

Demographic, Clinical, Radiological, and Surgical Outcome of Patients with Intestinal Tuberculosis: A Single-Center Retrospective Study

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Background: Intestinal tuberculosis (iTb) represents a potentially underrecognized clinical entity with limited clinical and radiological differentiating features. This study aims to assess the patterns of iTb clinical and radiological findings, along with the treatment approaches and the overall outcome.

Methods: This retrospective cross-sectional study included patients with histopathologically confirmed iTb who presented with acute abdomen and were surgically managed between September 2005 and October 2023. Clinical and sociodemographic variables, imaging features, surgical treatments, and overall outcomes were retrospectively analyzed.

Results: 96 patients with iTb were included, with a mean age of 36.1 ± 11.5 years and a relatively proportionate gender distribution. Abdominal pain was the most common presenting symptom (45.8%). The radiological features varied by the modality. Plain imaging showed non-specific findings, while ultrasonography showed loculated ascites (25%), and lymphadenopathy (22%). In computed tomography scans, multi-segmental symmetric intestinal thickening (53.1%) was the most prevalent finding. The most commonly performed surgical procedure was adhesiolysis (29.2%), with the ileocecal junction being the most commonly involved structure (39.6%). Histopathological examination of all the tissue biopsies revealed epithelioid granulomas. Postoperative complications occurred in 19 patients (19.8%), with surgical site infection being the most common complication (10.4%).

Conclusion: Intestinal obstruction is an underrecognized manifestation of tuberculosis, particularly in endemic regions. The non-specific clinical presentation, coupled with the limited utility of laboratory and radiological tests, often leads to delayed recognition and treatment. Maintaining a high index of suspicion is essential, especially in younger patients, inhabitants of endemic areas, or those with laboratory findings indicative of chronic inflammation. Prompt recognition is crucial to ensure the timely initiation of anti-tuberculosis therapy and to optimize patient outcomes through appropriate follow-up.

Keywords: Abdominal tuberculosis, bowel obstruction, acute abdomen, exploratory laparotomy, Yemen

Introduction

Intestinal tuberculosis (iTb) is a form of extrapulmonary TB, accounting for approximately 10% of the extrapulmonary TB cases.¹ It can manifest alongside active pulmonary TB or independently without pulmonary involvement.² Despite its relatively low incidence, iTb represents a severe variant of TB, that more frequently develops in patients with malnutrition, or immunosuppression (eg, HIV infection).^{3,4} In addition, iTb carries a poor prognosis with an increased risk for intestinal obstruction, perforation, or strictures.⁵ This can be attributed, in part, to the indolent nature of iTb, along with the non-specific presentation that can overlap with several clinical entities.^{3,6} Hence, it has been occasionally referred to as the “great mimicker” in the literature.⁷ Several reports have documented the invasive nature of iTb, involving the peritoneum, lymph nodes, or intestinal lumens.⁸

There has been a notable increase in the incidence and prevalence of TB, even in developed countries. This trend has been highlighted by the United Nations in its resolution on the fight against tuberculosis.⁹ While pulmonary involvement accounts for the majority of TB cases, reports from endemic regions, such as India, have observed extrapulmonary involvement in approximately 20% of cases.^{10,11} Prior studies from the United States and Europe have also noted a significant increase in extrapulmonary TB.^{10,11} Notably, iTB has a variable incidence, likely influenced by the endemicity of the region. For instance, iTB has been reported at rates as low as 6% and 9% in Europe and the United States, respectively, while higher rates, rising to 28%, have been observed in South Africa.¹¹ It is unclear whether these figures represent an underdiagnosis of iTB or a possible underestimation of TB as a whole. Nonetheless, several reports have highlighted the concurrent pulmonary and intestinal involvement of TB, with incidence rates ranging from 13% to 67%.¹¹

In Yemen, Al-Shehari et al investigated the incidence of TB from 2006 to 2018, focusing on the 13 years before the COVID-19 outbreak. A total of 92,482 patients were enrolled in the TB program records from 22 governorates.¹² The incidence increased significantly in all age groups, with the sharpest increase in children under 15. Pediatric TB accounted for 9.6% of all cases. The incidence has more than doubled in the northern region of Yemen.¹² Despite these alarming figures, they may still represent an underestimation of the true incidence and prevalence. The indolent nature of TB, combined with its prolonged inoculation period even in suspected cases, and the impact of the ongoing war in Yemen—resulting in limited access to healthcare facilities and restricted surveillance and monitoring program outreach—likely contribute to this underestimation.^{12,13} The effect of war seems to be noted in a recent report by the WHO indicating that there were 13,000 new cases of tuberculosis in Yemen in 2017, with 47 infections per 100,000 population including 2.4% of newly diagnosed and 19% of previously treated multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB) patients.¹⁴ While iTB represents an aggressive form of TB infections, it is medically treatable, with most intestinal manifestations manageable with antitubercular treatment. However, due to the challenges in diagnosing iTB, delayed recognition and treatment can lead to complications such as intestinal obstruction, perforation, abscess, or fistula development that necessitate surgical interventions.⁶ This study aims to delve into the patterns of iTB presentation, imaging findings, surgical interventions, and overall outcomes in patients without a prior TB diagnosis.

Materials and Method

Study Design

This retrospective cross-sectional study included patients who presented with intestinal obstruction and underwent surgical exploration at Al-Nasar Hospital in IBB, Yemen, between September 2005 and October 2023. The Ibb University's ethics committee approved the study protocol (ID: IBBUNI.AC.YEM. 2022.1–50) which was carried out in accordance with the Declaration of Helsinki and all patients provided informed consent before data capturing. The requirement for participant consent was waived due to the retrospective nature of the study and the absence of identifiable information.

Study Population

The study population comprised adult patients with a presumptive diagnosis of intestinal obstruction based on supportive clinical and radiological findings. Exclusion criteria were patients with a pre-established TB diagnosis, those managed conservatively, individuals with incomplete charts or lacking pre-operative imaging, HIV-infected or immunosuppressed patients, and those lacking post-operative histopathological confirmation of iTB.

Data Collection

Data were retrieved from the Al-Nasar Hospital registry, identifying cases meeting the study criteria. Collected information encompassed baseline sociodemographic characteristics (age, sex, educational level, and residence), clinical signs and symptoms, blood laboratory results, plain radiography findings, abdominal ultrasound (US) results, abdominal computed tomography (CT) scan findings, surgical procedures performed, surgical findings, operative time, postoperative hospitalization duration, complications, and outcomes. The postoperative phase involved examining surgical complications, hospitalization, and death, with patients monitored for 12 months or until death. The Yemen National Tuberculosis

and Leprosy Program initiated anti-tuberculosis therapy for tuberculosis patients, using Isoniazid, Rifampicin, Pyrazinamide, Ethambutol, and Streptomycin. All Patients were followed by medical (pulmonologists) and surgical (surgeon) teams providing care. The data were gathered via independent chart reviews conducted by the investigator. Following this, the collected data underwent a thorough assessment for accuracy, completeness, and consistency. Any contradictory findings or that lack the required information prompted a subsequent review and reevaluation of the charts.

Statistical Analysis

SPSS software for Windows (version 22; SPSS, Chicago, IL, USA) was used for statistical analyses. Categorical variables are displayed as absolute numbers and percentages, whereas continuous variables are displayed as mean \pm SD and (range). Before statistical analysis, the normality of the data was assessed using the Shapiro–Wilk test.

Result

A total of 3417 patients diagnosed and operated on due to acute abdomen were identified, and 96 (2.6%) were diagnosed with abdominal tuberculosis. The mean age was 36.1 ± 11.5 years (range: 18–75 years), and 49 (51.0%) were female. The rates of Khat chewing, illiteracy, and family history of TB were 76 (79.2%), 42 (43.8%), and 9 (9.4%), respectively. Abdominal pain was the most common gastrointestinal symptom 44 (45.8%). Other symptoms such as fever, weight loss, night sweating, general weakness, and loss of appetite were reported in 65 (67.7%), 33 (34.4%), 17 (17.7%), 13 (13.5%), and 12 (12.5%) patients, respectively. The main physical examination finding was abdominal tenderness in 46 (47.9%) patients, followed by ascites in 42 (43.8%) patients (Table 1).

Table 1 Baseline Characteristics and Clinical Presentation of Patients

Variables	N (%)
Age (year), Mean \pm SD	36.1 \pm 11.5 (range: 18–75 years)
Age between 18–34 years	47 (49.0%)
Age between 35–59 years	34 (35.4%)
Age \geq 60 years	15 (15.6%)
Sex	
Male	47 (49.0%)
Female	49 (51.0%)
Socioeconomic status	
Very low	45 (46.9%)
Low	29 (30.2%)
Medium	22 (22.9%)
Comorbidities	
History of chronic liver disease	13 (13.5%)
History of household member with tuberculosis	9 (9.4%)
Diabetes mellitus	21 (21.9%)
Khat chewing	76 (79.2%)

(Continued)

Table 1 (Continued).

Variables	N (%)
Hypertension	15 (15.6%)
Chronic renal failure	4 (4.2%)
Educational level	
Illiterate	42 (43.8%)
Complete primary school	35 (36.5%)
Complete high school	19 (19.8%)
Gastrointestinal Symptoms	
Abdominal Pain	44 (45.8%)
Vomiting	11 (11.5%)
Constipation	6 (6.2%)
Abdominal Distention	9 (9.4%)
Diarrhea	11 (11.5%)
Abdominal mass	10 (10.4%)
Bloody Stool	5 (5.2%)
Nonspecific symptoms	
Fever	65 (67.7%)
Weight loss	33 (34.4%)
Night sweating	17 (17.7%)
Weakness	13 (13.5%)
Loss of appetite	12 (12.5%)
Abdominal signs	
Abdominal tenderness	46 (47.9%)
Ascites	42 (43.8%)
Splenomegaly	6 (6.2%)
Hepatomegaly	2 (2.1%)

Abbreviation: SD, standard deviation.

Laboratory and Radiological Findings

The mean hemoglobin (g/dL) level was 11.2 ± 1.9 (range: 7–15) and 56 (58.3%) of patients had anemia. Leukocytosis and elevated erythrocyte sedimentation rate (ESR) were presented in 45 (46.9%) and 68 (70.8%) of patients, respectively. On plain radiography, the most common finding was distended intestinal coils in 37 (38.5%) patients, with normal findings reported in 20.8% of patients. The most commonly seen ultrasonographic finding was loculated ascites (25.0%) (Table 2). In CT imaging, multi-segmental symmetric intestinal mural thickening (53.1%) was the most common sign. Other CT findings included solid masses (36.5%), ascites (26%), enlarged lymph nodes (19.8%), and non-enhancing central necrosis and rim enhancement (3.1%) (Figure 1).

Table 2 Laboratory and Radiologic Findings of Patients

Variables	N (%)
Hemoglobin (g/dL), Mean \pm SD	11.2 \pm 1.9 (range: 7–15)
Anemia*	56 (58.3%)
WBC, Mean \pm SD	9265.6 \pm 2787.1 (range: 4×10^3 – 13.5×10^3)
Leukocytosis	45 (46.9%)
Elevated ESR	68 (70.8%)
Plain Xray findings	
Distended coils of Intestine	37 (38.5%)
No obvious finding	20 (20.8%)
Free gas under the diaphragm	18 (18.8%)
Multiple air-fluid levels	17 (17.7%)
Calcified mesenteric lymph nodes	4 (4.2%)
Ultrasonography findings	
Loculated ascites	24 (25.0%)
Enlarged lymph nodes	22 (22.9%)
Bowel wall thickening	22 (22.9%)
Peritoneal thickening	18 (18.8%)
Abscess formation	10 (10.4%)
Computed tomography findings	
Multi-segmental symmetric intestinal mural thickening	51 (53.1%)
Solid masses	35 (36.5%)
Ascites	25 (26.0%)
Enlarged lymph nodes	19 (19.8%)
Non-enhancing central necrosis and rim enhancement	3 (3.1%)

Note: *Anemia: defined as hemoglobin less than 12 g/dL.

Abbreviations: ESR, Erythrocyte sedimentation rate; SD, standard deviation; WBC, white blood cell.

Surgical Procedures/Findings

All patients underwent exploratory laparotomy, and the distribution of the intraoperative findings is shown in Table 3. The mean operative time was 76.5 ± 24.5 minutes (range: 40–125 min). The most common site of involvement was the ileocecal junction (39.6%), and the main operative finding was band adhesion in 20 (20.8%) patients, followed by multiple tubercles in 17 (17.7%) patients (Figure 2). The most commonly performed surgical procedures were adhesiolysis in 28 patients (29.2%), followed by diagnostic laparotomy and biopsy in 27 patients (28.1%). Strictureplasty, limited ileocolic resection with ileo-ascending colon anastomosis, resection and side-to-side anastomosis, right hemicolectomy, and ileostomy with ileostomy closure after 6 months were performed in 15 (15.6%), 14 (14.6%), 9 (9.4%), 2 (2.1%), and 1 (1.0%) patient, respectively. The length of hospital stay ranged from 1 to 27 days, with an average of 9 days.

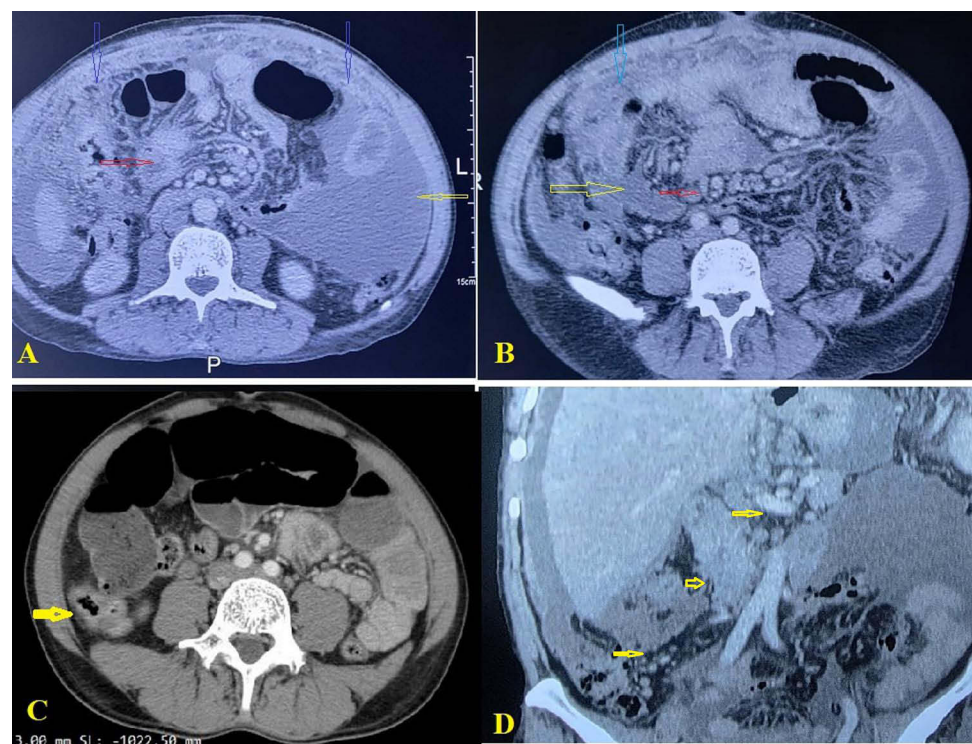


Figure 1 Abdominal computed tomography scan with intravenous contrast: **(A)**; Axial image showing moderate dense ascites, omental and diffuse peritoneal thickening, and enlarged mesenteric iliac lymph nodes. **(B)**; Axial image showing segmental bowel thickening with inflammatory changes and small bowel and enlarged mesenteric iliac lymph nodes with omental nodules. **(C)**; Axial image showing small bowel perforation with granulomatous reaction (yellow arrow). **(D)**; Coronal image showing dense ascites and omental thickening (yellow arrow).

Postoperative Complications and Outcome

Postoperative complications occurred in 19 (19.8%) patients, including surgical site infection, wound dehiscence/abdominal rupture, paralytic ileus, intra-abdominal abscess/peritonitis, enterocutaneous fistula, and septicemia in 10 (10.4%), 2 (2.1), 4 (4.2%), 1 (1.0%), 2 (2.1%), and 1 (1.0%) patient, respectively (Table 3). Patients with wound dehiscence/abdominal rupture, intra-abdominal abscess/peritonitis, enterocutaneous fistula, and septicemia were treated with a temporary ileostomy. All patients received anti-tuberculosis therapy, and after 9 months of treatment, clinical recovery without complications was achieved in all patients, except for one patient who expired during follow-up.

Table 3 Operative and Postoperative Characteristics of Patients

Variables	N (%)
Operative time (min), Mean \pm SD	76.5 \pm 24.5 (range: 40–125 min)
Site of involvement	
Ileocecal region	38 (39.6%)
Small bowel	21 (21.9%)
Small bowel and colon	13 (13.5%)
Large bowel	13 (13.5%)
Extraintestinal but intra-abdominal	11 (11.5%)

(Continued)

Table 3 (Continued).

Variables	N (%)
Operative findings	
Bands and adhesion	20 (20.8%)
Multiple tubercles	17 (17.7%)
Ileocecal mass and mesenteric thickening	14 (14.6%)
Mesenteric lymphadenitis	14 (14.6%)
Multiple stricture	13 (13.5%)
Bowel perforation	9 (9.4%)
Peritoneal adhesion with cocoon formation	9 (9.4%)
Operative procedure	
Adhesiolysis and evacuation of pus	28 (29.2%)
Diagnostic laparotomy and biopsy	27 (28.1%)
Strictureplasty	15 (15.6%)
Limited ileocolic resection with ileo-ascending colon anastomosis	14 (14.6%)
Resection and end-to-end anastomosis	9 (9.4%)
Right hemicolectomy	2 (2.1%)
Ileostomy with the closure of ileostomy after 6 months	1 (1.0%)
Postoperative complications*	19 (19.8%)
Surgical site infections	10 (10.4%)
Wound dehiscence/ burst abdomen	2 (2.1%)
Paralytic ileus	4 (4.2%)
Intraabdominal abscess/ peritonitis	1 (1.0%)
Enterocutaneous fistula	2 (2.1%)
Septicemia	1 (1.0%)

Note: *Some patients had multiple complications.

Abbreviation: SD, standard deviation.

Microbiological Features

The postoperative Acid-fast bacilli test was positive in most cases 75 (78.1%). Histopathological examination of all the tissue biopsies revealed epithelioid granulomas (100%). Caseous necrosis and Langhans giant cells were also observed. The TB-polymerase chain reaction (PCR) result was available for 73 cases and was positive in most cases 66 (68.8%) (Table 4).

Discussion

The epidemiological trajectory of TB has exhibited fluctuations in recent years, with escalating incidence primarily observed in lower-income nations. This trend is influenced by several factors related to the economic regression since COVID-19 with diminished healthcare expenditure, along with inadequate social protection. Furthermore, the increased rates of immunosuppressive conditions (eg, HIV), introduction of several biological therapies, and increased prevalence of multi-drug-resistant TB compounded by suboptimal treatment have influenced the overall incidence and prevalence of TB.^{6,15}

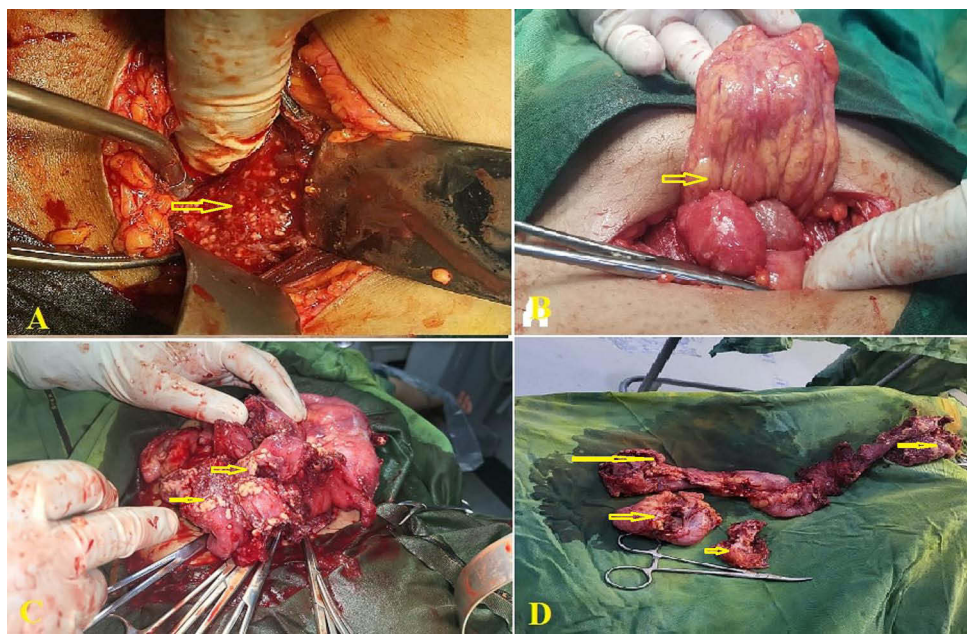


Figure 2 Intraoperative images showing: (A); intraoperative peritoneal nodules v. (B); Small bowel surface covered in diffuse miliary nodules (yellow arrow). (C); Numerous granulomas in the peritoneal wall (yellow arrow). (D); Resected part of the ileocaecal region showing strictures lesion (arrow) in the terminal ileum.

In this study, the mean age of affected individuals was 36.1 ± 11.5 years, in line with preceding national and regional assessments.^{8,16–18} Nevertheless, these findings deviate from prior observations which reported an older age group of overall small intestinal obstruction patients. For instance, a population-based analysis by Behman et al reported a mean age of 61.2 years.¹⁹ Similar to our findings were also reported by Cheng et al with a mean age of 37 years.²⁰ While our investigation did not unveil a significant gender predilection, approximately 46.9% of patients hailed from economically disadvantaged backgrounds. These findings align with previous studies with socioeconomic backgrounds, where individuals from such strata encounter restricted access to healthcare amenities and are subjected to less targeted TB screening.^{8,20,21}

The clinical diagnosis of iTB poses considerable challenges, as the majority of patients present with nonspecific symptoms such as weight loss, anemia, and fever with night sweats.²¹ In addition, the frequencies of these symptoms vary significantly in the literature. For instance, a study by Farina et al reported weight loss and night sweat in merely

Table 4 Microbiological Features of Patients

Variables	N (%)
Acid-fast bacilli	
Negative	19 (19.8%)
Positive	75 (78.1%)
Not done	2 (2.1%)
TB-PCR	
Negative	7 (7.3%)
Positive	66 (68.8%)
Not done	23 (24.0%)

Abbreviations: PCR, Polymerase chain reaction; TB, Tuberculosis.

9.7% and 1.8%, respectively.²² In our study, abdominal pain was the most frequently reported symptom (45.8%), accompanied by other nonspecific symptoms such as fever, weight loss, night sweats, general weakness, and loss of appetite. Dhali et al reported similar frequencies, with abdominal pain being the presenting symptom in (39.7%) of patients.²³ The physical examination in iTB varies depending on the site of GI involvement and may include hepatosplenomegaly, abdominal tenderness, or palpable masses.^{24,25} However, these findings appear to be of limited utility, for instance, less than half of our patients exhibited abdominal tenderness, and splenomegaly or hepatomegaly was noted in 6.2% and 2.1% of our patients.

Similarly, the utility of laboratory testing in iTB is limited, as evidenced by the non-specific nature of findings such as normocytic anemia and elevated inflammatory markers, notably an elevated ESR.⁸ In our investigation, the mean hemoglobin value was recorded at 11.2 ± 1.9 g/dL, with 56 patients (58.3%) presenting with anemia, and 68 cases (70.8%) displaying elevated ESR levels. These findings lack the diagnostic specificity, however, can be suggestive of a chronic inflammatory process that would not be anticipated in acute abdomen.^{26,27} The radiological findings in iTB may mimic several gastrointestinal pathologies.²⁸ For instance, plain X-ray imaging may reveal features such as mural thickening, distended bowel loops, or signs of perforation such as air under the diaphragm.²⁹ Among our patients, distended bowel loops were the most prevalent finding in plain X-ray imaging in 38.5% of the patients.

Abdominal US is a common initial radiologic modality for detecting lymphadenopathy, peritoneal or omental thickening, ascites, mesenteric abnormalities, and gut wall thickening.³⁰ Nevertheless, these findings were seen in the minority of the patients in our study (Table 2). Abdominal CT imaging was the most sensitive modality in our study, with (53.1%) of the patients having multi-segmental mural thickening, along solid masses (36.5%), ascites (26.0%), enlarged lymph nodes (19.8%), and non-enhancing-central-necrosis and rim enhancement (3.1%). These findings align relatively with prior reports, albeit with variations in reported rates across different studies.³¹ For example, Sinan et al reported the CT scan findings of 49 patients with proven iTB within 20 years and found that peritoneal involvement was the most common feature (77.5%) followed by ascites (55.2%). Other CT scan findings included diffuse lymphadenopathy (46.9%), bowel wall thickening (38%), and solid organ involvement (20.4%).³² In another report, Deshpande et al mentioned that the commonest pattern of iTB involvement was circumferential bowel wall thickening without bowel stratification with mild luminal narrowing.³³ Nonetheless, the diagnostic utility of radiological studies in our investigation was limited, consistent with several reports indicating high rates of iTB misdiagnosis due to the lack of radiological specificity.^{33–35}

The management of iTB predominantly relies on conventional anti-tuberculosis therapy, typically resulting in remission and complete recovery.³⁶ Surgical interventions are reserved for advanced or complicated cases, such as bowel obstruction or perforation. Several surgical approaches are proposed, with the determination of appropriate intervention based on the underlying pathology and the involved gastrointestinal structures. In our study, intestinal adhesions were the most common intra-operative finding, with adhesiolysis being the most frequently performed intervention in our cohort (29.2%). Similar observations were reported by Chalya et al and Weledji et al, where adhesiolysis was frequently performed, likely attributable to the similar prevalence of intra-operative findings such as bands or adhesions.^{37,38} However, a more conservative approach, such as strictureplasty, has been advocated for localized strictures, as it offers advantages over repeat resections and entero-anastomoses by preserving the integrity of the small intestine and mitigating the risk of short bowel syndrome or blind loops.³⁷ Nonetheless, segmental resection may be warranted in cases of extended strictures or concurrent perforations.^{6,39}

In our study, nine patients (9.4%) developed perforations around strictures, necessitating excision with side-to-side anastomosis. Alternative approaches have been described in the literature including exteriorization of perforated loops, which present an appropriate approach for acute cases with perforative peritonitis.⁶

Mortality rates attributable to iTB exhibit considerable variability, ranging from 14% to 50% in low-income countries and 6% to 37% in high-income countries.¹¹ Morbidities associated with iTB include delayed wound healing, incisional hernia, recurrent obstruction, and fecal fistula.^{36,37} Bowel perforation causes significant death rates and is thought to exacerbate iTB in up to 11% of adult cases, which might be attributed to the late hospital presentation.⁴⁰ Our study identified surgical site infection as the primary postoperative complication, consistent with findings from prior investigations.^{38,41,42} In addition, one case expired during postoperative follow-up. Other complications reported in this study included wound dehiscence/abdominal rupture, intra-abdominal abscess/peritonitis, enterocutaneous fistula,

and septicemia. In another report, Cheng et al found 43.2% of postoperative complications, with fistula (27%) and surgical site infections (21.6%) being the most prevalent postoperative complications.²⁰

Study Limitations

The study has several limitations. The retrospective design limits generalizability and introduces potential selection bias, particularly due to the reliance on available medical records, which may be incomplete or inaccurately documented. Additionally, the absence of postoperative follow-up hindered further evaluation of tuberculosis cases, including the identification of concurrent pulmonary or extra-pulmonary involvement, as well as long-term follow-up to assess the initiation of anti-tuberculosis therapy. Moreover, the lack of a control group restricted our ability to conduct a comprehensive analysis of potential risk factors or prognostic indicators.

Conclusion

Intestinal obstruction is an underrecognized manifestation of tuberculosis, particularly in endemic regions. The non-specific clinical presentation, coupled with the limited utility of laboratory and radiological tests, often leads to delayed recognition and treatment. Maintaining a high index of suspicion is essential, especially in younger patients, inhabitants of endemic areas, or those with laboratory findings indicative of chronic inflammation. Prompt recognition is crucial to ensure the timely initiation of anti-tuberculosis therapy and to optimize patient outcomes through appropriate follow-up.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The Ibb University's ethics committee approved the study protocol and all patients provided informed consent before data capturing.

Consent for Publication

All authors reviewed the manuscript and approved its submission.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests.

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