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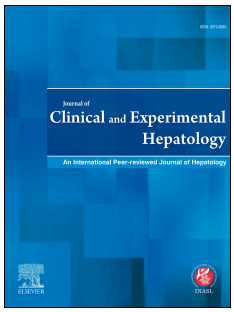

Tuberculosis in cirrhosis- A diagnostic and management conundrum

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Tuberculosis in cirrhosis- A diagnostic and management conundrum

Short Title: Tuberculosis in cirrhosis

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Abstract

Background

Diagnosis and management of tuberculosis (TB) in patients with cirrhosis remains challenging. We studied the clinical spectrum, diagnosis, and management of TB alongwith assessment of diagnostic utility of various laboratory investigations in this cohort.

Methods

Retrospective review of records of patients with cirrhosis (July 2017 and December 2019) was done. Out of 30 patients with cirrhosis and TB, 20 patients with pleural/peritoneal TB (cases) were compared with 20 consecutively selected spontaneous bacterial peritonitis (SBP) controls. Composite of clinical, laboratory, radiologic features and response to anti-tubercular therapy (ATT) was taken as gold standard to diagnose TB.

Results

Extrapulmonary TB (EPTB) (n=23,76.7%) was more common. Overall, 9(30%) patients presented with ATT-induced hepatitis. Patients with pleural/peritoneal TB had less severe hepatic dysfunction as compared to SBP group with significantly lower CTP [8±1.5 vs 9±1.7 (p=0.01)], MELD [16.3 ± 5.8 vs 20.2±6.6 (p=0.02)] and MELD-Na [18.8± 5.9 vs 22.5±7.1 (p=0.03)] scores. Median ascitic/pleural fluid total protein [2.7 (2.4-3.1) vs 1.1 (0.9-1.2); p<0.0001] and adenosine deaminase (ADA) levels [34.5 (30.3-42.7) vs 15 (13-16); p<0.0001] were significantly higher in the TB group. Total protein levels had a sensitivity and specificity 81% and 93.3%, respectively at cut off value of >2 g/dl with an AUROC of 0.89 [(0.79-0.96); p<0.001] whereas ADA levels at cut off >26 IU/L showed 80% sensitivity and 90% specificity to diagnose pleural/peritoneal TB with an AUROC of 0.93 [(0.82-0.97); p<0.001]. Only 11(36.7%), and 8 (26.6%) patients showed positivity on GeneXpert and mTB-PCR, respectively. Patients with Child-Turcotte-Pugh score ≤ 7 and 8-10 tolerated well two and one hepatotoxic drugs, respectively.

Conclusions

EPTB is more frequent in patients with cirrhosis. Relatively lower cut-offs of ascitic/pleural fluid total protein and ADA may be useful to diagnose EPTB in patients with high pre-test probability. Individualized ATT with close monitoring and dynamic modifications is effective and well-tolerated.

Keywords: Tuberculosis; Chronic liver disease; Cirrhosis; Adenosine deaminase; Gene Xpert MTB/RIF; TB-PCR; Anti-tuberculosis therapy.

Introduction

Tuberculosis (TB) is the tenth leading cause of mortality due to a single infectious agent worldwide [1]. India has the highest burden of TB with nearly 2.5 million new cases and half a million deaths reported in 2019[2]. TB is 10-15 times more common in patients with cirrhosis with high case fatality [3–5] and risk of reactivation [6].

Making a precise diagnosis of TB in patients with cirrhosis is challenging, given the higher incidence of extrapulmonary TB (EPTB) [7,8] and limited accuracy of the available tests. *Mycobacterium Tuberculosis* (MTB) culture takes 6-8 weeks. Laparoscopy with peritoneal biopsy, which is the gold standard to diagnose peritoneal TB, may not be feasible in patients with cirrhosis due to coagulopathy and thrombocytopenia. Newer nucleic acid amplification tests (NAATs) such as GeneXpert MTB/RIF (GeneXpert) and multiplex TB-polymerase chain reaction (mTB-PCR) have shown good sensitivity and specificity in sputum positive TB[9] with quick turn-around times. Unfortunately, their performance has been suboptimal in paucibacillary EPTB cases [10–12].

Apart from the diagnostic challenge, management of these patients is an arduous task with no consensus on the use of first-line anti-tubercular therapy (ATT). Isoniazid, rifampicin, and pyrazinamide are hepatotoxic [13] and can cause drug-induced liver injury (DILI) which may lead to high short-term mortality[5].

To address the aforementioned gaps in knowledge, we studied the clinical spectrum, diagnosis, and management of TB in patients with cirrhosis. A special emphasis was laid on evaluating the ability of ascitic/pleural fluid investigations to diagnose and discriminate peritoneal and/or pleural TB from spontaneous bacterial peritonitis (SBP) and/or empyema (SBE).

Material and methods

Study Participants

We retrospectively screened inpatient and outpatient records of all patients who presented to the Liver clinic of our institute between July 2017 and December 2019. Patients with cirrhosis who were diagnosed and treated for TB were considered for enrolment based on inclusion and exclusion criteria (Supplementary Figure 1). Twenty consecutive

patients with SBP were taken as controls for comparison with pleural/peritoneal TB (cases). The study was approved by the Institute's Ethics Committee and adhered to the Declaration of Helsinki.

Study definitions

Diagnosis of Tuberculosis

Pulmonary TB was diagnosed if there was sputum positivity for acid-fast bacilli (AFB)/MTB by Ziehl-Neilson (ZN) staining or Gene Xpert or mTB-PCR and/or if there were chest imaging (X-ray/computed tomography, CT) findings consistent with TB. Diagnosis of extrapulmonary TB was mostly presumptive and was based on combination of clinical, laboratory, and/or radiologic features alongwith response to ATT, in the absence of pulmonary involvement. If ascitic or pleural fluid or other appropriate body specimen was found to be positive for AFB/MTB by ZN staining or Gene Xpert or mTB- PCR or if there was characteristic finding of TB on histopathology then diagnosis of EPTB was considered definite.

Response to treatment: Subjective and/or objective improvement in presenting symptoms such reduction in ascites/regaining of diuretic responsiveness (reduced dose of diuretics) and/or resolution of pleural effusion and/or cold abscess and/or regression of lymphadenopathy depending on site of tubercular involvement.

ATT-induced hepatitis or ATT-DILI: ATT-induced hepatitis in patients with cirrhosis was defined as a rise in transaminases by >2 times the baseline value or bilirubin >2 mg/dl, after exclusion of other possible causes [7,14,15].

Control definition (Spontaneous Bacterial Peritonitis)

SBP was diagnosed if the ascitic fluid absolute polymorphonuclear leukocyte (PMN) count was ≥250 cells/ ml with or without culture positivity in the absence of any intra-abdominal or surgically treatable source of infection[16]. Acute kidney injury (AKI) and diuretic non-responsive ascites were defined as per international ascites club guidelines[16,17].

Diagnosis of Cirrhosis

The diagnosis of cirrhosis[18] was based on clinical, radiological, histological, and/or liver stiffness measurement (LSM) of ≥12.5 Kpa. The severity of cirrhosis was determined by Child-Turcot-Pugh (CTP)[19], Model for End-Stage Liver Disease (MELD) and MELD-Sodium (MELD-Na) scores[20].

Clinical and Laboratory Assessment

Demographic characteristics, history, clinical examination, and available laboratory and radiological investigations were recorded and analyzed. Ascitic and/or pleural fluid investigations comprising of total and differential leukocyte counts with biochemistry and microbiological parameters encompassing total protein, sugar, serum ascitic albumin gradient (SAAG)/ Serum pleural fluid albumin gradient (SPAG), gram's staining, and bacterial culture were also noted. Specific investigations for diagnosis of TB including microscopy for AFB using ZN staining, adenosine deaminase (ADA) level determination using Giusti method[21], GeneXpert MTB/RIF (Cepheid, USA), and mTB-PCR [22] on appropriate specimens were also recorded.

Management

Medical records were meticulously reviewed for ATT used with dosage, duration, dose modifications, adverse events, and treatment discontinuations, if any. Any improvement or deterioration in the patient's clinical symptoms and investigations were recorded.

Statistical analysis

Statistical analysis was done using SPSS software version 22.0 (SPSS Inc., Chicago, IL). The results of quantitative variables are presented as mean with standard deviation (SD) and/or median with 95% confidence interval (CI), depending on distribution attributes and as proportions with percentages for qualitative variables. Comparison between groups was done using Chi-square and Fischer exact tests for categorical variables and student's t-test and Mann-Whitney u-test for parametric and non-parametric variables, respectively. Diagnostic utility of ADA and ascitic fluid protein was assessed using sensitivity and specificity at various cut-offs based on the area under respective receiver operator curves (AUROC) using clinical diagnosis and response to ATT as the gold standard. P-value of ≤ 0.05 was considered as statistically significant.

Results

Patient recruitment and demographic variables

Out of 40 patients with cirrhosis and TB, thirty cases fulfilling the inclusion criteria were included (Supplementary Figure 1). Among the 30 patients with cirrhosis and TB, 20 cases with pleural/peritoneal involvement (cases) were

compared with 20 consecutive patients with cirrhosis and SBP (controls). The baseline demographic characteristics and etiology of cirrhosis were comparable between the two groups as shown in Table 1.

Spectrum of tubercular involvement and clinical presentation

EPTB (n=23,76.7%) was much more common than PTB (n=7, 23.3%) (Table 2). On comparing clinical presentation of patients with pleural/peritoneal TB and SBP, fever was the most common presenting complaint in both the groups [TB group: n=13 (65%), SBP group: n=10 (50%)], followed by pain abdomen in 10 (50%) and 8 (40%) patients with TB and SBP, respectively. Four (20%) patients in the TB group presented with new-onset ascites whereas diuretic intractable ascites with or without AKI was seen in 5 (25%) and 11 (55%) patients with TB and SBP, respectively. Jaundice as a presenting complaint was seen in 5 (25%) cases with pleural/peritoneal TB, which was attributed to ATT-DILI. Only, 2 (10%) patients in each group were asymptomatic at presentation

Overall, respiratory symptoms of dyspnea [n=7 (23.3%)] and productive cough [n=7(23.3%)] were seen only in patients with pleural and/or lung parenchymal involvement. Acute upper gastrointestinal bleeding (n=5, 25%), hepatic encephalopathy (n=5, 25%) and concomitant infections (n=7, 35%) were seen exclusively in the SBP group (Supplementary Table 1).

Baseline laboratory investigations and severity of cirrhosis

Patients with pleural/peritoneal TB had less severe hepatic dysfunction as compared to SBP group with significantly lower CTP [8±1.5 vs 9±1.7 (p=0.01)], MELD [16.3 ± 5.8 vs 20.2±6.6 (p=0.02)] and MELD-Na [18.8± 5.9 vs 22.5±7.1 (p=0.03)] scores. CTP class C was more frequent in SBP group [9(45%) vs 4 (20%) (p=0.04)] (Table 1). SBP patients had significantly lower hemoglobin [9.8 (8.9-10) vs 10.4 (9.8-11.9) (p=0.02)], higher creatinine [1.4(1.2-1.9) vs 1(0.9-1.2) (p=0.03)] and INR [1.8(1.4-1.9) vs 1.5(1.4-1.7) (p=0.05)] whereas other baseline biochemical parameters were comparable between the two groups (Supplementary table 2).

Cytological and biochemical characteristics of ascitic and/or pleural fluid

On comparing peritoneal and/or pleural EPTB (n=20) cases with SBP (n=30) group, patients with TB had significantly higher lymphocyte percentage [85% (75-94) vs 18% (12-23) (p<0.0001)] whereas PMN cells were significantly higher

in patients with SBP [82 (77-88) vs 15 (6-25) (p<0.0001)] (Table 3). Median total protein [2.7 (2.4-3.1) vs 1.1 (0.9-1.2); p<0.0001] and ADA levels [34.5 (30.3-42.7) vs 15 (13-16); p<0.0001] were significantly higher in TB group (Supplementary Figure 2 and 3). Total protein levels had a sensitivity and specificity 81% and 93.3%, respectively at cut off value of >2 g/dl with an AUROC of 0.89 [(0.79-0.96); p<0.001] whereas ADA levels at cut off >26 IU/L showed 80% sensitivity and 90% specificity to diagnose pleural/peritoneal TB with an AUROC of 0.93 [(0.82-0.97); p<0.001] (Figure 1 and Figure 2).

Performance of various diagnostic tests of TB

All the seven PTB patients had positive sputum GeneXpert, whereas 5(71.4%) patients had sputum AFB positivity and 6(85.7%) patients had mTB-PCR positivity. However, among the 23 EPTB cases, only one had AFB positivity (on aspiration cytology of retroperitoneal lymph node) with detection of MTB by GeneXpert and mTB-PCR in only 4(17.3%) and 2(8.6%) patients, respectively. Overall, out of 30 patients with TB, only 6(20%), 11(36.7%), and 8 (26.6%) patients showed detection of MTB/AFB on microscopy, GeneXpert, and mTB-PCR, respectively (Supplementary Table 3).

Radiological evaluation in TB patients

Among 23 patients with EPTB, 10 (43.5%) patients had pleural effusion (5 TB effusion, 3 pleuro-peritoneal TB, 2 right-sided transudative effusion). Thirteen (56.5%) had no lung parenchymal abnormality on chest imaging that suggested active PTB. Ascites, peritoneal or omental thickening, peritoneal enhancement, and/or hypoattenuating necrotic intraabdominal lymph nodes were seen in 18(78.3%), 4(17.3%), 2(8.6%), and 4(17.3%) patients on abdominal contrast-enhanced CT. Ascites was loculated in only 3 (16.7%) patients (Supplementary Table 4).

ATT: combinations, modifications, duration, and side-effects

Patients with CTP score ≤ 7 received two and those with CTP score between 8-10 received one hepatotoxic drug. Rifampicin was the drug of choice in all patients receiving a single hepatotoxic drug. Nine (30%) patients who presented with ATT-DILI were initiated on all the three first-line hepatotoxic ATT drugs simultaneously in peripheral centers before being referred to our institute. Among the hepatic-safe regimens, intravenous amikacin was used in 7(23.3%) patients whereas intramuscular streptomycin was used in 2 patients. Levofloxacin was the most frequently used second-line drug (n=26,86.6%) and showed no major side-effects. AKI due to amikacin was encountered in 4

out of 7 patients within 2 weeks of initiation and was replaced by oral levofloxacin. The composition of the ATT regimens used was dynamic and their duration was variable ranging between 9-18 months (Table 4).

Discussion

Cirrhosis-related immune dysfunction contributes to a higher incidence of active TB, and false negative laboratory investigations, especially tuberculin skin tests and interferon-gamma release assays [23]. The diagnostic difficulty may lead to delayed initiation of ATT and increased morbidity and mortality. This study highlights that early diagnosis with appropriate investigations and carefully selected ATT regimens can improve the overall outcome in this difficult to treat cohort.

The majority of TB patients in our study were middle-aged males. The older age of our cohort as compared to the general population with TB can be attributed to the exclusive inclusion of patients with cirrhosis. The most common etiology of cirrhosis in our study was alcohol, which has also been reported to be an independent risk factor for TB in multiple previous studies [3,8,24,25].

PTB accounts for 80-85% of cases in the general population and is relatively easier to diagnose[1] whereas more frequent EPTB in cirrhosis poses a diagnostic conundrum. A high index of suspicion for TB must be kept in patients with cirrhosis due to the nonspecific and diverse clinical presentations of EPTB. Constitutional symptoms, like anorexia, fever and weight loss which are clinically helpful in making a diagnosis of TB, may not be reliable in patients with cirrhosis[26]. More than three-fourths of patients in our study had EPTB with peritoneal and/or pleural involvement as opposed to TB- lymphadenitis in immunocompetent individuals[1]. Previous studies from India[4,7] and other Southeast-Asian countries[8,27,28] have reported a similar higher incidence of EPTB in patients with cirrhosis. Higher incidence of EPTB can be explained by an inadequate initial immune response to contain MTB as well as increased risk of reactivation in cirrhosis.

Lower mean CTP and MELD scores in the TB group as compared to SBP group in our study suggests that development of SBP may need a greater degree of liver dysfunction and immune paresis. Similar observations were seen in an earlier study by Huang et al[28] in which the SBP was more common in CTP class C patients. New onset ascites or

recent loss of diuretic response in an appropriate clinical scenario may act as clinical cues to initiate work up for peritoneal TB.

Like previous studies, TB patients in our study had significantly higher median total protein and ADA levels than SBP patients. CD4+ T-lymphocytes mediated Th1 response is the primary immune response to MTB and activity of ADA correlates with the number, degree of maturation, and stimulation of lymphocytes[29]. However in patients with cirrhosis, a blunted immune response may not lead to a remarkably high increase in ADA levels [8,30]. We found a relatively lower cut-off of ADA (>26 IU/L) for diagnosing TB similar to Lee et al[30]. Multiple studies from the Southeast-Asian region have shown similar performance of ADA to diagnose ascitic/pleural TB, with cut-offs ranging between 30-45 IU/L however, these studies included patients without cirrhosis also[8,29–31]. We found a lower cut-off of >2 g/dl of ascitic/pleural fluid protein level to suspect TB as compared to previous studies [8,30], which may be because of a higher number of patients with alcohol-related cirrhosis who have a greater degree of immune dysregulation, malnutrition, and sarcopenia[26].

NAATs have shown sensitivity ranging between 40-70% with up to 100% specificity in diagnosing peritoneal TB[10,32]. Only 1 EPTB patient showed positive ZN staining with just 4 (17.3%) and 2 (8.6%) patients showing positive GeneXpert and mTB-PCR, respectively. Similar low positivity rates of GeneXpert in body fluids has been reported from previous studies[33,34]. Paucibacillary nature of EPTB likely results in poor positivity of NAATs. However, a positive result on NAATs along with corroboratory clinical findings should be sufficient to commence ATT without waiting for cultures.

In the present study, most patients had atypical radiological findings of EPTB. Non-specificity of radiologic findings in EPTB especially peritoneal and/or pleural TB has been reported previously, especially in the patients with cirrhosis due to altered immune response [5,7,8]. Though radiologic evaluation may not be diagnostic of TB in patients with cirrhosis, it may be helpful to detect organ involvement and accessible sites for tissue acquisition.

Management of TB in cirrhosis is challenging and needs individualization. Firstly, the diagnosis of TB should be certain before initiating ATT. Unfortunately, nearly 60% of patients receive empirical ATT [35] suggesting poor specificity of diagnostic tests. The second issue is of hepatoxicity of three first-line antitubercular drugs and poorly defined diagnostic criteria of ATT-induced hepatitis in patients with cirrhosis [5]. Our clinical practice is to stop

hepatotoxic drugs if there is a relative rise of transaminases by >2 times from baseline or a rise in bilirubin to >2 mg/dl. Nearly, one-third of patients in our study presented with ATT-induced hepatitis likely due to the initiation of all three hepatotoxic anti-tubercular drugs simultaneously. This underpins the need of increasing awareness among the primary health care providers about the possibility of presence of yet undiagnosed underlying chronic liver disease and the need for baseline evaluation of liver functions, especially in at-risk patients, before initiation of first-line ATT.

In our study, most patients showed gradual improvement in their CTP scores. Periodic recalculation of CTP score with the sequential addition of the most effective ATT drugs (Rifampicin and Isoniazid) is of paramount importance. Fluoroquinolones including levofloxacin and ofloxacin have shown good efficacy and safety as a part of hepatic-safe ATT regimen in patients with cirrhosis[24]. However, the use of aminoglycosides like streptomycin and amikacin is limited in cirrhosis due to the risk of AKI and the presence of coagulopathy.

The treatment duration in our study ranged from 9-18 months depending upon baseline and dynamic changes in CTP score, ability to give first-line ATT drugs, and side effects leading to regimen modification. Carefully selected and individualized ATT with close follow up and concurrent management of underlying cirrhosis and its complications has shown satisfactory response in previous studies also with no effect of TB on mortality post 1 year of diagnosis and treatment[5,7,8,15].

The retrospective nature of our study limited our ability to accurately assess the initial clinical presentation, concurrent medications, compliance with diet restriction, dose of diuretics and any genetic associations with ATT induced hepatitis in our study population. Information regarding tuberculin skin testing and MTB culture was missing. Since patients were seen by all authors in their respective wards and clinics, uniformity in ATT regimens and duration was not maintained. Such non-uniformity further stresses upon the need for consensus guidelines to manage such patients based on accurate and extensive data on the efficacy and safety of various ATT regimens. All SBP patients were admitted which may have contributed to their higher CTP and MELD scores. As this is a single-center study, the cut-offs for total protein and ADA are only suggestive and may not be generalized.

Figure 3 outlines the proposed algorithm to manage TB in cirrhosis based on our experience.

Conclusions

EPTB is more common in cirrhosis and reaching a conclusive diagnosis is often difficult. A high index of suspicion and relatively lower cut-offs of ascitic or pleural fluid total protein and ADA may be useful to diagnose EPTB in patients with high pre-test probability. Individualized ATT with close monitoring and dynamic modifications is effective and well-tolerated by most patients resulting in excellent outcomes.

Compliance with Ethical standards

Conflict of interest: All the authors declare no conflict of interests. All authors had access to the study data and approved the final manuscript.

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Figure legends

Figure 1

Area under receiver operator curve (AUROC) for total protein levels in respective body fluids to diagnose pleural and/or peritoneal tuberculosis.

Figure 2

Area under receiver operator curve (AUROC) for adenosine deaminase (ADA) levels in respective body fluids to diagnose pleural and/or peritoneal tuberculosis.

Figure 3

Proposed algorithm for diagnosis and management extra-pulmonary tuberculosis (EPTB) in patients with cirrhosis.

TLC: Total leucocyte count; DLC: Differential leucocyte count; SAAG: Serum ascitic albumin gradient; SPAG: Serum pleural fluid albumin gradient; ADA: Adenosine deaminase; NAATs: Nucleic acid amplification tests; CECT: Contrast-enhanced computed tomography; AFB: Acid-fast bacilli; ATT: Anti-tuberculosis therapy; CTP: Child-Turcotte-Pugh Score; LFT: Liver function tests; DILI: Drug-induced liver injury; AST: Aspartate aminotransferase; ALT: Alanine Aminotransferase

Table 1: Baseline characteristics of the Pleural/Peritoneal Tuberculosis and Spontaneous Bacterial Peritonitis groups

	Pleural/peritoneal Tuberculosis Group (n=20)	Spontaneous Bacterial Peritonitis Group (n=20)	p
Age (median, 95%CI), years	49.5 (44.2-51)	52.5 (46.2-56)	0.43
Sex (Males: Females)	19:1	18:2	0.32
Etiology of chronic liver disease			
Alcohol	11 (55%)	9 (45%)	0.52
Chronic hepatitis C	3 (15%)	2 (10%)	
Autoimmune hepatitis	2 (10%)	1 (5%)	
Non-alcoholic fatty liver disease	2 (10%)	4 (20%)	
Cryptogenic	1 (5%)	1 (5%)	
Chronic hepatitis B	1(5%)	2(10%)	
Chronic Budd Chiari syndrome	-	1(5%)	
CTP Class			
CTP-A	2 (10%)	1 (5)	**0.04**
CTP-B	14 (70%)	10 (50%)	
CTP-C	4 (20%)	9 (45%)	
Baseline Severity Scores (mean ± SD)			
CTP Score	8 ± 1.5	9 ± 1.7	**0.01**
MELD	16.3 ± 5.8	20.2 ± 6.6	**0.02**
MELDNa	18.8 ± 5.9	22.5 ± 7.1	**0.03**

CTP- Child Turcotte Pugh Score; MELD-Model for End Stage Liver Disease; MELDNa- Model for End Stage Liver Disease with Sodium

Table 2: Site of Tuberculosis

Pulmonary Tuberculosis	**7 (23.3%)**
Extrapulmonary Involvement	**23 (76.7%)**
• Peritoneal	11 (48%)
• Pleural Effusion	5 (22%)
• Pleuroperitoneal	3 (13%)
• Psoas Abscess	1 (4.3%)
• Disseminated (Lung/Peritoneum/Lymph nodes)	1 (4.3%)
• Lymph Node (Retroperitoneal)	1 (4.3%)
• Knee arthritis	1 (4.3%)

Table 3: Ascitic fluid cytology and biochemical analysis among the pleural/peritoneal tuberculosis and spontaneous bacterial peritonitis patients

Ascitic/Pleural fluid parameter [median (95% CI)]	Pleural/Peritoneal Tuberculosis (n=20)	Spontaneous Bacterial Peritonitis (n=20)	p
SAAG/SPAG	1.3 (1.2-1.4)	1.8 (1.6-1.8)	**<0.0001**
TLC (cells/ml)	320 (220-576)	550 (460-658)	0.34
Polymorphonuclear cells (%)	15 (6-25)	82 (77-88)	**<0.0001**
Lymphocytes (%)	85 (75-94)	18 (12-23)	**<0.0001**
Sugar (mg/dL)	114 (97-145)	133 (121-145)	0.07
Total protein (g/dL)	2.7 (2.4-3.1)	1.1 (0.9-1.2)	**<0.0001**
ADA (IU/L)	34.5 (30.3-42.7)	15 (13-16)	**<0.0001**

SAAG-Serum-Ascitic Albumin Gradient; SPAG- Serum-Pleural fluid Albumin Gradient; TLC- Total Leucocyte Count; ADA- Adenosine Deaminase

Table 4: Anti-Tuberculosis treatment (ATT) regimens, duration and side-effects

S No	CTP	Site of TB	Regimen †	Duration (Months)	Side Effects
1	7B	Peritoneal	HRE	11	None
2	7B	Disseminated	HREL- 3 months; HRE-7 months	10	None
3	7B	Peritoneal	HREL	12	None
4	10C	Peritoneal	LEA-1 month; LE-2 months; LER-15 months	18	Acute Kidney Injury due to Amikacin
5	7B	Peritoneal	LER-1 months; HRE-11 months	12	None
6	8B	Peritoneal	REL- 2 months; HRE-9 months	11	None
7	10C	Pleuroperitoneal	LEA-1 month; LER-12 months	13	None
8	11C	Pleural effusion	LE-1 month; RLE-12 months	13	ATT induced hepatitis at presentation (H, Z)
9	9B	Pulmonary	HRZE- 14 days; LEA-1 month; RLE-11 months	12	ATT induced hepatitis on H and Z, Acute Kidney Injury with Amikacin
10	10C	Pleuroperitoneal	LER- 2 months; HRE-10 months	12	None
11	6A	Pleural effusion	HREL- 3 months; HRE-6 months	9	None
12	5A	Peritoneal	HREL- 3 months; HRE -7 months	10	None
13	9B	Pleural effusion	REL-13 months	13	ATT induced hepatitis at presentation
14	7B	Peritoneal	RLE- 2 months; HRE- 9 months	11	None
15	7B	Pleural effusion	RLE -2 months; HRE-8 months	10	None
16	8B	Pulmonary	RLES-2 months; RLE-3 months; HRE- 6 month	11	ATT induced hepatitis at presentation
17	6A	Psoas Abscess	HREL-3 months; HRE-6 months	9	None

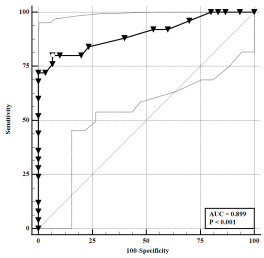
18	6A	Pulmonary	HREL-3 months; HRE-6 months	9	None
19	7B	Pulmonary	HREL-3 months; HRE-7 months	10	None
20	8B	Pulmonary	HRZE-10 days; ELS-1 month; RELS-2 months; HRE- 8 months	10	ATT induced hepatitis at presentation
21	8B	Peritoneal	RELA-1 month; REL-11	12	Acute Kidney Injury with Amikacin
22	9B	Pleuroperitoneal	HRZE- 9 days; RLE-1 month; HRE-9 month	10	ATT induced hepatitis at presentation
23	7B	Lymph Node (Retroperitoneal)	HRE-9 month	9	None
24	9B	Peritoneal	RELA- 1 month; RLE- 12 months	13	Autoimmune Hepatitis related transaminitis
25	9B	Peritoneal	RELA- 1 month; RLE- 12 months	13	Acute Kidney Injury with Amikacin
26	9B	Peritoneal	HRZE- 7 days; LEA- 1 month; RLE- 1 months; HRE- 9 months	11	ATT induced hepatitis at presentation
27	10C	Pulmonary	RLE- 3 months; HRE- 8 months	11	None
28	8B	Pulmonary	HRZE- 10 days; HRE-12 months	12	ATT induced hepatitis at presentation
29	6A	Left knee arthritis	HRE-13 months	13	None
30	9B	Pleural effusion	HRZE- 16 days; RLE- 2 months; HRE-8 months	10	ATT induced hepatitis at presentation

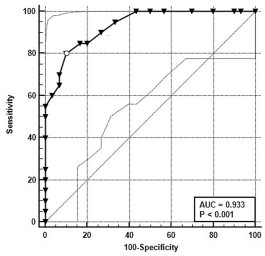
CTP-Baseline Child Turcotte Pugh Score; MELD-Baseline Model for End Stage Liver Disease Score; ZN-Ziehl-Neelson; ATT- Anti-Tuberculosis Therapy; FNAC- Fine Needle Aspiration Cytology.

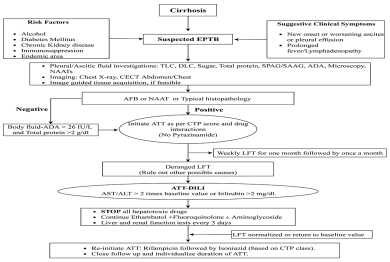
†H- Isoniazid (5 mg/kg q24h); R- Rifampicin (10 mg/kg q24h); Z-Pyrazinamide (25 mg/kg, q24h); E-Ethambutol (15 mg/kg q24h); S- Streptomycin (15 mg/kg Intramuscular q24h); A-Amikacin (15 mg/kg; Intravenous, q24h, 5 times/week); L-Levofloxacin (10-15 mg /kg q24h);

‡All patient underwent regular recalculation of CTP scores after repeating clinical and laboratory tests during follow up and ATT was modified accordingly and individualized.

§Patient who had ATT induced hepatitis at presentation received full dose first line ATT-regimen elsewhere and then referred to our institute; all had previously undiagnosed underlying chronic liver disease



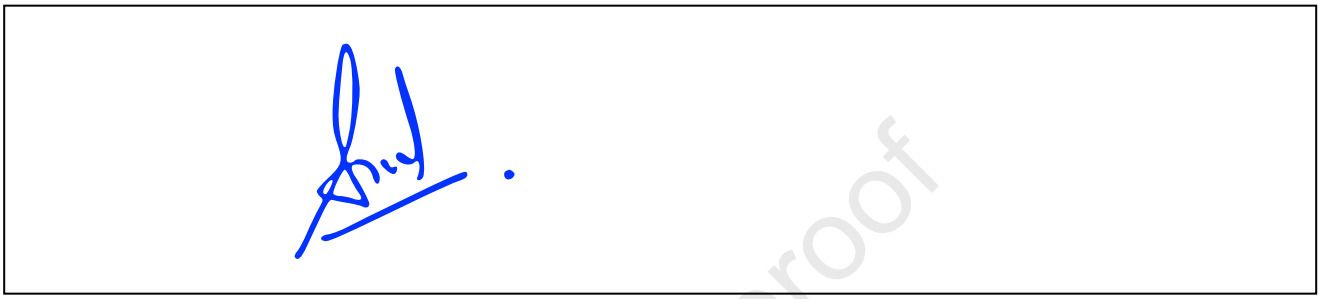




Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:



List of Abbreviations

TB- Tuberculosis; SBP- Spontaneous Bacterial Peritonitis; ADA- Adenosine deaminase; AUROC- Area under receiver operator curve; CTP-Child-Turcotte-Pugh; ATT- Anti-tubercular therapy; EPTB- Extrapulmonary Tuberculosis; MTB- *Mycobacterium Tuberculosis;* NAAT- Nucleic acid amplification test; mTB-PCR- multiplex TB-polymerase chain reaction; DILI- Drug-induced liver injury; SBE- Spontaneous bacterial empyema; AFB- Acid-fast bacilli; ZN- Ziehl-Neilson; CT- Computed tomography; AKI- Acute kidney injury; LSM: Liver stiffness measurement; MELD- Model for End-stage liver disease; MELD-Na- Model for End-stage liver disease with sodium; SAAG- Serum-ascitic albumin gradient; SPAG-Serum- pleural fluid albumin gradient; SD- Standard deviation; CI- Confidence interval