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# ORIGINAL RESEARCH

## Study of bacterial infections in liver cirrhosis and their effect on short term prognosis prediction by MELD-Na score

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***ABSTRACT:***

**Background:** Cirrhosis of Liver is a chronic disease with liver cell failure which can progress to an irreversible stage. This study was conducted to assess the prevalence of bacterial infections in liver cirrhosis, to assess the effect of bacterial infection on MELD-Na score and on the short-term prognosis in Cirrhosis patients and to study the spectrum of bacterial infections and resistance to antibiotics in patients with cirrhosis. **Materials & methods:** A total of 60 patients were taken for the study. Only those patients were included in which confirmed diagnosis of liver cirrhosis was established. Incidence of bacterial infection was assessed. Correlation of it with MELD-Na score was analysed. All results were recorded and analysed by SPSS software. **Results:** Mean Age of the cases was 49.85 year with standard deviation of 10.99. In 36.7% cases culture was found negative but clinically and bio-chemically the cases were diagnosed as Bacterial infection. Escherichia coli was found in nearly half of the culture (60%) followed by Acid Fast Bacilli (16%). In nearly two third cases (64%) bacteria were multi drug sensitive. In the group of liver cirrhoses cases with infection, the mean MELD-Na score was significantly reducing after 7 days of antibiotic treatment ($p<0.05$). This indicates that antibiotic therapy is effective in significantly improve MELD-Na score in infectious cases. **Conclusion:** The prevalence of bacterial infections was 78.3% in liver cirrhosis cases. Hepatic encephalopathy, renal failure, fulminant hepatitis, SBP and severe anaemia cases with bacterial infections significantly improve after antibiotic therapy and other supportive treatment.

**Key words:** Bacterial, Liver, Cirrhosis

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### INTRODUCTION

Cirrhosis of Liver is a chronic disease with liver cell failure which can progress to an irreversible stage. Currently Cirrhosis of the liver is the 11th most common cause of death worldwide. Cirrhosis is among the top 20 causes of disability-adjusted life years and years of life lost, responsible for 1.6% and 2.1% of the burden globally. One of the most significant clinical complications of decompensated liver cirrhosis is bacterial infections. They are more predominant particularly in patients admitted in hospital and they are linked with greater mortality and morbidity rates.[1- 3]

Bacterial infections frequently lead to the advancement of liver failure, manifestation of complications such as hepatic encephalopathy, gastrointestinal bleeding, acute on chronic liver failure and hepatorenal syndrome. Infections may be present on admission or progress during hospitalization in 30 to 40 % of patients having liver cirrhosis. Various prognostic scoring systems have been developed and used to predict the prognosis of patients with liver cirrhosis and for defining the most proper treatment. After approximately forty years, the Child score was substituted by the modified Child Turcotte Pugh (CTP) score for evaluating the prognosis of cirrhosis.[4, 5] Another prognostic score, the Model for End Stage Liver Disease (MELD) score is more useful and reproducible than the CTP score, because it does not include independent variables such as ascites and hepatic encephalopathy. Cirrhotic patients frequently progress to dilutional hyponatraemia due to changed vascular haemodynamics. Initiation of these mechanisms associates with the grade of portal hypertension. Hyponatraemia forecasts poorer outcomes and is an independent predictor of survival evaluated at 3rdand 12th months. A improved score comprising of serum sodium – named the "MELD sodium" score (MELD-Na)

– was recommended as an substitute to the MELD score MELD-Na was applied for allocation of liver transplant in 2016, since hyponatraemia in liver cirrhosis is a crucial forecaster of fatality among patients in liver transplant waitlist. The data available concerning the prognostic utility of MELD-Na score in predicting short-term prognosis in cirrhotic patients in India are scant.[6- 10] With this background, this study was conducted to assess the prevalence of bacterial infections in liver cirrhosis, to assess the effect of bacterial infection on MELDNa score and on the short-term prognosis in Cirrhosis patients and to study the spectrum of bacterial infections and resistance to antibiotics in patients with cirrhosis.

## MATERIALS & METHODS

A total of 60 patients were taken for the study. Approval was taken from the Institutional Ethical Committee before commencing the study. Written and Informed Consent was obtained from all patients. All patients were informed regarding the purpose, procedures, risks and benefits of the study in their own vernacular language.

### Inclusion Criteria

Patients with following characteristics were included in the study:

- Age ≥ 18 years
- Newly diagnosed or a known case of cirrhosis
  Criteria for selection of cirrhosis patients
  - Ultrasound or Computerised Tomogram of the abdomen showing liver parenchymal disease, shrunken, nodular, liver with coarse echotexture.
  - or
  - Evidence of liver disease of more than 6 months duration and/or evidence of portal hypertension on ultrasonography or upper gastrointestinal endoscopy
- Fever>380C and Tachycardia (>90)
- Polymorphonuclear leucocytois (>12000/cmm ) or the presence of >10% immature neutrophils (band forms)
- Raised CRP >100mg/ml
- Raised LDH>, serology detecting IgM antibody for specific bacterium

### Exclusion Criteria

Cases with any of the following criteria were excluded from the study:

- Age < 18 years
- Active GI bleed,
- Malignancy anywhere in the body except hepatocellular carcinoma
- Acute or chronic renal failure on dialysis
- HIV patients
- Pregnant Women

Calculation of MELD-Na score

MELD Score = 3.78×ln[serum bilirubin (mg/dL)] + 11.2×ln[INR] + 9.57×ln[serum creatinine (mg/dL)] + 6.43

MELD scores are reported as whole numbers (rounded if fraction). Any value less than one rounded to 1 (i.e. if bilirubin is 0.8 a value of 1.0 is used)

MELD-Na=MELD+1.32 x (137-Na) - [0.033 x MELD x (137-Na)]

### Definitions related to infection:

The diagnostic criteria for bacterial infection were listed as follows. (1) Spontaneous bacterial peritonitis (SBP): neutrophils count ≥250/mm3 in ascitic fluid. (2) Pneumonia: clinical manifestations of infection associated with imaging examination showing new pulmonary infiltration. (3) Urinary tract infection (UTI): high white blood cell (WBC) count (> 10/field) was found in urinary sediment accompanied by positive culture results of urine or innumerable WBC per field with negative culture results of urine. (4) Bacteremia: positive blood culture. (5) Skin and soft tissue infection (SSTI): symptoms of infection, such as redness, inflation, high temperature, and pain on the skin. (6) Spontaneous bacterial empyema (SBE): neutrophils number in pleural fluid ≥250/ mm3. (7) Infectious diarrhea: diarrhea with stool microscopic examination showing WBC or routine stool culture showing evidence of pathogenic microorganisms. (8) Cholangitis: right upper abdominal pain, cholestasis, or radiologic evidence of biliary obstruction. (9) Unproven infection: the existence of fever and leukocytosis needs antibiotic treatment with no recognizable sources

Since there is no single test to define bacterial infection, definition of "bacterial infection" was consisted of presence of any three of the following with leucocytois or microbiological test being positive

- Fever>380C and Tachycardia (>90)
- Polymorphonuclear leucocytois (>12000/cmm ) or the presence of >10% immature neutrophils (band forms)
- Raised CRP >100mg/ml
- Raised LDH>, serology detecting IgM antibody for specific bacterium
- Microbiological tests for bacteria (gram stain, & culture of blood, body fluids, secretions, urine, stool)

All data were entered in the Microsoft excel sheet and was analysed using SPSS software. Qualitative data were presented in form of frequency and percentage. Quantitative data were presented in term of mean and standard deviation. For comparison of output variables, chi-square test was used to for qualitative variables and unpaired t test was used for qualitative variables. P values less than 0.05 was considered as statistically significant.

## RESULTS

Mean Age of the cases was 49.85 year with standard deviation of 10.99. The youngest patient was 18 year old and the eldest was of 67 years. Males were more than 2/3 of the study subjects. Among the 60 cases higher than normal mean values were observed for Serum Bilirubin, PT/INR, Serum Urea, and Serum Creatinin. The mean values for serum Sodium and potassium were within

normal range. Mean serum Prolactine value was very high indicating high risk of organ dysfunction due to systemic inflammation. Mean S. Lactate Dehydrogenase value was also above the normal range which point toward the cell injury. 60 cases of liver cirrhosis, one or another type of bacterial infection was found in 47 cases (78.3%) cases. Out of 60 cases of liver cirrhosis one forth cases showed positive urine culture which was highest compared to the other sites of infection. This was followed by SBP in 15% cases. In 36.7% cases culture was found negative but clinically and bio-chemically the cases were diagnosed as Bacterial infection. Escherichia coli was found in nearly half of the culture (60%) followed by Acid Fast Bacilli (16%). In nearly two third cases (64%) bacteria were multi drug sensitive. In the group of liver cirrhoses cases with infection, the mean MELD-Na score was significantly reducing after 7 days of antibiotic treatment ($p<0.05$) This indicates that antibiotic therapy is effective in significantly improve MELD-Na score in infectious cases.

**Table 1:** Spectrum of laboratory Test results in all cases (n=60)

| Variables | Mean | Std. Deviation | lowest | highest |
|---|---|---|---|---|
| **S. Bilirubin (mg/dl)** | 3.53 | 1.54 | 1 | 7 |
| **S. Lactate (mmol/L)** | 2.78 | 1.62 | 1 | 10 |
| **PT/INR** | 1.77 | 0.56 | 1 | 3 |
| **Urea (mg/dL)** | 32.85 | 15.21 | 17 | 85 |
| **Creatinine (mg/dL)** | 1.47 | 0.81 | 1 | 4 |
| **S. Sodium (mEq/L)** | 135.08 | 5.17 | 126 | 150 |
| **S. Potassium (mEq/L)** | 3.82 | 0.68 | 3 | 6 |
| **Procalcitonin (ng/mL)** | 11.60 | 11.63 | 0 | 35 |
| **S. LDH (U/L)** | 322.43 | 59.01 | 224 | 452 |

**Table 2:** Bacterial Infection among Cases of cirrhosis

| Infection | Frequency(n) | Percent |
|---|---|---|
| **Absent** | 13 | 21.7 |
| **Present** | 47 | 78.3 |
| **Total** | 60 | 100.0 |

**Table 3:** Outcome of bacteriological study from various sources of infection

| Culture | Frequency | Percent |
|---|---|---|
| **Urine Culture positive** | 16 | 26.7 |
| **Spontaneous Bacterial Peritonitis** | 9 | 15.0 |
| **Culture negative but clinically and bio-chemically diagnosed as Bacterial infection** | 22 | 36.7 |
| **No pathogens detected** | 13 | 21.7 |
| **Total** | 60 | 100.0 |

**Table 4:** Bacterial Spectrum of Bacteria isolated (n=47)

| Bacteria Detected | Frequency | Percent |
|---|---|---|
| **AFB** | 4 | 16.0 |
| **E. coli** | 15 | 60.0 |
| **Enterococcus Faecalis** | 1 | 4.0 |
| **Klebsiella Pneumonia** | 3 | 12.0 |
| **Streptococci Pneumonia** | 2 | 8.0 |
| **Total** | 25 | 100.0 |

## DISCUSSION

Cirrhosis is the most common cause of morbidity and mortality worldwide, and bacterial infections are very common in patients with cirrhosis, often leading to mortality. In patients with cirrhosis, there is an increased risk of dying from sepsis compared with that from other complications. Multiple-drug-resistant (MDR) bacteria are more common because of antimicrobial resistance.[11]

In the present study mean age of the cases was 49.85 year with standard deviation of 10.99. In the present study in the 60 cases of liver cirrhosis, bacterial infections were detected in 78.3% cases. Liver cirrhosis has multiple causal factors, the most common is alcoholic liver disease and hepatitis C. The natural course of the disease process is altered by various complications like ascites, hepatic encephalopathy, gastrointestinal bleeding; hepato pulmonary and hepato renal syndromes and bacterial infections.[12]

**Table 5:** Drug sensitivity of Bacteria isolated from cases of cirrhosis with infection

| Sensitivity | Frequency | Percent |
|---|---|---|
| **Multisensitive** | 16 | 64.0 |
| **Aminoglycoside** | 5 | 20.0 |
| **Cefoperazone** | 2 | 8.0 |
| **Vancomycin** | 2 | 8.0 |
| **Total** | 25 | 100.0 |

**Table 6:** Comparison of mean MELD-Na score before and after antibiotic therapy in infected cases

| Variables | Infection Present (n=47) | |
|---|---|---|
| | Mean | Std. Deviation |
| **MELD-Na before antibiotic Rx** | 23.00 | 6.196 |
| **MELD-Na after 7days of Rx** | 19.77* | 6.130 |
| P-value | 0.013 | |

*mean of 40 cases as 7 cases died before 7 days

In the present study one forth cases showed urinary tract as site of infection as evidenced by positive urine culture (26.7%) which was higher as compared to the other sites of infection. This was followed by SBP in 15% cases. In 36.7% cases culture was found negative but clinically and bio-chemically the cases were diagnosed as Bacterial infection.

A study by Lameirao Gomes C et al reported that the infections were detected in 70.7% of cirrhotic patients. In the same study the infections found in cirrhotics were urinary tract infections (UTI;32.4%), lower respiratory tract infections were found in 29.2%, spontaneous bacterial peritonitis (SBP) in ;26.1%, and cellulitis in 6.2%.[13]

In the present study Escherichia coli was found to be the most common infective bacteria, isolated in more than half of the cultures (60%) followed by Acid Fast Bacilli (16%).

Lameirao Gomes C et al found that the great majority of microbiological agents identified were E. coli. The studies by Taneja SK et al, Bunchorntavakul C et al and Gustot T et al showed that 50–70% of the cases were culture positive , and the organisms isolated were gram-negative bacilli (GNB), especially E. coli( 60%), gram positive cocci (GPC), in around 30–35%, and mixed flora in 5–10%. In SBP and UTI, predominant organisms was GNB (E. coli and Klebsiella) , while in pneumonia GPC(Streptococcus pneumoniae) was predominant and procedure associated bacteremia GPC(Staphylococcus aureus) was isolated.[3, 6, 13, 14]

In the present study mean MELD-Na score was 22.57 at the time of admission. After antibiotic therapy the score was improved to 21.35, however, the improvement was not statistically significant ($p > 0.05$). When the change in mean MELD-Na score compared separately in cases with infection and cases without infection, the mean MELD-Na score was significantly reduced after 7 days of antibiotic treatment ($p<0.05$) in cases having bacterial infection. However; in the group of cases without infection there was no significant reduction in mean MELD-Na score. This indicates that antibiotic therapy has positive effect in improving MELD-Na score.

A study by Acharya G et al found that the MELD-Na score in patient with liver cirrhosis was 24.46. Their study reported that those who died have higher score compared to those who survived after one month. Various studies in France and the USA have found that the MELD score is better than the CTP score.[15- 17]

In a study done by Biggins et al, in 753 American residents with Liver cirrhosis majority due to chronic hepatitis C and alcoholic liver disease, 6 month mortality rate in Patients with MELD-Na scores of 20, 30 and 40 was 6, 16 and 37%, respectively.[18]

A study by Bas Ormeci B et al, alcoholic liver disease, followed by hepatitis C infection and nonalcoholic steatohepatitis were the most common cause of cirrhosis. Patients with advanced liver disease, as indicated by the high prevalence of "ascites (77%), hepatic encephalopathy (38%), mean model of end-stage liver disease (MELD) score (21±8), MELD sodium (MELD-Na) score (24±8), and Child-Turcotte-Pugh score (10±2)".[19]

Diagnosis of infections is one of the major difficulties in the management of infected patients with cirrhosis. In 50–70% of case infections are culture positive. Classical clinical parameters do not allow to differentiate infected from non-infected patients during decompensation of cirrhosis,, often leading to a delay in the diagnosis and the management of bacterial infection. Broad spectrum antibiotic coverage is frequently started without the evidence of infection in decompensated cirrhosis with stepping up of antibiotic classes in cases of clinical deterioration. To help physicians to make prompt and adequate decisions there is a need to create and/or validate new tools for diagnosis of bacterial infection in cirrhosis.[20]

To better define the epidemiological changes that are occurring in bacterial infections in cirrhosis there is a need to create and/or validate new tools for diagnosis of bacterial infections in cirrhosis. The mean MELD-Na score was significantly reduced after 7 days of antibiotic treatment ($p<0.05$) in cases having bacterial infection. However; in the group of cases without infection there was no significant reduction in mean MELD-Na score. This indicates that early antibiotic therapy has favorable effect on MELD-Na score.

## CONCLUSION

The prevalence of bacterial infections was 78.3% in liver cirrhosis cases. Hepatic encephalopathy, renal failure, fulminant hepatitis, SBP and severe anaemia cases with bacterial infections significantly improve after antibiotic therapy and other supportive treatment.

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