

TUBERCULOSIS IN CIRRHOSIS OF LIVER: A DIAGNOSTIC AND TREATMENT ENIGMA

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Abstract

Background: Patients who have cirrhosis have an increased risk of contracting tuberculosis. When cirrhosis is present, conventional therapy of tuberculosis and timely detection of the disease are both challenging. Specifically, this study examined the hepatotoxicity of the standard ATT regimen and the radiological and clinicopathological features of TB in individuals with cirrhosis of the liver. **Method:** This observational study was conducted at the Institute of Medical Sciences and SUM Hospital in Bhubaneswar, India, and involved fifty patients who had just been diagnosed with pulmonary and extrapulmonary tuberculosis and who also had cirrhosis of the liver as an underlying condition. Between the months of September 2019 and September 2021, the patients were assigned to either indoor or outdoor facilities inside the hospital. **Results:** There was a 47.86±7.98-year-old mean. The ratio of men to women was 6.14:1. ALD was the most prevalent cause of cirrhosis (52%), followed by viral infection (24%), cryptogenic disease (16%), and nonalcoholic steatosis (8%). Class A (16%), class C (28%), and Class B (56%) comprised the CTP cohorts, respectively. Extrapulmonary TB accounted for 80% of cases, with pulmonary TB accounting for 20%. Loss of appetite (82%) was the most prevalent symptom, followed by fever (76%), weight loss (52%), refractory ascites (28%), abdominal discomfort (22%), and cough (12%). The radiological findings for the majority of the patients were splenomegaly (26%) and moderate to extensive ascites with floating echogenic debris (26%), as well as SAIO with paralytic ileus (26%). The most frequent diagnostic findings in the lungs of cirrhosis patients with tuberculosis were several atelectatic bands (28%) and cavities in the right middle lobe and left lingula (28%). In this study, patients with altered baseline LFT (SLE) regimens (88% of patients) got Streptomycin, Levofloxacin, and Ethambutol (SLE) regimens. In contrast, patients with normal baseline LFT (HRZE) regimens (12%) received traditional ATT regimens (ATT). DILI affected 10% of the patients overall. Differences in age ($p=0.124$) and sex ($p=0.342$) were not statistically significant in the individuals who had DILI. Four CTP-class A patients were switched from an SLE regimen to a 4-drug regimen during the research. **Conclusion:** It might be challenging to diagnose tuberculosis when cirrhosis is present. In patients with cirrhosis, the treatment of tuberculosis is significantly more difficult because of the underlying impairment in liver function. The degree of cirrhosis should be taken into consideration when formulating specific recommendations for the use of alcohol therapy regimens.

Keywords: Child Turcotte Pugh, Liver Cirrhosis, Tuberculosis regimen, DILI.

INTRODUCTION

Any individual is susceptible to contracting tuberculosis; however, some individuals are at a greater risk than others. In 2021, around 10.6 million people will get TB, according to the World Health Organization (WHO). This information was included in the worldwide TB report that was released.¹ The death rate due to tuberculosis was estimated to reach 1.6 million in the year 2021.¹

As a result of the immunocompromised condition of the host, the risk of tuberculosis is elevated by a factor of fourteen in individuals who have cirrhosis, and this risk is

compounded in cases with decompensated cirrhosis.² The majority of them have liver function grades B or C, according to CTP. As a result, the likelihood of developing TB, whether it be pulmonary or extrapulmonary, is increased for people.¹ In some instances, the signs and symptoms of both disorders may be similar to one another. The likelihood of patients with cirrhosis experiencing extrapulmonary symptoms, such as peritonitis and disseminated tuberculosis, is higher than the likelihood of those who do not have the condition. Because of the bacteria's enhanced virulence, the likelihood of multidrug-resistant tuberculosis is higher.¹

Several diagnostic tests may be altered, which makes it difficult to diagnose tuberculosis in patients who have cirrhosis. There are known problems associated with the usual treatment for tuberculosis, including drug-induced liver damage (DILI) and liver enzyme increases. The rates of substantial liver enzyme increase that have been documented on conventional treatment range anywhere from five per cent to thirty per cent.^{3,4,13,14}

Every single one of the radiological and clinicopathological features of tuberculosis in conjunction with liver cirrhosis is missing appropriate evidence. When it comes to the administration of ATT in the different CTP grades, there are no precise procedures. As a result of the absence of comprehensive research in Eastern India, the purpose of this study was to investigate the same.

METHODS

The locations of this observational research were Bhubaneswar's Institute of Medical Sciences and SUM Hospital India, and it included fifty patients who were diagnosed with pulmonary and extrapulmonary tuberculosis. These patients were hospitalized with cirrhosis of the liver and were treated in either indoor or outdoor facilities. The study lasted for twenty-four months, beginning in September 2019 and ending in September 2021. Participation in the trial was open to patients having a history of cirrhosis and TB, whether it be pulmonary or extrapulmonary. The existence of biochemical evidence and radiological imaging confirmed this. A refusal to participate, HIV positivity, pregnancy, long-term steroid medication, chemotherapy, and chronic obstructive pulmonary disease were the reasons for exclusion.

The Child-Pugh score was used to determine the stage of cirrhosis. The patient's symptoms, including the duration of their illness, abdominal distension, jaundice, oliguria, fever, night sweats, cough with sputum expectoration, and jaundice, were all documented in great detail in their medical history. Following that, the patient was subjected to a comprehensive physical examination, which was then followed by the observation of the radiological, biochemical, and CBNAAT examinations of the tissue and fluids. The development of any liver damage caused by ATT was closely observed in patients, and their specific ATT regimen was recorded and managed accordingly. To diagnose DILI, one of the following has to be true: When ALT is five times the ULN, ALP is two times the ULN, or when ALT is three times the ULN, and total bilirubin is two times the ULN, the results are considered abnormal.⁵

Statistical analysis

The information was entered into a worksheet created in Microsoft® Excel 2019 and then exported into SPSS version 21.0. Categorical data was shown either as a percentage or as a frequency table. Two methods for representing numerical data were the mean and standard deviation. To compare the non-normative data from the

two groups, we used the Mann-Whitney U test. When comparing categories in this research, the Chi-square test was used. Statistical significance was defined as a p-value below 0.05.

RESULTS

General characteristics

The average age of the patients who participated in this study was 47.86 years, with a standard deviation of 7.98 years. Nearly three-quarters of the patients, or 39%, were between the age range of 41 to 50 years old. There was a ratio of 6.14 men to every single female. Class B of the CTP contained the majority of the patients, which accounted for 56% of the total, followed by class C (28%) and class A (16%). The average score on the CTP was 8.1, with a standard deviation of 1.2. In terms of cirrhosis, the bulk of instances were caused by ALD, which accounted for 52% of all cases. Following closely behind were cases of cryptogenic (16%), viral infection (24%), and NASH (8%). The most common symptom was a lack of appetite, which was experienced by 82% of patients. This was followed by fever, which was experienced by 76% of patients, and weight loss, which was experienced by 52% of patients. Only twelve percent of patients reported having a cough (Table 1).

Table 1: General characteristics of the study population

	Frequency	Percentage
Age group (Years)		
31-40	11	22.0
41-50	19	38.8
>50	20	40.8
Sex		
Male	43	86.0
Female	7	14.0
CTP Score		
Class-A	8	16
Class-B	28	56
Class-C	14	28
Aetiology of cirrhosis		
ALD	26	52
Viral	12	24
Cryptogenic	8	16
NASH	4	8
Clinical symptoms		
Loss of appetite	41	82
Fever	38	76
Weight loss	26	52
Increasing ascites not responding to diuretics	14	28
Pain abdomen	11	22
Cough	6	12

Radiological findings in study patients

Splenomegaly and moderate to extensive ascites with floating echogenic debris, as well as SAIO with paralytic ileus, were seen in twenty-six per cent of the patients. In 16% of cases, moderate to extensive ascites, dilated intravenous veins with hepatic veins, and a known cause of acute coronary artery ligation and femoral artery thrombosis were found (Table 2).

Table 2: Radiological findings of cirrhosis

Radiological finding of cirrhosis	Frequency	Percentage
Moderate to gross ascites with floating echogenic debris and SAIO	13	26
Splenomegaly	13	26
Moderate ascites	11	22
Dilated IVC and hepatic veins	8	16
Known cause of acute on chronic liver failure	8	16
Moderate bilateral pleural effusion	8	16

Diagnosis of TB

Both the right middle lobe and the left lung lingula, as well as ADA ascitic fluid and numerous atelectatic bands in both lower lobes, were abnormalities that were seen in the 28% of patients who participated in this research (Table 3).

Table 3: Diagnosis of TB

TB Diagnosis	Frequency	Percentage
Cavitation in the right middle lobe and left lung lingula	14	28
ADA ascitic fluid	14	28
Multiple elastic bands in bilateral lower lobes	14	28
NCCT thorax- a feature of soft tissue swelling noted over the right sternoclavicular joint	13	26
Pleural fluid CBNAAT positive	8	16
Hepatomegaly	5	10
Bilateral mild pleural effusion with fissural effusion,	5	10
Gross ascites with particulate debris	5	10
Fibrotic opacities with a small cavity in the left upper zone	5	10
Omental caking	5	10
TB lymphadenopathy	2	4
CECT showing consolidation in bilateral upper lobe with an associated tree in bud opacities	2	4

Site of involvement

Among the sites of involvement, extrapulmonary involvement was the most prevalent (80%), followed by pulmonary involvement (20%).

Treatment regimen involved

Eighty-eight per cent of the patients (n=44) in this research were being treated with the SLE regimen. In contrast, twelve per cent (n=6) were prescribed the HRZE regimen.

For this research, four patients were moved from an SLE regimen to a four-drug regimen. These individuals were all classified as CTP-class A patients.

Comparison of age and sex based on DILI

DILI was present in a total of 10 per cent of the individuals who took part in this experiment. According to the data presented in Table 4, there was no noticeable difference in terms of age or gender between patients who had DILI and those who did not have DILI.

Table 4: Comparison of age and sex based on DILI

	DILI (n=5)	No DILI (n=45)	P-value
Age (years)	56.00 [48.50, 57.50]	46.00 [40.50, 54.50]	0.124
Sex [M: F]	5:0	38:7	0.342

DISCUSSION

A mean age of 47.86 years (standard deviation: 7.98 years) was shown by the data for the patients who took part in this study. Our findings corroborate those of Baijal et al., who determined that 46.82 years was the average age of the Indian population.⁶ Contrary to what Hung et al. found, the age is lower in cirrhotic people. The non-TB group had an average age of 61.5 ± 14.2 years, whereas the TB group had an average age of 61.0 ± 14.8 years, with a p-value of 0.895 when comparing the two groups. However, differences in geographic location are just one of several factors that influence tuberculosis in cirrhosis.⁷ In another study by Bhargava et al., the mean age of cirrhosis patients was 41.28 ± 4.61 years.⁸

86% of the patients in our study were men. Our findings concur with those of Bhargava et al., who discovered a male-to-female ratio of 4:1.8. In the study conducted by Baijal et al., the male-to-female ratio was 5:1.⁶

Patients classified as CTP class B comprised the bulk of participants in our study (56%). The study by Bhargava et al. categorized all cirrhotic patients as follows, with a mean value of 9.38 ± 1.89: 60 per cent of the children fell into the B (8–10) group, 24 per cent into the C (>11) group, and 16 per cent into the A (<7) group. All patients with TB with cirrhosis fell into the Child's B (57.14%) and Child's A (42.85%) categories, with a mean value of 8.71 ± 2.06.⁸

Out of all the study participants, alcohol liver disease accounted for 52% of the cases of cirrhosis. However, Mukherjee et al. discovered in their multicentric investigation that the most prevalent cause of chronic liver disease in general and non-cirrhotic chronic liver disease (which accounts for 40.8% of all cirrhotic chronic liver disease) was Hepatitis B (33%).⁹ They claimed that the etiological profile of CLD in India, as shown by our data, demonstrates the current epidemiological change in the country. Bhargava et al.'s study found that the leading cause of 66% of cases of cirrhosis was alcohol use, which was followed by chronic hepatitis B infection (27%), cryptogenic sickness (13%), heart failure (2%), and Wilson's disease (1%). There was no chronic hepatitis C in any of the cirrhosis patients.⁸

In our research, viruses accounted for 24% of the causes of cirrhosis, with hepatitis B prevalence being at 20%. Mishra et al. found that alcohol use (63.3%) was the most prevalent cause of illness in the East Coast population of Odisha, followed by viral reasons (19.8%) with a prevalence of hepatitis B and other non-viral and nonalcoholic causes.¹⁰ According to Baijal et al.'s research, alcohol (30, 60%); post-viral infection, such as hepatitis B and C (14, 28%); and other reasons (6, 12%) were the etiological variables that led to liver cirrhosis.⁶

In our research, the extrapulmonary site of involvement was used the most often (80%), followed by the pulmonary site (20%). In a research conducted by Baijal and colleagues, pulmonary tuberculosis was found in forty per cent of the patients. In contrast, extrapulmonary tuberculosis was found in sixty per cent of the cases.⁷

Additionally, Cho et al. have observed that individuals with cirrhosis had a greater rate of extrapulmonary involvement.¹¹

In this particular research, twenty-eight per cent of the patients exhibited cavitation in both the right middle lobe and the left lung lingula. Additionally, the ADA ascitic fluid was elevated, and there were many atelactic bands in both lower lobes.

The DILI rate within the parameters of this study was 10%. DILI barely makes up 1% of all instances of acute liver damage that gastroenterologists see, even though it is the most prevalent cause of acute liver failure in Western nations. The incidence of DILI is fifteen times greater in western India than it is in the rest of the country, according to Saigal et al.'s data.¹² The prevalence of tuberculosis (TB) among patients with cirrhosis is about five times greater than the 1.6% prevalence in the general population, according to Baijal et al.⁶

CONCLUSION

In conclusion, standardizing the use of ATT in patients with chronic liver disease and hepatic cirrhosis is critically necessary. A damaged immune system is already a problem with cirrhosis, and adding TB to the mix only makes things worse for treatment. Step one in navigating this challenging landscape would be to lay down some ground rules based on what the experts think. The only reasonable way to untangle this particular Gordian knot is to collect a prospective database, which would be achievable with these rules.

Abbreviations

TB- Tuberculosis

ATT- Anti-Tubercular Therapy

ALD- Alcoholic Liver Disease

CTP- Child Turcot Pugh

NASH- Nonalcoholic Steato Hepatitis

SAIO- Sub-Acute Intestinal Obstruction

ADA Adenosine Deaminase

LFT- Liver Function Test

SLE -Streptomycin, Levofloxacin, Ethambutol

DILI- Drug-induced liver injury

ULN- Upper limit of normal

ACLF- Acute, chronic liver failure

IVC- Inferior Vena Cava

NCCT -Non-contrast Computerized Tomography

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