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Hepatobiliary tuberculosis in the developing world

Esguerra-Paculan MJA *et al.* Hepatobiliary tuberculosis

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Abstract

BACKGROUND

Hepatobiliary tuberculosis is a challenging disease that poses diagnostic difficulties due to its resemblance to other etiologies. Delayed diagnosis may lead to inadequate treatment, thus necessitating an urgent need for accurate diagnosis and appropriate management.

AIM

To systematically review case reports on hepatobiliary tuberculosis, focusing on symptomatology, diagnostic procedures, management, and outcomes to provide patient safety and ensure an uneventful recovery.

METHODS

A systematic search was conducted on PubMed from 1992 to 2022, using keywords such as hepatobiliary, liver, tuberculosis cholangitis, cholangiopathy, and mycobacterium. Only case reports or case series in English were included in the study, and research papers published as abstracts were excluded. The search yielded a total of 132 cases, which were further narrowed down to 17 case studies, consisting of 24 cases of hepatobiliary tuberculosis.

RESULTS

The 10 most common symptoms observed in these cases were fever, abdominal pain, weight loss, jaundice, anorexia, generalized weakness, pruritus, chills, fatigue, and chest

pains. Objective findings in these cases included hepatomegaly, hepatic nodules, elevated liver enzymes, and elevated bilirubin. CT scan and ultrasound of the abdomen were the most useful diagnostic tools reported. Histologic demonstration of *Mycobacterium tuberculosis* confirmed the cases of hepatobiliary tuberculosis. Treatment regimens commonly used included Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol. Out of the 24 cases, 18 presented improvements while 4 had completely recovered.

CONCLUSION

Hepatobiliary tuberculosis is a disease that requires accurate diagnosis and appropriate management to avoid complications.

Key Words: Tuberculosis; Hepatic/diagnosis; Cholangitis; Sclerosing/complications; Ultrasonography; Interventional/methods; Biopsy; Needle/utilization; Treatment Outcome

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Core Tip: Hepatobiliary tuberculosis presents diagnostic challenges due to its similarity to other conditions, emphasizing the need for timely and accurate diagnosis. This systematic review of 24 cases highlights the common symptoms, diagnostic procedures, and treatment outcomes. Fever, abdominal pain, weight loss, and jaundice were the most frequent symptoms observed. Computed tomography scan and ultrasound were effective diagnostic tools, while histologic confirmation confirmed the presence of *Mycobacterium tuberculosis*. Treatment with Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol showed positive outcomes in the majority of cases. This study underscores the importance of precise diagnosis and appropriate management to ensure successful recovery and patient safety.

INTRODUCTION

⁵ Tuberculosis (TB) is an airborne disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*), commonly known as tubercle bacilli. The transmission of TB occurs through the air rather than surface contact. The Center for Disease Control^[1] has identified several factors that increase the likelihood of transmission, including the susceptibility of the exposed individual, infectiousness of individuals with TB disease, environmental conditions affecting the concentration of *M. tuberculosis*, and the proximity, frequency, and duration of exposure.

Once infection takes place, tubercle bacilli are engulfed by macrophages and can spread through lymphatic channels or the bloodstream, triggering a systemic response. This dissemination allows the bacilli to reach various parts of the body, including the brain, larynx, lymph nodes, lungs, spine, bones, kidneys, and liver, resulting in miliary tuberculosis or disseminated TB.

Upon reaching the target organ, macrophages surround the bacilli, forming a barrier known as a granuloma, which contains and controls the infection. This controlled granuloma is termed latent tuberculosis infection and is neither infectious nor contagious. If the immune system fails to contain the tubercle bacilli, they multiply rapidly, leading to active TB disease.

This paper focuses specifically on the spread of *M. tuberculosis* into the liver in the context of hepatobiliary TB. Disseminated TB often affects the liver as the bacillus travels through hematogenous spread. Early diagnosis and appropriate treatment of hepatobiliary TB are crucial for preventing complications and ensuring patient safety.

³ Hepatobiliary TB has a high prevalence, particularly in developing countries during the late 1980s and early 1990s^[2]. Certain racial and ethnic groups experience higher TB case rates due to factors such as being born in countries with a high TB prevalence, ⁴ HIV infection, low socioeconomic status, and exposure to TB in high-risk settings^[2]. Non-United States-born individuals contribute to approximately 70% of TB cases in the United States^[2]. Populations at increased risk of latent TB infection or TB disease

include those experiencing homelessness, limited access to medical care, low-income populations, and individuals engaged in substance abuse^[2].

The prognosis of TB infection is influenced by various factors, including hepatobiliary or miliary TB, steroid therapy, age less than 20 years, cachexia, HIV, liver cirrhosis, and liver failure^[3,4]. Liver TB is a common presentation in patients who die from tuberculous disease, accounting for 50%-80% of cases^[4]. Untreated miliary tuberculosis carries a nearly 100% mortality rate^[5]. However, timely access to critical care intervention, anti-tuberculous therapy, and possibly corticosteroid use may reduce the occurrence of severe complications and mortality. Biochemistry data can aid in predicting clinical outcomes, emphasizing the importance of early treatment to prevent disease spread and reduce mortality^[5].

According to the World Health Organization (WHO) (2022), undernutrition is the leading cause of the global count of 1.9 million new cases of TB disease. The WHO South-East Asian Region has the highest number of new cases at 43%, followed by the African Region with 25%. ⁹ Eight countries, including India, China, Indonesia, Philippines, Pakistan, Nigeria, Bangladesh, and South Africa, account for two-thirds of TB cases^[6]. Treatment failure and drug resistance pose significant challenges, particularly with multi-drug resistant tuberculosis (MDR-TB), which is a public health crisis and security threat. The majority of affected individuals reside in the aforementioned eight countries, where efforts to eradicate the disease are challenging. Without proper treatment, 45% of the TB-infected population in these countries will succumb to the disease^[6].

The discrepancy in TB treatment outcomes between developed and developing countries is striking, with a mortality rate of 2% in developed countries compared to 45% in underdeveloped countries. It is crucial to address this disparity in order to reduce the risk of mortality. Closing this gap would provide individuals in developing countries with firsthand experience of the acute presentation of tuberculous disease and enable them to gain important insights into the existing treatment modalities for TB.

Hepatobiliary tuberculosis is a rare manifestation of miliary tuberculosis, typically originating from *M. tuberculosis* infection in the lungs or gastrointestinal tract^[7]. The presentation of this form of TB is nonspecific, and there is a lack of imaging studies that can raise a high index of suspicion. Although multiple cases of miliary tuberculosis have been reported in Western journals, its prevalence is endemic and often underreported in developing countries like the Philippines. Early initiation of appropriate anti-tuberculous treatment is associated with a favorable prognosis for this disease, emphasizing the importance of timely therapy.

The Philippines ranks third in terms of TB prevalence, following South Africa and Lesotho, according to the WHO^[8]. With approximately one million Filipinos diagnosed with active TB disease, urgent action is required. The WHO aims to eliminate TB by 2030, making the situation in the Philippines a focal point as the country continues to report active cases and daily loss of lives due to this highly curable disease. The neglect of TB in children, which is difficult to diagnose and treat, along with the intertwining challenges of malnutrition and tuberculosis, further emphasizes the need for concerted efforts to improve the health and quality of life of Filipinos.

Despite being curable and preventable, in 2020, the burden of TB was concentrated in certain countries, with 86% of new cases occurring in these high-burden countries. The top eight countries in terms of TB burden include India, China, Indonesia, Philippines, Pakistan, Nigeria, Bangladesh, and South Africa. Among these countries, MDR-TB poses a significant public health crisis and health security threat, as only one in three individuals with MDR-TB seek treatment. Insufficient funding for health programs, not limited to tuberculosis, in low- and middle-income countries remains a major obstacle in combating this global issue.

MDR-TB arises from inadequate and ineffective treatment in low-income countries, leading to drug resistance and posing a threat to tuberculosis control efforts. Patient resistance and emotional struggles, including anger and denial, can hinder treatment adherence. Special considerations are needed for individuals with HIV and those

receiving antiretroviral therapy due to potential drug interactions and the need to modulate immune responses to overcome drug resistance in these populations^[9].

A study conducted in the Philippines from 2011 to 2015 focused on disseminated TB and found that patients with miliary TB were typically young and without comorbidities. Long latency periods and non-pulmonary symptoms were observed before diagnosis. Co-infection with HIV, liver cirrhosis, and alcoholism were identified as predisposing conditions. Hepatobiliary tuberculosis was present in 0.2% of the studied population, with confirmation achieved through various diagnostic methods. Bacteriologic confirmation of extrapulmonary TB, particularly in the liver, remains challenging due to limited access to resources like computed tomography (CT) scans in the Philippines^[10].

The incidence of TB increases progressively with age, particularly among the elderly. Reactivation of dormant lesions is the most common cause of tuberculosis in this age group, likely due to age-related changes in the immune system. Diagnosis of active TB in the elderly can be challenging due to nonspecific and subtle symptoms. Poor tolerance to anti-TB drugs and reduced treatment adherence in the elderly can lead to treatment failure and the development of MDR-TB. In regions heavily affected by the TB epidemic, infectivity in the elderly peaks at 65 years of age, with men being the most affected^[11].

A study conducted by Wu *et al*^[12] reported common clinical complaints in patients with tuberculosis, including mild fever, right upper quadrant pain, hepatomegaly, weakness, and night sweats. Serum analysis revealed increased alkaline phosphatase (ALP) levels and normal transaminase levels, indicating liver involvement. Imaging techniques such as ultrasound, CT scan, and magnetic resonance imaging (MRI) were used to confirm the diagnosis of hepatobiliary TB, showing features such as multiple lesions of varying density on CT scan and specific characteristics on MRI^[12,13].

In a retrospective study of 320 TB cases, suspected hepatobiliary tuberculosis was identified through abnormal liver function tests and imaging findings. Among the patients, 68 showed hepatobiliary involvement, and 40 were diagnosed with

hepatobiliary tuberculosis. Common symptoms included fever, weight loss, jaundice, hepatomegaly, and splenomegaly. Elevated levels of bilirubin, alanine aminotransferase, aspartate aminotransferase (AST), and ALP were documented, supporting the importance of early diagnosis and management based on laboratory findings^[14].

Yu and Sheng^[15] published a paper discussing a case of liver tuberculosis presenting as fever of unknown origin. Initially, ultrasound and CT scan did not provide significant findings, but PET/CT showed diffuse increased metabolic activity with focal areas of increased activity, aiding in the identification of a site for biopsy and a correct diagnosis. This case highlights the importance of considering liver tuberculosis as a potential cause in cases of fever of unknown origin, especially when other laboratory analyses show non-specific slight elevation of liver enzymes. This approach to diagnosis opens up new possibilities for identifying the correct biopsy site in such cases^[15].

A systematic review of Indian literature examined the delays in TB diagnosis and treatment, focusing on symptom onset, diagnostic delays, and treatment delays. The review revealed a median treatment delay of 55.3 d, with 48% of patients initially consulting private physicians and an average of 2.7 consultations before receiving TB treatment. The study highlighted the urgent need for new strategies to reduce diagnostic and treatment delays by establishing a first-contact healthcare provider system to address patients' health needs promptly^[16].

In another study by Singh *et al*^[14], laboratory findings in patients with hepatobiliary tuberculosis (HBTB) were investigated. The study found elevated levels of bilirubin, ALT, AST, and ALP in cases of hepatic, biliary, and HBTB. Jaundice was frequently observed in biliary tuberculosis, while hepatomegaly was more common in hepatic TB cases. The study emphasized the importance of considering both clinical features and laboratory findings to effectively evaluate hepatobiliary tuberculosis.

This paper aims to address the management of hepatobiliary tuberculosis and ensure patient safety and successful recovery. By identifying common symptoms, healthcare providers can promptly request additional laboratory and ancillary procedures to

detect hepatobiliary or miliary tuberculosis as early as possible. The goal of this paper is to provide recommendations for expediting the treatment of tuberculosis patients.

MATERIALS AND METHODS

This study followed the PRISMA guidelines^[17] and aimed to summarize previously reported cases of hepatobiliary tuberculosis. The systematic review followed five steps: Framing the question, identifying relevant work, assessing study quality, summarizing the evidence, and interpreting the findings^[18]. The search terms used were: ("tuberculosis" OR "mycobacterium") AND ("cholangiopathy" OR "cholangitis" OR "hepatobiliary"). The search was conducted on March 21, 2022. Multiple resources were searched for case reports without language restrictions. Clinical presentation, diagnostic modalities, interventions, treatment, and outcomes were recorded for analysis. Study quality was assessed based on selection criteria, including histopathologic confirmation and clearly stated outcomes. Tabulation of study characteristics facilitated comparisons. The focus of this paper is on the diagnosis, management, and outcomes of hepatobiliary tuberculosis, including medical and surgical approaches. Miliary tuberculosis studies were also included.

Data sources

A wide range of medical and scientific databases were searched from 1992 to 2022 to identify studies and case reports on hepatobiliary tuberculosis. The search was conducted in libraries including PubMed/MEDLINE using keywords related to hepatobiliary tuberculosis. No restrictions were placed on publication dates within the specified range, and language preferences were not considered during the initial publication of the papers.

Inclusion criteria and outcomes

Case reports or case series published between 1992 and 2022 were eligible for selection. In cases of duplication, the most recent studies were chosen for analysis. Abstracts and

incomplete papers were excluded, as well as studies published in languages other than English. Each retrieved study was screened based on the title and abstract to ensure that it contained full-text case reports with complete details for data extraction. Preference was given to studies that provided comprehensive information, and availability of adequate follow-up data for transcription was also considered.

Study selection and data extraction

During the study selection and data extraction process, relevant papers were identified based on the titles and abstracts. Full-length papers meeting the eligibility criteria were then identified. A standardized form was used to extract data from the selected studies, including information on the characteristics of the subjects, clinical presentation, diagnostic tests, anti-tubercular drugs used, and outcomes. Any discrepancies in the study selection were resolved.

Clinical presentation and diagnostic modalities

The clinical presentation of the selected case reports was carefully examined, considering the duration of symptoms, associated subjective complaints, laboratory and ancillary procedures performed, the diagnosis, and the outcome. While not all reports included recorded values for certain laboratory parameters, such as AST, ALT, ALP, and bilirubin, the available data were retained for further analysis. The clinical diagnosis at the time of consultation was an important factor in data collection. In cases where two diagnoses were present, with hepatobiliary tuberculosis being an incidental finding, both diagnoses were included.

The diagnostic modalities employed in each case leading to the primary diagnosis were retrieved and summarized in a table for comparison and analysis. The detection of acid-fast bacilli through culture was a significant aspect of this study. The sample specimens could be obtained from various body cavities, tissues, or bodily fluids, not necessarily limited to the liver. Clinical findings were cross-referenced with other available data.

Medical management and outcomes

The medical management approaches for hepatobiliary tuberculosis were itemized and documented based on each case. Surgical interventions were also noted. The outcomes resulting from the management strategies were categorized as improved, recovered, or deceased.

Quality assessment

The collected materials were carefully assessed to ensure their credibility and reliability. The primary focus was on selecting peer-reviewed papers, but if a paper was not peer-reviewed, its credibility was evaluated based on several factors. These factors included the depth of information coverage, objectivity, identification of biases, currency of the information, authority from reputable and unbiased organizations, and the purpose of the paper. This step was crucial for establishing the trustworthiness of the overall summary and generating reliable inferences. Only high-quality studies that were considered credible and unbiased were included in the analysis. Papers that received a low score in the quality assessment were still included in the study selection, but inferences were avoided when drawing conclusions from these papers^[18,19].

Statistical analysis

Descriptive statistics, such as the mean, SD, frequency, and median, were used to characterize the data. These measures provided a concise summary of the key features of the collected information.

Narrative synthesis

A narrative synthesis approach was employed to merge and synthesize the gathered information. This synthesis focused on addressing the diagnostic challenges associated with hepatobiliary/miliary tuberculosis as reported in the selected journals. The findings from the different case reports were interpreted with caution, taking into

consideration the demographics of the research subjects and identifying the most common presentations of hepatobiliary tuberculosis.

6 **RESULTS**

Using the designated search strategy, a total of 132 references were initially identified. Among them, 17 duplicates were excluded. After carefully analyzing the titles and abstracts, an additional 77 references were deemed unrelated to the topic and excluded. Finally, 21 references were excluded based on specific criteria, as shown in the flow chart below. The remaining 38 references, consisting of case reports and case series, were included in the analysis. A comprehensive summary of the collected data can be found in Table 1, while Table 2 provides an overview of the gathered data. The quality analysis of the included papers is presented in Table 3.

Characteristics of the included cases

The cases mentioned in the included references originated from various countries, including Taiwan, Japan, India, Turkey, Ireland, China, Sénégal, Thailand, Portugal, United Kingdom, and the USA. The reported cases were distributed as follows: Taiwan (37.50%), Japan (12.50%), India (8.33%), Turkey (8.33%), Ireland (8.33%), China (8.33%), Sénégal (4.17%), Thailand (4.17%), Portugal (4.17%), United Kingdom (4.17%), and the United States (4.17%). A total of 24 patients were included in the analysis, with 15 (62.50%) being male and a mean age of 64.22 years (ranging from 14 to 80 years old). All patients were diagnosed with hepatobiliary tuberculosis, and in 14 cases, the diagnosis was confirmed through histopathology.

Clinical presentation of hepatobiliary tuberculosis

The most common clinical presentations of hepatobiliary tuberculosis were fever and abdominal pain, accounting for 37.50% of the cases. Other common symptoms included weight loss (29.17%), jaundice (25%), anorexia (16.67%), generalized weakness (16.67%), and non-specific symptoms such as chills associated with fever. In two cases,

generalized weakness and fatigue were reported. One asymptomatic patient was incidentally diagnosed with miliary tuberculosis through routine ultrasound examination. These non-specific symptoms were correlated with objective findings. Miliary tuberculosis can manifest in various organs of the human body, leading to symptoms such as neurologic symptoms, chest pains, vomiting, dark urine, pale stools, groin swelling, cough, diarrhea, and upper gastrointestinal bleeding.

Clinical findings

Among the patients included in the study, 37.50% exhibited hepatomegaly and/or hepatic nodules. Liver enzyme and bilirubin levels were evaluated in 4 cases, leading to further diagnostic investigations such as ultrasound and CT scan. Other symptoms observed in the 24 cases included pleural effusion, splenomegaly, duodenal abnormality, and spontaneous bacterial peritonitis. The population also presented with comorbidities, including pulmonary tuberculosis in 4 out of 24 cases, gastric cancer, systemic lupus erythematosus, hypertension, type II diabetes mellitus, and chronic obstructive pulmonary disease (COPD).

Delays in management

A delay in seeking treatment despite the onset of symptoms was observed in 5 patients, with an average delay of 2 mo. One case report described a patient with a history of fever for 2 and a half years before seeking medical care. These delays highlight the need to address healthcare-seeking behaviors and improve early detection to ensure timely treatment and better outcomes. Prolonged delays can lead to a more difficult and protracted treatment course. Surgical intervention was required for one patient.

Medical management

All reported cases received medical management. The majority of cases (95.83%) were treated with a combination of Rifampicin and Ethambutol. Isoniazid was administered to 91.67% of the cases, while Pyrazinamide was prescribed to 87.50% of the patients.

Levofloxacin was given to 12.50% of the population. Among the cases, 16.67% (4 cases) fully recovered, and 58.33% (14 cases) showed improvement from their initial condition. Four patients (16.67%) died, including two who succumbed to septic shock due to late diagnosis, one with stage 4 carcinoma on top of miliary tuberculosis, and another with acute biliary episode concomitant with liver failure. Two of the deceased patients were above 60 years old, while the other two were in their late 30s and early 50s and died due to septic shock. Mortality in this study was directly associated with delayed diagnosis and did not appear to be correlated with the age of the patient. The treatment approach for tuberculosis followed the guidelines set by the WHO, with different drugs administered on different days (daily or with skip days). The combination known as RIPE (Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol) was commonly used for tuberculosis treatment. The duration of medication varied based on the severity of the disease.

DISCUSSION

This systematic review focuses on the clinical presentation, diagnostic modalities, treatment, and outcomes of patients with hepatobiliary or miliary tuberculosis from different countries. Hepatobiliary tuberculosis presents challenges in diagnosis, particularly in developing countries where diagnostic tools may be limited^[20]. Miliary tuberculosis primarily affects elderly individuals, the urban poor, and immunocompromised patients, and it is believed to spread *via* hematogenous dissemination through the hepatic artery. Some studies suggest that hepatobiliary tuberculosis is present in all cases of miliary tuberculosis, with or without pulmonary involvement^[21,22].

The patients included in the published cases of hepatobiliary tuberculosis ranged in age from 14 to 80 years old, with a female-to-male ratio of 3:5. TB remains a significant health problem in the Kingdom of Saudi Arabia, and the study identified non-Saudi countries with a high incidence of both pulmonary and extrapulmonary tuberculosis^[23]. The incidence of tuberculosis varies between males and females, and a subject's

predisposition to the disease is influenced by the country of origin where tuberculosis is endemic.

Most patients with hepatobiliary tuberculosis presented with non-specific symptoms such as fever, abdominal pain, jaundice, weight loss, fever with chills, anorexia, generalized weakness, and pruritus. Jaundice and pruritus are particularly suspicious of liver involvement. These findings are consistent with a previous study on hepatobiliary and pancreatic tuberculosis, which reported abdominal pain as the most common symptom, followed by jaundice, fever, anorexia, and weight loss^[24].

Malnutrition is a major contributor to tuberculosis in developing nations. Therefore, obtaining accurate weight and height measurements to determine ideal body weight for each reported case may be important. This information could provide insights into the nutritional needs of patients with hepatobiliary tuberculosis. Anorexia, loss of appetite, and generalized body weakness can exacerbate malnutrition and hinder recovery.

Hepatobiliary ultrasound or CT scans revealed hepatomegaly and hepatic nodules in the majority of the subjects (8 out of 23), indicating the presence of hepatobiliary tuberculosis. Clinical and laboratory findings in patients with hepatobiliary tuberculosis have shown an increased incidence of *M. tuberculosis* in extrapulmonary locations, particularly among immunosuppressed individuals and young children. Diagnosis of hepatobiliary tuberculosis can be confirmed by elevated levels of bilirubin, ALT, AST, and ALP. Percutaneous transhepatic cholangiography can serve as a confirmatory test for visualized liver masses^[14,25].

Tuberculosis cases are more prevalent among young people aged 10-24 years, with an estimated 1.78 million cases since 2012, accounting for 17% of all new tuberculosis cases globally. In 2019, the second and third highest incidence of tuberculosis cases was observed in the population over 65 years old. It is hypothesized that tuberculosis in the elderly may result from reactivation of latent infections from their youth or newly acquired infections due to their vulnerability. These findings may explain the higher prevalence of miliary and hepatobiliary tuberculosis in the population with a mean age

of 64.22 years, as comorbidities, such as hypertension, and other variables may render the elderly population immunocompromised^[26-28].

While CT scans or ultrasounds can detect the presence of liver masses, they cannot differentiate between hepatoma and hepatobiliary tuberculosis^[29]. Liver biopsy is considered the gold standard for diagnosing hepatobiliary tuberculosis. A CT-guided fine needle aspiration biopsy can reveal caseating granulomas with lymphocytes, multinucleate giant cells, and epithelioid cells, which are compatible with tuberculosis. This method can rule out hepatocellular carcinoma. Computed tomography scan imaging of confirmed cases shows multiple lesions with varying densities, representing different pathological stages of hepatic tuberculosis, such as tuberculous granuloma, liquefaction necrosis, fibrosis, and calcification. A clinicopathologic analysis of 86 cases in Turkey identified the infectious etiology of liver granulomas caused by tuberculosis, characterized by necrotizing, palisading granulomas. Out of the 10 cases tested, only one stained positive with acid-fast bacilli, while the others showed positivity through PCR. Tissue analysis is essential for accurately diagnosing tuberculous infections and differentiating them from other causes of liver disease, such as primary biliary cirrhosis, tumors, and sarcoidosis^[30].

Hepatobiliary ultrasound or CT scans can detect hepatomegaly and hepatic nodules, indicating hepatobiliary tuberculosis. Tuberculosis cases are more common among young people and the elderly, with the latter group potentially experiencing reactivation of latent infections or acquiring new infections due to vulnerability. Liver biopsy is crucial for confirming hepatobiliary tuberculosis and distinguishing it from other liver diseases.

Abdominal ultrasound is a readily available and cost-effective diagnostic tool that raises suspicion of hepatobiliary tuberculosis compared to malignancy^[31]. Chen *et al*^[31] conducted a study exploring different imaging modalities and highlighted the challenges in diagnosing tuberculous liver. They observed hyperechoic mass-like lesions on ultrasound, and these findings were confirmed by ultrasound-guided percutaneous needle biopsy. Ultrasound is commonly used as the initial modality for

screening liver parenchymal lesions, but its findings can be vague and require additional percutaneous aspiration or tissue sampling for confirmation^[31]. The combination of ultrasound and contrast-enhanced CT can enhance the specificity of sonographic findings^[32]. However, it is worth noting that ultrasound detected a lower number of hepatobiliary lesions caused by hepatobiliary tuberculosis compared to CT scan, making CT scan the preferred imaging modality^[32].

Liver biopsy played a significant role, accounting for 58.33% of cases in this study. Biopsies were obtained through hepatectomy, CT scan, or ultrasound-guided percutaneous biopsy, enabling the identification of tuberculoma for histopathological examination^[14].

In this study, 12.5% of subjects were diagnosed with *M. tuberculosis* using endoscopic retrograde cholangiopancreatography (ERCP). Saluja *et al*^[24] reported attempting ERCP in five patients, where bile was aspirated through the hilar stricture. One patient demonstrated acid-fast bacilli during bile cytology. Only four patients were diagnosed perioperatively, while the remaining cases were diagnosed using various diagnostic modalities over a two-decade analysis of hepatobiliary and pancreatic tuberculosis^[24].

The diagnosis of hepatobiliary tuberculosis relies on multiple diagnostic modalities, as no single radiologic approach can secure an accurate diagnosis. The gold standard remains the detection of acid-fast bacilli through the polymerase chain reaction for *M. tuberculosis* or a positive T-SPOT TB test^[29]. The T-SPOT TB test is a single visit blood test that utilizes T cells to reduce assay variability and maximize sensitivity in detecting tuberculosis^[29].

All subjects included in this study received anti-tubercular therapy. The majority of cases (87.50%) underwent the standard 7-mo rifampicin, isoniazid, pyrazinamide, and ethambutol (RIPE) regimen^[33]. Treatment regimens for tuberculous infection vary based on individual characteristics and drug resistance profiles. In addition to the RIPE regimen, a 4-mo Rifapentine-moxifloxacin TB Treatment Regimen and a 9-mo RIPE TB Treatment Regimen are recommended for specific patient populations^[33].

Abdominal ultrasound serves as an initial screening tool for hepatobiliary tuberculosis, but CT scan remains the preferred imaging modality. Liver biopsy is crucial for histopathological confirmation. Various diagnostic modalities contribute to accurate diagnosis, and the gold standard involves detecting acid-fast bacilli through molecular techniques or a positive T-SPOT TB test. Treatment regimens are tailored based on individual factors and include different combinations of anti-tubercular drugs.

In this case report, 75% of the subjects showed improvement and recovery with the indicated treatment regimen. A portion of the subjects, 16.67%, unfortunately, died due to associated immunodeficiency and other end-stage diseases during the tuberculosis diagnosis, while 4.17% dropped out of the study and were lost to follow-up. The positive outcomes of recovery and improvement can be attributed to the recommended treatment for tuberculosis.

Hepatobiliary tuberculosis poses a diagnostic challenge that was addressed by the papers in this review. Among the patients, all except one who was initially managed as a case of gastric cancer with a liver mass, which was thought to be liver metastases, died. Three of the deceased patients died of shock; one was non-compliant with medications despite receiving treatment for hepatobiliary tuberculosis, one healthy female died due to fulminant liver failure resulting from widespread tuberculosis infection, and the last patient died of end-stage liver disease due to delays in diagnosis. However, the remaining 24 subjects showed recovery, improvement, and good clinical response.

The common finding in the four deceased cases was the presence of a chronic illness, either unrelated or caused by tuberculosis itself. The delay in management led to liver failure in three cases, while the other death occurred during a wedge resection procedure for gastric cancer. Early diagnosis and management, particularly through CT scan-guided biopsy during the early stage of the disease, could have potentially prevented these deaths.

This systematic review of hepatobiliary tuberculosis highlights the symptoms observed in cases of hepatobiliary tuberculosis, the diagnostic approaches employed in

the included case reports, and the management strategies for diagnosed cases. Symptoms such as fever, abdominal pain, weight loss, anorexia, generalized weakness, along with jaundice and pruritus, should raise suspicion of liver involvement. The disease can spread hematologically, originating from a pulmonary tuberculosis diagnosis and affecting extrapulmonary sites.

The majority of the cases presented in the systematic review showed positive outcomes, which can be attributed to different diagnostic modalities and the high index of suspicion among clinicians. The most commonly used diagnostic modalities included CT scan of the abdomen, liver biopsy, and abdominal ultrasound, among others.

The study revealed that Taiwan, Japan, India, Turkey, China, and Ireland reported the highest number of cases. However, this does not imply that these countries are the only ones affected by tuberculosis. It highlights the underreporting of tuberculosis cases and the existence of other endemic countries, including the Philippines, South Africa, and Lesotho, which have limited journal publications. Case reports from these countries can provide valuable insights to others with limited exposure to tubercular cases^[34].

The present medical management recommended by the CDC should be continued to ensure patient safety and desirable outcomes^[6]. Rifampicin, isoniazid, pyrazinamide, and ethambutol are the mainstay treatment for tuberculosis, displaying promising results with improvement and recovery rates close to 100%^[9].

Hepatobiliary tuberculosis is difficult to diagnose, and delays in treatment due to delayed diagnosis can facilitate infection transmission, worsen the disease, and potentially lead to death^[35,36]. The therapeutic approaches developed since 1944 and their continuous evolution serve as tools to combat the tuberculosis endemic through early detection, a high index of suspicion, and treatment compliance^[37].

In hepatobiliary tuberculosis, the infection primarily affects the liver and/or the biliary system, whereas soft tissue tuberculosis refers to tuberculosis infection in the soft tissues of the body, such as muscles, tendons, and ligaments^[38]. Tuberculosis treatment may lead to side effects such as gastrointestinal symptoms, liver toxicity, skin rashes, peripheral neuropathy, and visual disturbances, but regular monitoring and prompt

reporting of any unusual symptoms are essential for successful management. Some current relevant differentials for hepatobiliary tuberculosis are post-COVID-19 cholangiopathy^[39,40], hemophagocytic lymphohistiocytosis^[41,42] and cytomegalovirus infection^[43].

CONCLUSION

In conclusion, this study recommends a systematic approach for managing hepatobiliary tuberculosis and miliary tuberculosis, with the aim of eradicating all forms of tuberculosis and initiating therapy at the earliest possible time. Key indicators for suspicion of hepatobiliary TB include fever, abdominal pain, weight loss, anorexia, and generalized weakness, particularly in the presence of jaundice or pruritus. Ultrasound is a recommended initial imaging modality due to its affordability and accessibility, followed by a CT scan if ultrasound results are inconclusive. Liver biopsy is crucial in differentiating hepatobiliary TB from hepatoma and should be performed for patients with suspicious lesions. Routine liver enzyme and bilirubin tests can aid in early detection of hepatobiliary TB. Case reports and Mantoux tuberculin skin testing are essential for monitoring and treating pulmonary tuberculosis in high-risk populations. These recommendations are derived from a comprehensive analysis of case reports and are applicable to various forms of tuberculosis. Timely treatment initiation may be based on clinical suspicion rather than awaiting confirmatory test results. Overall, a high index of suspicion and bedside procedures for obtaining tissue diagnosis are vital in managing tuberculosis.

ARTICLE HIGHLIGHTS

Research background

Tuberculosis (TB) is a highly contagious ⁵airborne disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*), and its transmission occurs through the air. The Center for Disease Control has identified several factors affecting TB transmission, including the susceptibility of exposed individuals, infectiousness of TB patients, environmental

conditions, and proximity and duration of exposure. Once infected, tubercle bacilli can spread throughout the body, leading to various manifestations, including hepatobiliary tuberculosis (TB affecting the liver and biliary system). Early diagnosis and appropriate treatment of hepatobiliary TB are crucial for preventing complications and ensuring patient safety. Hepatobiliary TB has a significant prevalence, especially in developing countries, and specific populations are at increased risk, such as non-US-born individuals and those with ⁴ HIV infection, low socioeconomic status, or exposure to TB in high-risk settings.

Research motivation

The main focus of this study is to investigate the spread of *M. tuberculosis* into the liver, specifically in the context of hepatobiliary TB. Early diagnosis and appropriate management are essential to prevent severe complications and reduce mortality rates associated with TB infection. Addressing the discrepancies in TB treatment outcomes between developed and developing countries is crucial to improving global health and reducing mortality risks, particularly for individuals in low-income countries. Moreover, the high prevalence of TB in certain regions and the challenges posed by multi-drug-resistant TB necessitate urgent action and innovative approaches to combat this public health crisis. By examining hepatobiliary TB in the Philippines and understanding the unique challenges faced in the region, this study aims to contribute to TB control efforts and improve patient outcomes.

Research objectives

The main objectives of this study include identifying common symptoms and laboratory findings associated with hepatobiliary TB to facilitate early detection and diagnosis. By understanding the clinical features and laboratory data, healthcare providers can promptly initiate appropriate diagnostic procedures to confirm hepatobiliary or miliary tuberculosis. The study aims to provide recommendations for expediting TB treatment and improving patient safety and recovery rates. Additionally,

the research seeks to shed light on the challenges of TB diagnosis and treatment delays, particularly in developing countries, and identify potential strategies to reduce such delays and enhance patient care. By analyzing liver function test results and imaging findings, the study intends to enhance the evaluation of hepatobiliary TB, leading to more effective management strategies. Through these objectives, the research strives to contribute to the overall efforts to eliminate TB by 2030, as outlined by the World Health Organization.

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Research methods

This study conducted a systematic review following PRISMA guidelines to summarize cases of hepatobiliary tuberculosis (HBTB). The research question was framed, and relevant studies were identified using specified search terms without language restrictions. Clinical presentation, diagnostic modalities, interventions, treatment, and outcomes were recorded from selected case reports published between 1992 and 2022. The study quality was assessed based on selection criteria, including histopathologic confirmation and clear outcomes. Data were extracted using a standardized form, and discrepancies in study selection were resolved. The clinical presentation, diagnostic modalities, and acid-fast bacilli detection were analyzed. Medical and surgical management approaches were documented, and outcomes were categorized as improved, recovered, or deceased. The collected materials were carefully assessed for credibility and reliability, focusing on peer-reviewed papers. Descriptive statistics were used to characterize the data, and a narrative synthesis approach was employed to interpret the findings and address diagnostic challenges related to hepatobiliary/miliary tuberculosis.

Research results

The systematic review of 38 case reports and case series on HBTB revealed important findings. Clinical presentation commonly included fever and abdominal pain (37.50%), along with weight loss (29.17%), jaundice (25.00%), and anorexia (16.67%).

Hepatomegaly and/or hepatic nodules were observed in 37.50% of the cases, with liver enzyme and bilirubin levels playing a role in further diagnostic investigations. Comorbidities such as pulmonary tuberculosis, gastric cancer, and systemic lupus erythematosus were identified in the patient population. Delays in seeking treatment were observed in five patients, underscoring the importance of early detection and timely intervention. Surgical intervention was required for one patient. Medical management was the primary treatment approach for HBTB, with a combination of Rifampicin, Ethambutol, Isoniazid, and Pyrazinamide being commonly used. The majority of patients (58.33%) showed improvement, 16.67% fully recovered, and 16.67% succumbed to the disease, with delayed diagnosis and septic shock being contributing factors to mortality. The study contributes valuable insights into the clinical presentation, management, and outcomes of HBTB, emphasizing the significance of timely interventions to improve patient prognosis. Further research is needed to address the challenges associated with delayed diagnosis and management to reduce morbidity and mortality rates in HBTB cases.

Research conclusions

This systematic review contributes to the understanding of hepatobiliary tuberculosis by highlighting its clinical presentation and diagnostic challenges, particularly in developing countries with limited resources. It sheds light on the association between miliary tuberculosis and hepatobiliary tuberculosis, with or without pulmonary involvement. The study emphasizes the importance of early detection and timely intervention to improve patient outcomes. The research proposes a systematic approach for managing hepatobiliary tuberculosis and miliary tuberculosis. It recommends using ultrasound as an initial screening tool, followed by computed tomography scan if needed, for detecting hepatomegaly and hepatic nodules. Liver biopsy is crucial in confirming hepatobiliary tuberculosis and distinguishing it from other liver diseases. The study emphasizes the use of a high index of suspicion and bedside procedures for obtaining tissue diagnosis.

Research perspectives

The direction of future research should focus on addressing the challenges in diagnosing hepatobiliary tuberculosis, especially in countries with a high incidence of tuberculosis. Improving diagnostic tools and methods in resource-limited settings is crucial to facilitate early detection and timely treatment. Additionally, further studies should explore the association between miliary tuberculosis and hepatobiliary tuberculosis to better understand the disease's pathogenesis and clinical manifestations. Research efforts should also aim to identify risk factors associated with delayed diagnosis and management, leading to better strategies for reducing morbidity and mortality rates. Furthermore, investigating the efficacy and safety of different treatment regimens for hepatobiliary tuberculosis will help optimize therapeutic approaches and improve patient outcomes. Collaborative efforts among researchers and healthcare providers are essential in eradicating tuberculosis and implementing effective management protocols worldwide.

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Table 1 PRISMA-P search strategy

Item	Description
Identification	Record identified through Sources: PubMed ($n = 132$) database search ($n = 132$)
Screening	Records after duplicates were removed ($n = 115$) Records screened ($n = 115$) Records excluded ($n = 77$)
Eligibility	Full-text articles assessed for eligibility ($n = 38$) Full-text articles excluded ($n = 21$); full text not found = 8; not hepatobiliary tuberculosis = 10; not a case report = 20; and individual patient data not available = 3
Included	² Studies included in qualitative synthesis ($n = 17$) Studies included in quantitative synthesis (meta-analysis; $n = 17$)

Table 2 Summary of systematically reviewed clinical cases of hepatobiliary/miliary tuberculosis

Ref.	Country	Age (yr)	Sex	Clinical presentation	Diagnostic modalities	Treatment	Outcome	Quality assessment
Patel, 2016	India	14	Female	Persistent, intermittent fever associated with chills, abdominal pain, anorexia for 1 mo; neurological symptoms	Ultrasound of abdomen with portosplenic doppler; CT scan of the abdomen; bacterial culture of liver abscess; mycobacterium growth indicator tube culture; MRI of the brain	Dexamethasone for meningitis; rifampicin, Isoniazid, pyrazinamide	Neurological symptoms regressed; significant improvement	High
Sahin, 2014	Turkey			Elevated enzymes	liver biopsy of the abdomen	Not specified	Not specified	Low

Diallo, 2016	Dakar, Sénégal	48	F	Cholestatic jaundice, right upper quadrant pain, fever (38.5 °C) and weak general condition, weight loss of 15 kg in 2 mo; on physical examination there was jaundice, fever, abdomen was soft, tenderness at the RUQ with hepatomegaly	Abdominal ultrasound; thoracoabdominal CT scan; liver biopsy	Rifampicin, isoniazid, pyrazinamide ethambutol; levofloxacin (included in the triple therapy for 10 d)	Good evolution: Clinical improvement;	High
Ozin, 2010	Turkey	43	Female	Initially complained of malaise and itching, with elevated liver enzymes and bilirubin; diagnosis: Hepatobiliary tuberculosis	Hepatobiliary and pancreas ultrasound; ERCP; liver biopsy	Rifampicin, isoniazid, pyrazinamide ethambutol	Liver function tests were improved	High

Jain, 2017	India	50	Male	Jaundice since 10 d associated with significant loss of weight & appetite; diagnosis: Hepatobiliary tuberculosis	Liver ultrasound; CT scan of the abdomen; MRCP; and liver biopsy; hepatectomy	Rifampicin, isoniazid, pyrazinamide ethambutol	Responded well	High
Chang, 2018	Taiwan	80	M	Smear-positive, culture confirmed pulmonary TB, fever and chills after 1 wk of treatment; abdominal pain; diagnosed with cholecystolithiasis	Abdominal ultrasound; sputum AFB	Laparoscopic cholecystectomy; rifampicin, isoniazid, pyrazinamide ethambutol	ABE were not noted	High
Chang, 2018	Taiwan	50	M	A male patient in his 50 s with comorbid, medically controlled DM and COPD was diagnosed with	Abdominal ultrasound; CT scan of the abdomen	Rifampicin, isoniazid, pyrazinamide ethambutol	Improved	High

Chang, 2018	Taiwan	50	M	pulmonary TB based on a histology report of a transbronchial lung biopsy and a mycobacterial; culture of bronchial washing sample; diagnosed with acute cholecystitis			Died of High refractory septic shock
				Hypertension and COPD, irregular medical control, diagnosed with smear-positive, culture-confirmed pulmonary TB. Two weeks prior to the commencement of standard anti-TB treatment, he had	Hepatobiliary and pancreas ultrasound	Rifampicin, isoniazid, pyrazinamide ethambutol	

Chang, 2018	Taiwan	20	Male	<p>pneumonia with respiratory failure and septic shock; multiple cholelithiasis was noted with dilated intrahepatic duct; treatment was halted</p> <p>Fever, chest pains, left pleural effusion</p> <p>Intermittent biliary obstruction due to a passing of stone</p>	Sputum-AFB	<p>Rifampicin, isoniazid, pyrazinamide ethambutol</p>	Improved	High
Yamashita, 2014	Japan	48	Female	<p>Past history of systemic lupus erythematosus developed autoimmune hepatitis, fever;</p>	CT scan of the liver abdomen; biopsy	<p>Isoniazid, rifampicin, ethambutol, pyrazinamide; subsequently</p>	Recovered liver function improved and no inflammation	Moderate

Yamane, 2010	Japan	47	Male	Incidental finding of an abnormality in the duodenum during endoscopy; no subjective symptoms; diagnosis: Tubercular papillitis of Vater	Esophagogastroduodenoscopy	Rifampicin, isoniazid, pyrazinamide, ethambutol and streptomycin	Improved after treatment of the duodenal lesion and colonic lesion	High
Ratanapree, 1991	Thailand	38	Male	2-month history of painless obstructive jaundice; cachectic and deeply icteric, with a normal temperature and an impalpable liver; diagnosis:	Ultrasound of hepatobiliary tree	Rifampicin, isoniazid, ethambutol	Good health	High

Tuberculosis of the
common bile duct

Tewari, 2009	Japan	70	Female	Episodes of mild upper abdominal pain and vomiting of 3 mo; mild jaundice for 2 mo that subsided on its own; diagnosis: Tubercular ampullary papillitis	Ultrasound of the abdomen; CT scan of the abdomen; EGD; ERCP; excision of the ampulla, with biopsy	Rifampicin, isoniazid, pyrazinamide ethambutol	Improved	High
Li, 2015	China	39	Female	10-d history of fatigue, anorexia, and jaundice. She had no abdominal pain or fever; diagnosis: Pelvic and Salpinx tuberculosis with secondary fulminant hepatic failure	CT scan of abdomen	Rifampicin, isoniazid, pyrazinamide ethambutol	Died as a consequence of ischemic cholangitis and pulmonary infection	High

Hickey, 1999	Ireland	50	Male	Pyrexia of unknown origin which was ongoing for 2.5 yr with multiple previous hospital admissions; diagnosis: Splenic tuberculosis	Ultrasound of the abdomen; abdominal CT scan	Rifampicin, isoniazid, pyrazinamide ethambutol	Well over 6 yr	High
Hickey, 1999	Ireland	70	Male	6-wk history of progressive jaundice, severe pruritus, dark urine, pale stools, and weight loss, with groin swelling	Percutaneous transhepatic cholangiography; biopsy of groin	Rifampicin, isoniazid, pyrazinamide ethambutol	No recurrence for 5 yr	High
Gaspar, 2018	Portugal	35	Male	Fatigue, fever, weight loss, cough, abdominal pain, diarrhea, pruritus, hepatomegaly; diagnosis: Hepatic	CT scan of abdomen	Rifampicin, isoniazid, pyrazinamide ethambutol	Discharge from the hospital	Mod

granuloma

Musumba, 2012	United Kingdom	47	Male	5-d intermittent rigors and sweats; cadaveric transplant 1 mo prior, and immunosuppressive therapy; diagnosis: Miliary tuberculosis	history of fever, night tomography/computed tomography; liver biopsy	Whole body positron emission tomography/computed tomography; liver biopsy	Rifampicin, isoniazid, pyrazinamide, ethambutol	Good clinical response	High
Poplin, 2020	USA	52	Male	1 mo hospitalized culture-negative spontaneous bacterial peritonitis, liver disease was incidentally found;	PTC, for abdomen	Liver biopsy; CT scan of abdomen	Rifampicin, ethambutol, levofloxacin, amikacin 3 times weekly	Died due to ABE	High

11	Huang, et.al. (2003)	Taiwan	47	Male	Epigastric pain; CT scan solitary liver nodule 13.5 cm tumor left lobe	Lobectomy, anti-TB Rifampicin, isoniazid, pyrazinamide ethambutol	Improved	High
	Huang, et.al. (2003)	Taiwan	57	Male	Malaise, weight loss; CT scan; solitary liver nodule 5.0 cm tumor at the left lobe	Wedge resection, anti-tb meds	Improved	High
	Huang, et.al. (2003)	Taiwan	63	Male	Managed for gastric cancer; CT scan; solitary liver nodule 2.0 cm at segment IV	Wedge biopsy	Expired	High
	Huang, et.al. (2003)	Taiwan	67	Female	Managed for gastric cancer; CT scan MULTIPLE small liver nodules at both	Biopsy, treatment refused	Dropped out of management	High

lobes

Huang, <i>et.al.</i> (2003)	Taiwan	71	Fem ale	Epigastric pain with upper gastrointestinal tract bleeding; CT scan; solitary liver nodule 12.0 cm at the left lobe; nodular density at the right lower lung field on chest X- ray	Left anti-tb meds	hepatectomy; isoniazid, pyrazinamid e ethambutol	Rifampicin, isoniazid, pyrazinamid e ethambutol	Improved	High
Zhang, 2014	China	30	Mal e	Weight loss, poor appetite, body weakness, abdominal distention, chest congestion	CT scan; FNAB		Rifampicin, isoniazid, pyrazinamid e ethambutol	Improved	High

TB: Tuberculosis; COPD: Chronic obstructive pulmonary disease; FNAB: RUQ: MRCP: ERCP: Endoscopic retrograde cholangiopancreatography; CT: Computed tomography; MRI: Magnetic resonance imaging; PCR: Polymerase chain reaction; ABE: Acute biliary events.

Table 3 Quality assessment of included cases of hepatobiliary and miliary tuberculosis

Ref.	Case number	Selection		Ascertainment		Causality		Reporting		Quality assessment
		Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	
		Did the patient(s) represent the whole case(s) of the medical center?	Was exposure adequately ascertained?	Was outcome adequately ascertained?	Were alternative causes may the observation ruled out?	Was there response to specific treatment tuberculosis?	Was there a histological confirmation for the diagnosis?	Was a up enough outcomes occur?	Is the case(s) long described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?	
Patel R, et.al. (2016)	1	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Patel R, et.al. (2016)	1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Sahin, et.al. (2014) ²	35	Yes	Yes	Yes	Yes	No	Yes	No	No	Low
Diallo, et.al. (2016)	1	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Ozin, et.al. (2010)	1	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	High
Jain, et.al. (2017)	1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Chang, et.al. (2018)	4	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Yamashita, et.al. (2014)	1	No	Yes	Yes	No	Yes	Yes	Yes	No	Low
Yamane, et.al. (2010)	1	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	High
Ratanarapee, et.al. (1991)	1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Tewari, et.al. (2009)	1	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	High

Li, et.al. (2015)	1	No	Yes	Yes	Yes	Yes	Yes	Yes	No	High
Hickey, et.al. (1990)	2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Gaspar, et.al. (2018)	12	Yes	No	Yes	Yes	No	Yes	No	Yes	Mod
Musumba, et.al. (2012)	1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Poplin, et.al.(2020)	1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Huang, et.al. (2003)	5	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	High
Zhang, et.al. (2014)	1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High

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