

Prevalence of Liver Cirrhosis with Tuberculosis and its Outcome

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Abstract

Background: Tuberculosis (TB) is a global disease; about one-third of the world's population is infected with *Mycobacterium* TB. Immunosuppressive states like cirrhosis of the liver can lead to higher prevalence of TB than in the general population. Treatment of TB in immunocompromised set up is challenging.

Materials and Methods: After ethical approval, the study was conducted as a prospective observational study and included 100 patients. Diagnosis of cirrhosis of liver and TB were made as per standard protocols. Ascites in the setting of cirrhosis was diagnosed when high serum albumin ascites gradient any of the findings of high adenosine deaminase levels more than 33 U/L in ascetic fluid. Pyrazinamide was completely avoided and a 9 months 3 drug regime (rifampicin, isoniazid, and ethambutol) was used. The outcome of the treatment was noted, and all the data were analyzed using Statistical Package for the Social Sciences (SPSS) (SPSS for Windows, version 12.0; SPSS; Chicago, IL, USA). Statistical significance was assumed at $P < 0.05$.

Results: In this study, the prevalence of TB was found in 7% of cirrhotic patients. Out of 79 male cirrhotics, 4 patients (2 had extrapulmonary disease) had TB (5.1%). Sex distribution was not statistically significant (odds ratio: 3.13; 95% confidence interval [CI]: 0.41-20.02). Among all cirrhotics, extrapulmonary cases (5%) out-numbered pulmonary cases (2%), but the difference was not significant. In majority of cirrhotics, etiology was alcoholism (66%) followed by chronic hepatitis B infection (27%). The most common complication seen in cirrhosis was sepsis. In overall cirrhotic patients, 60% were in Child' B (8-10). In this study, mortality was 13%.

Conclusions: (1) Prevalence of TB in cirrhotic patients was found to be 7%, (2) most common etiology of cirrhosis was alcoholism. (3) Extrapulmonary TB cases outnumbered the pulmonary TB cases in the present study.

Key words: Liver cirrhosis, Tuberculosis, Outcome

INTRODUCTION

Tuberculosis (TB) is a global disease; about one-third of the world's population is infected with *Mycobacterium* TB (M.TB). In the developing countries like Africa and Asia, an estimated 40-50% of the adult population is infected.¹ According to the World Health Organization (WHO) statistics for 2011, the estimated incidence of TB in India is 2.2 million cases out of a global incidence of 8.7 million cases.² In about 5-10% of infected persons, reactivation

occurs causing active TB.³ Any condition leading to immunosuppression can lead to activation of latent infection progressing to active disease.⁴ Cirrhosis of liver is considered to be an immunosuppressive state resulting in higher prevalence of TB than in the general population.⁵

Treatment of TB in patients with underlying cirrhosis is a challenge because of compromised liver functions and high risk of hepatotoxicity. Till date, the data on prevalence, clinical spectrum, complications, and treatment outcome of TB in cirrhotic are very limited. Hence, it was thought prudent to undertake this study, which could help in better management of cirrhotic patients with TB.

MATERIALS AND METHODS

This study was conducted in Department of Medicine and Department of Pulmonary and Sleep Medicine, NSCB

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Month of Submission : 01-2017
Month of Peer Review : 02-2017
Month of Acceptance : 02-2017
Month of Publishing : 03-2017

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Medical College Hospital, Jabalpur, Madhya Pradesh, during the period between October 2014 and October 2015. The study was a prospective observational study and included 100 consecutive patients of cirrhosis of liver who consented for the study and presented in outpatient department or admitted in NSCB Medical College and Affiliated Hospital, Jabalpur. The study was approved by ethical committee of the institution.

Exclusion Criteria

1. Not willing to give informed consent
2. HIV-positive patients
3. Pregnant females
4. Patients on long-term steroid therapy
5. Patients on chemotherapy
6. Old pulmonary TB (PTB) patients
7. Chronic obstructive pulmonary disease patients.

Diagnosis of cirrhosis of the liver was based on clinical and biochemical findings; and imaging (ultrasonography or computed tomography or magnetic resonance imaging). Esophagogastroduodenoscopy was done whenever indicated.

The diagnosis of TB in cirrhosis otherwise was similar as the diagnosis of TB in general population. Patients having fever, productive cough for more than 2 weeks, anorexia, weight loss were advised to do sputum acid-fast bacilli (AFB) examination, and Chest X-ray posterior anterior view to detect the active pulmonary lesion.⁶ Tubercular ascites was suspected in the setting of a new ascites in a patient with compensated cirrhosis in patients with increasing or resistant ascites despite diuretic treatment, in the background of constitutional symptoms such as anorexia, fever, and weight loss. Tubercular ascites in the setting of cirrhosis was diagnosed when high serum albumin ascites gradient, high protein ascites was present with a lymphocytic predominant high cell count fluid in the absence of alternate diagnosis. Any of the findings of high adenosine deaminase levels more than 33 U/L in ascetic fluid, detection of AFB or positive M.TB culture in body fluid was taken as a confirmatory test for diagnosis of tubercular ascites. The diagnosis of TB in other extrapulmonary sites was based on appropriate biochemical tests of body fluids, imaging or histology in selected cases.

Cirrhosis patients were categorized in Category A, B or C as per Child Turcotte Pugh classification (Table 1).⁷ The patients of TB were then started on modified anti-tuberculosis treatment (ATT) drug regimens according to 2010 WHO guidelines and recommendations by Dhiman *et al.*^{5,8}

Treatment Criteria for TB with Cirrhosis Patients⁸

- Child's A cirrhosis (score <7): Since pyrazinamide is potentially the most hepatotoxic drug, it was

Table 1: Child-Turcotte-Pugh Criteria for categorizing disease severity in cirrhotic patients⁷

| Parameter | 1 point | 2 points | 3 points |
|------------------------|---------|-------------------|-------------------|
| Serum bilirubin | | | |
| mol/L | 34 | 34-51 | >51 |
| Mg/dL | 2.0 | 2.0-3.0 | >3.0 |
| Serum albumin | | | |
| g/L | >35 | 30-35 | <30 |
| g/dL | >3.5 | 3.0-3.5 | <3.0 |
| Prothrombin time | | | |
| Seconds prolonged | 0-4 | 4-6 | >6 |
| INR | <1.7 | 1.7-2.3 | >2.3 |
| Ascites | None | Easily controlled | Poorly controlled |
| Hepatic encephalopathy | None | Minimal | Advanced |

INR: International normalized ratio

completely avoided and a 9 months 3 drug regime (rifampicin, isoniazid, and ethambutol) was used.

- Child's B cirrhosis (score between 8 and 10): A regimen containing 2 months of Isoniazid, ethambutol and streptomycin followed by 10 months of isoniazid and ethambutol was used.
- Child's C cirrhosis (score >11): No hepatotoxic drug was given, 18-24 months of streptomycin, ethambutol, and quinolones were used. Regular liver function test monitoring was done in all cirrhosis patients receiving anti-tubercular treatment and drug therapy was stopped or altered as per the values or clinical deterioration.

The outcome of the treatment was noted, and all the data were analyzed using Statistical Package for the Social Sciences (SPSS) (SPSS for Windows, version 12.0; SPSS; Chicago, IL, USA). Statistical significance was assumed at $P < 0.05$.

RESULTS

In this study, the prevalence of TB was found in 7% of cirrhotic patients. Mean age of patients of cirrhosis was 41.28 ± 4.61 years. The mean age was similar in cirrhotic patients with TB when compared to those without TB. Out of 79 male cirrhotics, 4 patients (2 had extrapulmonary disease) had TB (5.1%). However, among 21 cirrhotic females, 3 (14.3%) had TB (all had extrapulmonary disease). Although females had >3 times greater chances of TB in the present study, the difference was not statistically significant (odds ratio 3.13; 95% CI: 0.41-20.02). Among all cirrhotics, extrapulmonary cases (5%) out-numbered pulmonary cases (2%), but the difference was not significant. In the present study, we found 2 cases of PTB in patients with cirrhosis; among 5 cases of extra-PTB, 4 had abdominal TB (peritoneal TB) and 1 had spinal TB (Pott's spine).

In majority of cirrhotics, etiology was alcoholism (66%) followed by chronic hepatitis B infection (27%), cryptogenic (13%), cardiac failure (2%), and Wilson's disease (1%). Chronic hepatitis C could not be found in any cirrhotic patients.

The most common complication seen in cirrhosis was sepsis (other than spontaneous bacterial peritonitis [SBP]) in 25% cases followed by hepatic encephalopathy (14%), hepatorenal syndrome (10%), SBP (10%), hepatocellular carcinoma (9%), and gastrointestinal bleed (8%).

In patients of cirrhosis with TB, similar pattern of complications was seen. Sepsis was the most common complication (28.37%), in addition to SBP (14.28%).

In overall cirrhotic patients, 60% were in Child's B (8-10), 24% in Child's C (>11), and 16% were in Child's A (<7) category with a mean value of 9.38 ± 1.89 . In patients with TB and cirrhosis, all the patients were in Child's B (57.14%) and Child's A (42.85%) category with a mean value of 8.71 ± 2.06 . Comparison of mean Child's score between TB and non-TB subjects showed no significant difference by using Wilcoxon Mann-Whitney test ($Z = 0.78$; $P > 0.05$).

In the present study, out of 100 cases of cirrhosis, there were 13 deaths (13%). Of these 13 deaths, 2 cases had TB also. Cause of death in these 2 patients was found to be TB. The mortality of cirrhotic patients without TB was 11.8%. Out of total 7 cases of TB with cirrhosis, there were 2 deaths, i.e., 28.5% mortality (Table 2). However, this difference was not statistically significant. On comparing with the number of patients who were alive at 3 months of follow-up, there was 3 times greater chance of TB among those who died (odds ratio: 2.98; 95% CI: 0.25 - 20.87) however this difference was again not statistically significant.

Child Pugh Class A (compensated): Score <7; Child Pugh Class B (significant functional compromise): Score 8-10; Child Pugh Class C (decompensated): Score >11.

DISCUSSIONS

This study was done to find the prevalence, clinical profile, and outcome of patients of liver cirrhosis who were concurrently suffering from active TB. Total 100 cirrhotic patients who gave the consent for the study were included in the study.

Mean age of patients of cirrhosis was 41.28 ± 4.61 years, and male to female ratio was 4:1. We showed that the overall prevalence of TB in cirrhotic patients was 7% which was

similar to the prevalence seen in the study by Baijal *et al.* (in which it was 7.4%).⁹ The mean age of the patients was 46.42 years, and the male to female ratio was 5:1 in the same study.⁹ In another study, authors found that more than 70% of TB with cirrhosis cases occurred in the age group of 15-54 years, with a mean age of presentation of 49.34 years.¹⁰ A recent review by Kumar *et al.* suggests a higher prevalence of TB in patients with cirrhosis when compared to the general population. The high incidence of TB in patients with cirrhosis has been ascribed mainly to immune dysfunction with associated higher virulence as compared to the general population.⁶ In a cohort study of patients with liver cirrhosis from Denmark (1977-1993), the incidence of TB was 168.6/100,000. It was highest in men aged >65 years, with an incidence of 246/100,000.¹¹ Furthermore, patients with cirrhosis who acquired TB had a poor prognosis in that study.

We found that among male cirrhotics, 5.1% patients had TB, and among females 14.3% had TB, however, the difference was not statistically significant. In the study by Baijal *et al.* TB was more common among the males (8.36% in males versus 3.5% in females).⁹

We found that extra-PTB tends to be more common than pulmonary disease, but the difference could not reach significance. Among extra-PTB in cirrhotic patients, the majority had abdominal TB. Similar observation was seen in other studies. In the study by Baijal *et al.*, PTB was noted in 40% of cases and extrapulmonary TB in 60%.⁹ In another study, 31% patients with cirrhosis had extrapulmonary TB, as compared to 12% in the non-cirrhosis group with a predominance of peritoneal TB as seen in our case.¹² Recently, a study conducted in India also suggested that extrapulmonary TB (63%) was more common than PTB.¹³ Although the host defense systems are impaired in cirrhotics like in other immune-deficient states like HIV infection, there is no explanation why patients are more likely to develop extrapulmonary TB than PTB.

In our study, major etiologies of cirrhosis were found to be alcoholism (66%) followed by hepatitis B (27%) and cryptogenic (13%). In a study at KEM Hospital, Mumbai, authors reported that among 72 patients of cirrhosis, etiology of cirrhosis was alcoholism in 37 cases, hepatitis B in 25 cases and hepatitis C in 10 cases.¹⁴ In the study at GB Pant Hospital, New Delhi, authors observed that among 176 cases of cirrhosis, 104 were related to viral etiology, 40 with alcoholic liver disease, 26 cryptogenic and 6 with miscellaneous causes.¹⁵

In the present study, the most common complication found in cirrhosis was sepsis (other than SBP) which was seen 25% of cirrhotic patients, followed by hepatic

Table 2: Outcome of patients of cirrhosis with and without TB

| Outcome | Number of cirrhotics (N=100) | No TB (N=93) | TB (N=7) |
|------------------|------------------------------|--------------|----------|
| Death | 13 | 11 | 2 |
| Alive (3 months) | 87 | 82 | 5 |

TB: Tuberculosis

encephalopathy (14%), hepatorenal syndrome (10%), SBP (10%), hepatocellular carcinoma (9%), and gastrointestinal bleed (8%). Similar pattern of complications was seen in patients of cirrhosis with TB. Sepsis was the most common complication (28.37%) followed by SBP (14.28%). Theoretically, any deterioration of liver function due to ATT-induced hepatotoxicity in a patient with well-compensated or previously decompensated chronic liver disease may result in severe, acute deterioration, resulting in a clinical picture suggestive of acute-on-chronic liver failure resulting in high mortality. Fortunately, we did not come across such deterioration, most likely due to limited sample size. In our study, there was no statistical difference in the Child's Score and mortality among the cirrhotics who had TB when compared to those who did not. In the study by Sharma *et al.*, 35% of the patients treated with combination treatment developed hepatotoxicity and majority of these patients are from Child B and Child C as these patients have low albumin and poor nutritional status. The median Child's score of cirrhotics with TB in their cohort was 8.5 (5-12) and none of their patient died due to ATT.¹³

CONCLUSION

We concluded from our study that the prevalence of TB in cirrhosis was less and affects same age group as cirrhotics without TB. TB tends to occur more frequently in females, and extrapulmonary disease tend to occur more often than pulmonary disease. In contrast to other parts of India, hepatitis C virus related cirrhosis was not seen in our cohort. We could not demonstrate any difference in severity of liver disease in patients with or without TB, and the pattern of complications was also similar. Although mortality in patients of cirrhosis with TB tend to be higher

when compared to those without TB, the difference was insignificant. The major limitation in our study was of small sample size, and the results were not compared with patients of TB in general population.

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How to cite this article: Bhargava J, Rai R, Ramteke S. Prevalence of Liver Cirrhosis with Tuberculosis and its Outcome. *Int J Sci Stud* 2017;4(12):85-88.

Source of Support: Nil, **Conflict of Interest:** None declared.