levels of which rise in response to inflammation. High sensitivity CRP (hs-CRP) test measures low levels of CRP using Laser nephelometry. This test gives immediate results within 25 minutes and also with sensitivity down to 0.04 mg/l. It is a more sensitive inflammatory marker. (Ramamoorthy RD, et al. 2012)

Studies have supported the view that CRP levels increases in decompensated cirrhosis and infections in cirrhosis. (Cervoni JP, et al. 2012)

This study was conducted on 50 cirrhotic patients divided into 2 group according to either with or without SBP (30 patients with SBP & 20 patients without SBP). Our study included 28 male (56%) and 22 female (44%). There was no significant differences between both groups as regard age and gender with P values 0.071 & 0.103 respectively & that result agree with (Nakul Kadam et al., 2016) who found no significant difference between both groups as regard age & gender with P values 0.32 & 0.14 respectively.

There was no significant differences between both groups as regard hemoglobin and total leucocyte count with P values 0.071 and 0.463 respectively & that result agree with (Nakul Kadam et al., 2016) who found no significant difference between both groups as regard hemoglobin and total leucocyte count with P values 0.1 & 0.6 respectively.

In disagreement with our study, (Khaled Metwally et al., 2018) showed that there was significant differences between both groups as regard total leucocyte count with P vales 0.003.
As regard serum creatinine, Mean creatinine level was significantly higher in cases (3.15) compared to controls (1.19) with P value <0.001 (Table 3 & Figure 6).

(Tsung et al., 2013) study showed increase serum creatinine in SBP cases, he also studied impact of renal dysfunction in cirrhotic patients with bacterial infections and found that level of serum creatinine as a marker of renal impairment is markedly increased in patients who developed SBP.

(Tsung et al., 2013) study also agree with our study & with (Nakul Kadam et al., 2016) who found that mean Serum creatinine in SBP patients was significantly higher than the controls with (P value 0.0001). Increase levels of serum creatinine in cases of decompensated cirrhosis can occur due to a number of factors like excessive diuretic therapy, haematemesis, intravascular volume depletion, large volume paracentesis, shock and most importantly development of hepato renal syndrome. Infection is a well known entity that causes rise in serum creatinine in cases of cirrhosis of liver.

There was no significant differences between both groups as regard AST and ALT with P values 0.62 and 0.276 respectively & that result agree with (Nakul Kadam et al., 2016) who found no significant difference between both groups as regard AST and ALT with P values 0.14 & 0.70 respectively.

Also agree with, (Khaled Metwally et al., 2018) who showed that there was no significant differences between both groups as regard AST and ALT with P values 0.198 and 0.136 respectively.
There was no significant differences between both groups as regard total bilirubin with P values 0.234 & that agree with (Gabriela Bicca Thiele et al., 2014) which showed no significant difference between both groups as regard total bilirubin with P value 0.1.

In disagreement with our study (Khaled Metwally et al., 2018) showed that there was significant differences between both groups as regard total bilirubin with P values 0.001, similar to (Nakul Kadam et al., 2016) who found significant difference between both groups as regard total bilirubin with P value 0.004.

According to our study, Mean INR was significantly higher in cases (2.97) compared to controls (1.49) with P value <0.001 (Table 5 & Figure 8) & that agree with (Nakul Kadam et al., 2016) study in which INR of cases was significantly raised than the controls with P value of 0.0001 & our result was also similar to (Khaled Metwally et al., 2018) study that showed significant difference between both groups with P value less than 0.001.

In disagreement to our study, (Gabriela Bicca Thiele et al., 2014) study showed no significant difference between both groups as regard INR with P value 0.63.

Our study conducted on 17 cirrhotic patients with child score A & 17 cirrhotic patients with child score B & 16 cirrhotic patients with child score C and showed no significant difference between both groups as regard child Pugh score with P value was 0.759

Also agree with (Khaled Metwally et al., 2018) study which no significant difference between both groups according to child score with P value 0.73.
In contrast to previous studies, the study of (Nakul Kadam et al., 2016) 78% of patients with SBP were in Child’s class C or B, (p<0.05 compared to controls) suggesting that SBP adds to the additional burden for the prognosis of cirrhosis. It would be interesting to discuss that the original Child Pugh’s criteria only includes ascitis as one of the factors, whether SBP should be also added as an additional factor for estimating prognosis in cases of cirrhosis should be pondered upon.

In our study, highly sensitive CRP levels will be estimated after diagnosis of SBP and on 5th day after treatment with standard recommended antibiotic therapy (inj. cefotaxim 2 g 12 hourly for 5 days).

Mean CRP levels in our study was significantly higher in cases (81.29 mg/dl) compared to controls (29.88 mg/dl). P value was <0.001.

Also Mean CRP levels significantly decreased from 81.29 mg/dl pre-treatment to 51.9 mg/dl post-treatment. P value was <0.001. This suggests that early suspicion, detection and treatment of SBP do contribute to decrease the inflammation burden and overall prognosis of SBP patients.

The previous result agree with the study of (Nakul Kadam et al., 2016) that showed that mean hs-CRP level of the patients with SBP (77.20 ± 11.65) was significantly higher than that of the patients without spontaneous bacterial peritonitis (42.50 ± 7.48) (p<0.01) also the mean Hs-CRP levels at 5th day after initiation of antibiotic therapy or, discharge were significantly lower, compared to that of before initiation of antibiotic therapy (p<0.01).

(Guler K et al., 2009) studied serum hs-CRP level in cases of SBP and compared serum hs-CRP levels two days after standard antibiotic
treatment. There was statistically significant decrease in the mean serum hs-CRP level two days after antibiotic therapy.

ROC analysis was done for diagnosing SBP. It revealed significant Area Under Curve of 0.99 with 95% confidence interval ranged from 0.972 to 1.0 and P value <0.001. Best cutoff point was 47.07 at which sensitivity and specificity were 100% and 90% respectively. *(Figure 11 & Table 13)*

Limitations to our study, we studied 50 patients of liver cirrhosis which may not reflect pattern of disease in the community and requires a large population study compared to 140 patients in *(Nakul Kadam et al., 2016)* study & 300 patients in *(Khaled Metwally et al., 2018)* study, also most cases of liver cirrhosis in other studies occurred due to alcohol & compared to our study in which hepatitis C virus is the most common cause.
Summary

Among patients with LC accompanied by bacterial infections, spontaneous bacterial peritonitis (SBP) is the most common complication (10% to 30% cases) and often life-threatening, with mortality among ranging from 10% to 46% (Dever JB and Sheikh MY, 2015).

The gold standard method for the diagnosis of SBP is a polymorphonuclear cell (PMN) count of ≥250 cells/mm3 in the ascitic fluid, regardless of bacterial isolation (Solà E, et al., 2016). However, paracentesis is not always possible and can sometimes be too time-consuming for an early diagnosis of SBP (Gaya DR, et al. 2007).

Therefore, novel and useful biomarkers for early diagnosis of SBP are desirable. Laboratory methods for early prediction of response to the first treatment are also desirable because nonresponse to the first treatment is a predictor of mortality accompanied with SBP (Piano S, et al. 2016).

Studies have supported the view that CRP levels increases in decompensated cirrhosis and infections in cirrhosis. (Cervoni JP, et al. 2012)

The aim of this study is to clarify the role of high sensitive CRP as a prognostic factor in patient with spontaneous bacterial peritonitis

Patients :

This prospective study was conducted on 30 cases of cirrhosis with ascites who satisfied the criteria of SBP (elevated ascitic fluid absolute Polymorph Nuclear (PMN) leukocyte count of ≥250
cells/mm, in absence of any intra abdominal source of infection) & on a control group of 20 cirrhotic patient with ascitis & without SBP.

**Methods**

Highly sensitive CRP levels will be estimated after diagnosis of SBP and on 5th day after treatment with standard recommended antibiotic therapy (inj. cefotaxim 2 g 12 hourly for 5th days).

**Results**

There was no significant differences between both groups as regard age and gender with P values 0.071 & 0.103 respectively.

There was no significant differences between both groups as regard hemoglobin, total leucocyte count with P values 0.071, 0.463 respectively.

Mean creatinine level was significantly higher in cases (3.15) compared to controls (1.19). P value was <0.001.

Mean INR was significantly higher in cases (2.97) compared to controls (1.49). P value was <0.001

There were no significant differences between two groups as regard total bilirubin, AST and ALT. P values were 0.234, 0.620 and 0.276 respectively.

Mean CRP levels in our study was significantly higher in cases (81.29 mg/dl) compared to controls (29.88 mg/dl). P value was <0.001.

Also Mean CRP levels significantly decreased from 81.29 mg/dl pre-treatment to 51.9 mg/dl post-treatment. P value was <0.001.
suggests that early suspicion, detection and treatment of SBP do contribute to decrease the inflammation burden and overall prognosis of SBP patients.

We found that hs-CRP level was elevated in patients diagnosed with SBP compared to patient with ascitis and without SBP, also hs-CRP level declined after treatment of SBP with recommended antibiotic therapy.
Recommendations

We recommend using hs-CRP in ascitic fluid for diagnosis of SBP & for follow up after management with recommended antibiotics
Reference


Garcia-Tsao, G., Friedman, S., Iredale, J. and Pinzani, M., (2010.) Now there are many (stages) where before there was one: In search of a pathophysiological classification of cirrhosis. Hepatology, 51(4), pp.1445–1449.


Tsung,P,C.; Ryu,S,H.;Cha,I,H.; et al., (2013.) Predictive factors that influence the survival rates in LC patients with Spontaneous


المقدمة:

المرضى الذين يعانون من تليف الكبد هم في خطر كبير للالتهابات البكتيرية. لقد تم الإبلاغ عن 30% إلى 60% من المرضى المصابين بالإصابة بمرض الكبد يطورون عدوى بكتيرية، وححدوث العدوى البكتيرية لدى مرضى التليف الكبد هو 5-50% أضعاف أعلى من عموم السكان.

بين المرضى الذين يعانون من تليف الكبد المصاحب بالالتهابات البكتيرية، التهاب الپرتيوني البكتيري التلقائي هو أكثر المضاعفات شيوعاً (10% إلى 30%) وغالباً ما يهدد الحياة، مع معدل وفيات يتراوح بين 10% إلى 46%.

الطريقة المعنارية الذهبية لتشخيص الإلتهاب الپرتيوني البكتيري التلقائي هي عبارة عن خلية متحدة متوافقة من الخلايا ≤250 / mm3 في السائل الاستجابة، بغض النظر عن العزلة البكتيرية. ومع ذلك، لا يكون الجزء ممكنًا دائمًا ويمكن أن يكون مستهدفاً بالوقت في وقت مبكر من أجل التشخيص المبكر.

لذلك، من المرغوب فيه توجيهات الحيوية الجديدة والمفيدة للتشخيص المبكر لالتهاب الپرتيوني البكتيري التلقائي. كما أن الطرق المختبرية للتصنيع المبكر للعازابة للعلاج الأول تكون مرغوبة أيضًا لأن عدم الاستجابة للعلاج الأول هو توقع الوفيات المصاحبة لالتهاب الپرتيوني البكتيري التلقائي.

تم اكتشاف البروتين التفاعلي سي من قبل تيلنت وفرانسيس عام 1930 واقترحوا أنه يتم تصنيعه في الكبد، وهو بروتين طور حاد موجود في مجرى الدم وتترفع نسبته استجابة للالتهابات ويتم قياس البروتين التفاعلي سي عالي الحساسية باستخدام تقنية الليزر ويعطي نتائج فورية خلال 25 دقيقة.

أثبتت الدراسات أن البروتين التفاعلي سي عالي الحساسية يزيد في مرضى تليف الكبد مع الالتهاب الپرتيوني البكتيري التلقائي.
الهدف من البحث

الهدف من هذه الدراسة هو معرفة دور البروتين التفاعلي سي عالي الحساسية كعلامة تكهنية لالتهاب البروتين البكتيري التلقائي.
الخاضعين للدراسة وطرق الدراسة

اختيار المرضى:

30 مريضاً من مرضى التليف الكبدى مع استنقاء الذين استوفوا معايير تشخيص الالتهاب البكتериي البترولوتي التلقائي عن طريق اخذ عينة من السائل البترولوتي وحساب عدد كريات الدم متعادلة الانوية مع غياب أي مصدر عدوي داخل البطن.

سيكون هناك مجموعة مراقبة من 10 مرضى تليف الكبد مع استنقاء بدون الالتهاب البترولوتي البكتيري التلقائي.

معايير الاستبعاد:

- أمراض الشريان التاجي - داء السكري - اضطرابات الأوعية الدموية الكولاجينية
- التهاب المفاصل - تسوس الدم

طرق الدراسة:

ستتم قياس مستويات البروتين التفاعلي سي عالي الحساسية بعد تشخيص الالتهاب البترولوتي البكتيري التلقائي و بعد العلاج بالمضادات الحيوية الموصى بها في اليوم الخامس.

سيتم تقدير نسبة الهيموجلوتين و عدد كريات الدم البيضاء ووظائف الكبد ووظائف الكلي للمرضى المشاركين.

النتائج:

أثبت البحث أن نسبة البروتين التفاعلي سي عالي الحساسية تزداد في مرضى الالتهاب البترولوتي البكتيري التلقائي قبل العلاج وتنقل بعد العلاج بالمضادات الحيوية القياسي.

الخلاصة:

أنه يمكن استخدام البروتين التفاعلي سي عالي الحساسية كأداة تشخيصية لمرضى الاستماع البترولوتي البكتيري التلقائي كما أنه يقل بعد استخدام المضادات الانتهاك المناسب لذا يمكن استخدامه كابة تنبؤية للمريض.
البروتين التفاعلي سي عالي الحساسية في السائل البريتوني كعلامة منبئة بمسار الالتهاب البريتوني البكتيري التلقائي

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