Journal of Clinical and Nursing Research, 2025, Volume 9, Issue 10
http://ojs.bbwpublisher.com/index.php/JCNR
Online ISSN: 2208-3693
Print ISSN: 2208-3685

Co-infection of *Tropheryma Whipplei* and Mycobacterium tuberculosis in 39 Cases: A Case Series Study

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Abstract: *Background*: Whipple's Disease (WD) is a chronic and recurrent multisystem disease caused by *Tropheryma whipplei* (TW). Typically, MTB infection compromises the immune system. However, clinical reports of MTB and TW co-infection are rare. *Methods*: This study retrospectively analyzed the admission symptoms and biochemical test results of 39 patients co-infected with MTB and TW between January 1, 2023, and August 31, 2024, at the Infectious Disease Hospital of Heilongjiang Province, China. This study further compared the admission indicators between individuals with co-infections involving more than two pathogens (multi-infected) and those infected with only MTB and TW (Co-Infected). Results: The hospitalized patients had a median age of 50 (39–58) years. Most of the patients were male (69.23%, 27/39). Most patients presented with cough (87.18%, 34/39), sputum production (76.92%, 30/39), shortness of breath (64.10%, 25/39), and reduced appetite or even anorexia (53.85%, 21/39). However, fever (41.03%, 14/39) and fatigue (41.03%, 16/39) were less common. Among the patients who underwent these four biochemical tests, the majority (86.36%, 19/22) had an A/G ratio below the normal range at the time of admission, primarily due to an increase in serum globulin levels. Multi-Infected group had higher levels of alanine aminotransferase than the Co-Infected group (17 vs. 10, $p = 0.035$), and aspartate aminotransferase is also higher in the multi-infected group compared to the Co-Infected group (20 vs. 14, $p = 0.034$). *Conclusion*: This is the first study to report the coinfection of *Tropheryma whipplei* (TW) and *Mycobacterium tuberculosis* (MTB) in Heilongjiang Province, China. However, this study did not find significant differences from descriptions in existing literature. Therefore, this study has provided a descriptive analysis to serve as a reference for further understanding TW infections.

Keywords: *Mycobacterium tuberculosis*; *Tropheryma whipplei*; Pulmonary infection; Metagenomic next-generation sequencing

Online publication: Nov 6, 2025

1. Introduction

Whipple's Disease (WD) is a chronic, and recurrent multisystem disease caused by *Tropheryma whipplei* (TW) [1,2]. WD was first reported in 1907 by American pathologist George Hoyt Whipple, but the successful culture of TW strains was achieved only in 2000 [3,4]. WD is rare, with no reliable estimate of its actual prevalence, and as of 2007, only about 1,000 cases had been reported globally [1]. A recent review indicated that the prevalence in Italy and the United States is 3/1,000,000 and 9.8/1,000,000, respectively [5].

The clinical symptoms of WD are diverse and lack specificity [2]. Acute TW infections often present as self-limiting gastroenteritis, fever, cough, and bacteremia [1,2]. Most acute cases resolve with an immune response, while some progress to asymptomatic carriage or chronic infection, manifesting as endocarditis, encephalitis, arthritis, and more. Approximately 30% to 40% of WD patients exhibit pulmonary symptoms, including pneumonia, chronic cough, chest pain, dyspnea, pleural adhesions, and reduced lung capacity [6].

The amplification of TW 16S rRNA via PCR and its cell culture greatly advanced the understanding and treatment of Whipple's Disease [7]. In 2003, Bentley and Raoult independently completed the whole-genome sequencing of TW and conducted an analysis of its sequences [8,9]. Previous studies have indicated that this bacterium is difficult to culture *in vitro*, and diagnosis typically requires quantitative polymerase chain reaction (qPCR) and/or metagenomic next-generation sequencing (mNGS) techniques [6]. However, since neither qPCR nor mNGS are routine testing methods, infections caused by TW are often easily overlooked in clinical practice.

Between January 1, 2023, and August 31, 2024, this research has diagnosed 39 cases of pulmonary co-infection caused by TW and MTB. This study underscores the critical role of mNGS in identifying these pathogens. Our findings provide a valuable reference for further research on the interplay between Whipple's disease and tuberculosis and contribute to the development of relevant clinical guidelines.

2. Materials and methods

2.1. Patients and specimen collection

This study has retrospectively analyzed 18 bronchoalveolar lavage fluid (BALF) samples and 21 sputum samples that underwent mNGS testing between January 1, 2023, and August 31, 2024, at the Infectious Disease Hospital of Heilongjiang Province, China. All samples were collected in accordance with strict sterility protocols. This study collected baseline data of positive *T.whipplei*, including demographic information and laboratory data.

2.2. Diagnostic workflow for TW and MTB infection

Patients were diagnosed with MTB infection according to the National Diagnostic Criteria for Pulmonary Tuberculosis and the Classification of Tuberculosis [10–12]. The collected samples were sent to Dian Diagnostics for testing, and clinicians made a diagnosis of TW infection based on the test reports and clinical symptoms. In the absence of clear guidelines for diagnosing TW, the study referred to previously published literature, where TW was considered positive if at least three reads were mapped to the species level [3].

2.3. Statistical analysis

Data statistics and analysis were carried out in R (version 4.3.2). Continuous data were described using median (25^{th} and 75^{th} percentile quantile). Categorical data were presented as frequency and percentage (N (%)). The Wilcoxon rank-sum test was used to compare continuous data between groups, while Fisher's exact test was applied for

comparisons of categorical data between groups. $p < 0.05$ was considered to indicate statistical significance.

3. Results

Based on baseline characteristics, the hospitalized patients had a median age of 50 (39–58) years, a height of 170 (162–175) cm, a weight of 60 (55–66) kg, and a BMI of 20.76 (18.73–22.48) kg/m^2. Most of the patients were male (69.23%, 27/39, **Table 1**). Among those with known blood types, blood type O was the most common (23.08%, 9/39, **Table 1**). Socially, most patients were married (71.79%, 28/39, **Table 1**) and unemployed (61.54%, 24/39, **Table 1**).

Table 1. Baseline characteristic

Feature	N (%)
Sex	
Female	12 (30.77)
Male	27 (69.23)
Blood type	
A	7 (17.95)
AB	4 (10.26)
B	6 (15.38)
O	9 (23.08)
Unknown	13 (33.33)
Marital status	
Divorced	4 (10.26)
Married	28 (71.79)
Single	6 (15.38)
Widowed	1 (2.56)
Occupation	
Employee	2 (5.13)
Farmer	8 (20.51)
Retired	2 (5.13)
Student	2 (5.13)
Unemployed	24 (61.54)
Worker	1 (2.56)

Regarding admission symptoms, most patients presented with cough (87.18%, 34/39, **Table 2**), sputum production (76.92%, 30/39, **Table 2**), shortness of breath (64.10%, 25/39, **Table 2**), and reduced appetite or even anorexia (53.85%, 21/39, **Table 2**). However, fever (41.03%, 14/39, **Table 2**) and fatigue (41.03%, 16/39, **Table 2**) were less common.

Table 2. Admission symptoms

Feature	N (%)
Fever	14 (35.90)
Cough	34 (87.18)
Sputum	30 (76.92)
Fatigue	16 (41.03)
Tachypnea	14 (35.90)
Appetite loss	21 (53.85)

This study has plotted the biochemical test results of patients upon admission (**Figure 1**), focusing on total protein, albumin, globulin, and the albumin-to-globulin (A/G) ratio. The results showed that among the patients who underwent these four biochemical tests, the majority (86.36%, 19/22, **Figure 2**) had an A/G ratio (normal range: 1.5–2.5) below the normal range at the time of admission, primarily due to an increase in serum globulin levels.

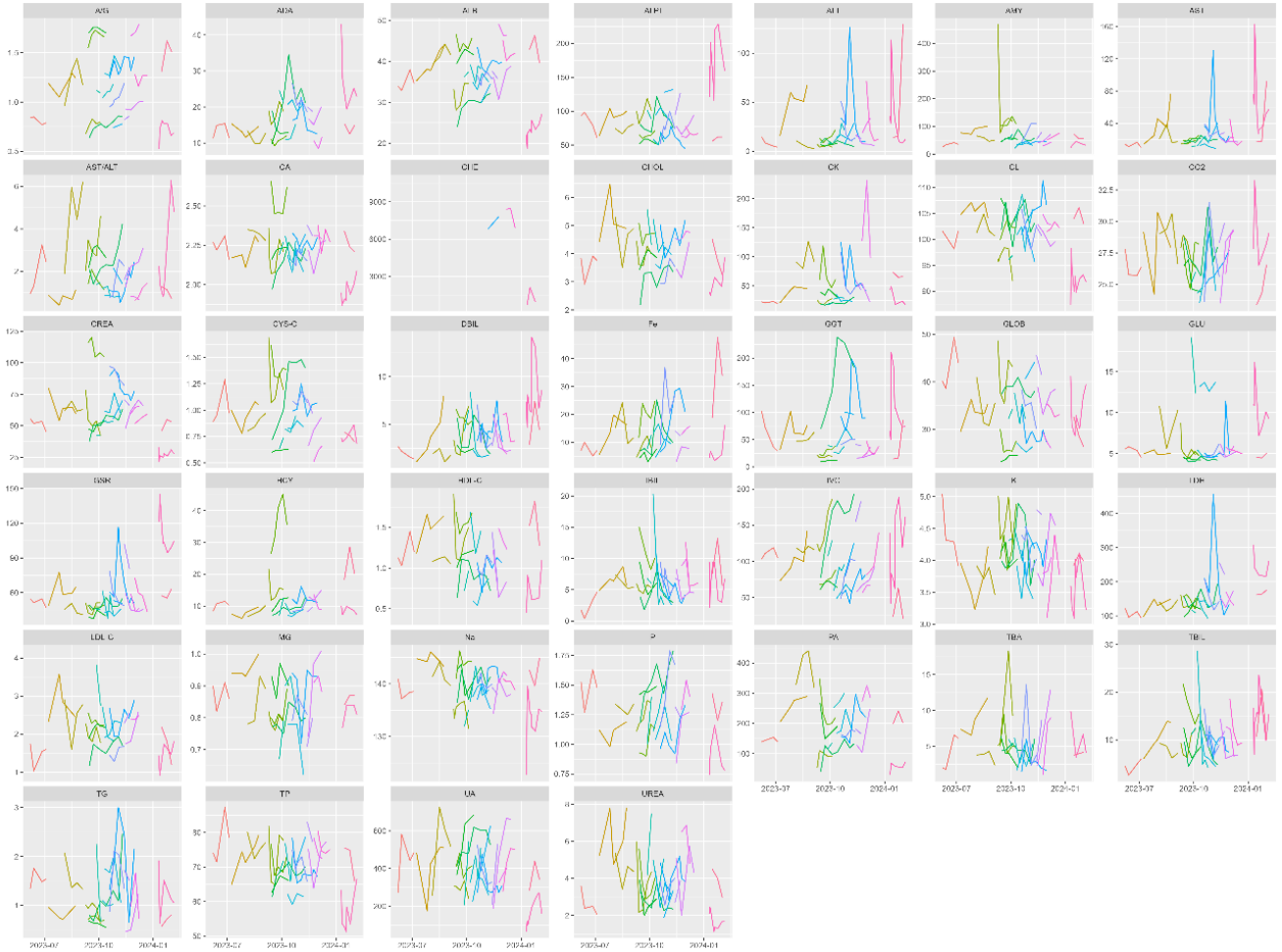

Figure 1. Biochemical test results of hospitalized patients.

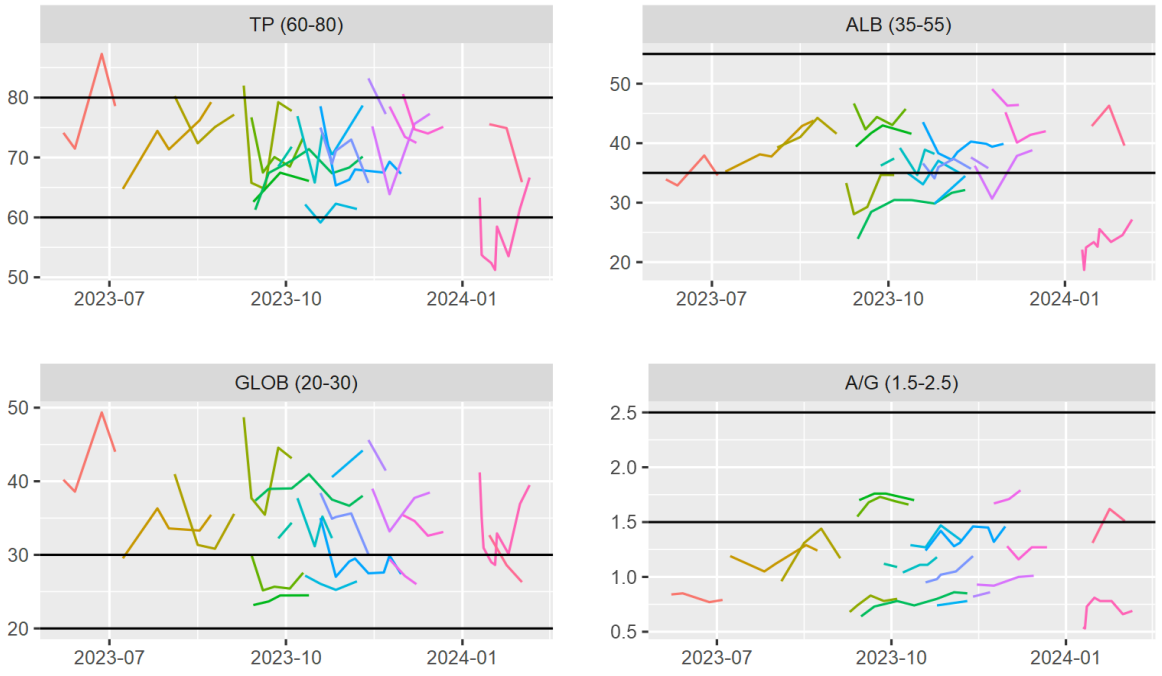

Figure 2. Biochemical test results of hospitalized patients (TP, ALB, GLOB, A/G).

Based on whole-genome sequencing results, we divided the population into two groups, those infected only with MTB and TW (labeled as 0, Co-Infected) and those infected with more than just MTB and TW (labeled as 1, multi-infected). After conducting a comparative analysis, the results indicate that the multi-infected group has higher levels of alanine aminotransferase than the Co-Infected group (17 vs. 10, $p = 0.035$, **Table 3**), and aspartate aminotransferase is also higher in the multi-infected group compared to the Co-Infected group (20 vs. 14, $p = 0.034$, **Table 3**).

Table 3. Comparison of admission characteristics between co-infected and multi-infected groups

Characteristic	Co-infected (N = 12)	Multi-infected (N = 27)	p
Sex			0.455
Female	5 (42%)	7 (26%)	
Male	7 (58%)	20 (74%)	
Blood type			0.553
A	2 (17%)	5 (19%)	
AB	0 (0%)	4 (15%)	
B	3 (25%)	3 (11%)	
O	2 (17%)	7 (26%)	
Unknown	5 (42%)	8 (30%)	
Marital status			0.615
Divorced	0 (0%)	4 (15%)	
Married	10 (83%)	18 (67%)	
Single	2 (17%)	4 (15%)	
Widowed	0 (0%)	1 (3.7%)	

Table 3 (Continued)

Characteristic	Co-infected (N = 12)	Multi-infected (N = 27)	p
Occupation			0.079
Employee	0 (0%)	2 (7.4%)	
Farmer	0 (0%)	8 (30%)	
Retired	1 (8.3%)	1 (3.7%)	
Student	0 (0%)	2 (7.4%)	
Unemployed	11 (92%)	13 (48%)	
Worker	0 (0%)	1 (3.7%)	
Age	57 (45, 62)	48 (36, 57)	0.152
Height	165 (160, 170)	174 (164, 178)	0.020
Weight	57 (51, 63)	60 (56, 67)	0.228
BMI	20.8 (18.2, 23.1)	20.6 (18.7, 22.3)	0.845
A/G	1.08 (0.90, 1.20)	1.10 (0.82, 1.31)	0.838
Unknown	4	13	
ADA	14 (11, 20)	18 (15, 20)	0.339
Unknown	4	13	
ALB	37 (35, 39)	37 (34, 44)	0.664
Unknown	4	13	
ALPI	87 (69, 102)	78 (63, 94)	0.365
Unknown	4	13	
ALT	10 (8, 14)	17 (13, 34)	0.035
Unknown	4	13	
AMY	53 (32, 63)	43 (36, 53)	0.764
Unknown	4	13	
AST	14 (13, 18)	20 (15, 37)	0.034
Unknown	4	13	
AST/ALT	1.64 (1.07, 2.10)	1.26 (0.88, 2.03)	0.413
Unknown	4	13	
CA	2.27 (2.19, 2.33)	2.27 (2.16, 2.36)	0.945
Unknown	4	13	
CHOL	4.96 (4.13, 5.45)	4.32 (3.43, 4.55)	0.142
Unknown	4	13	
CK	29 (22, 54)	46 (36, 73)	0.145
Unknown	4	13	
CL	103.0 (101.4, 104.7)	102.1 (100.8, 104.8)	0.714
Unknown	4	13	
CO2	28.41 (25.24, 29.15)	27.14 (23.60, 28.30)	0.275
Unknown	4	13	
CREA	59 (55, 66)	61 (47, 89)	0.92
Unknown	4	13	
CYS-C	0.95 (0.81, 1.09)	0.81 (0.71, 1.11)	0.616
Unknown	4	13	
DBIL	3.90 (2.30, 4.50)	3.70 (2.90, 6.10)	0.562

Table 3 (Continued)

Characteristic	Co-infected (N = 12)	Multi-infected (N = 27)	p
Unknown	4	13	
Fe	11.9 (7.4, 15.0)	6.7 (4.6, 11.7)	0.070
Unknown	4	13	
GGT	35 (27, 74)	30 (18, 48)	0.441
Unknown	4	13	
GLOB	35.0 (30.8, 40.4)	35.5 (30.0, 39.0)	0.973
Unknown	4	13	
GLU	5.34 (5.08, 8.18)	5.19 (4.57, 6.17)	0.473
Unknown	4	13	
GSR	53 (47, 58)	60 (49, 73)	0.33
Unknown	4	13	
HCY	9.6 (7.3, 11.7)	12.6 (8.2, 18.3)	0.133
Unknown	4	13	
HDL-C	1.16 (0.90, 1.57)	1.15 (0.79, 1.50)	0.918
Unknown	4	13	
IBIL	7.3 (5.9, 10.1)	8.6 (6.8, 9.5)	0.516
Unknown	4	13	
IVC	96 (76, 113)	65 (53, 115)	0.162
Unknown	4	13	
K	4.19 (3.98, 4.52)	4.01 (3.80, 4.40)	0.245
Unknown	4	13	
LDH	135 (120, 167)	162 (155, 210)	0.07
Unknown	4	13	
LDL-C	2.53 (1.97, 3.37)	2.24 (1.74, 2.56)	0.194
Unknown	4	13	
MG	0.90 (0.80, 0.92)	0.80 (0.77, 0.85)	0.259
Unknown	4	13	
Na	140.4 (137.5, 141.7)	138.8 (136.4, 140.9)	0.402
Unknown	4	13	
P	1.15 (1.06, 1.34)	1.09 (0.93, 1.29)	0.275
Unknown	4	13	
PA	182 (127, 228)	165 (128, 268)	0.868
Unknown	4	13	
TBA	6.10 (3.21, 7.22)	3.69 (1.68, 5.02)	0.11
Unknown	4	13	
TBIL	11.5 (7.7, 14.0)	12.7 (9.6, 16.6)	0.393
Unknown	4	13	
TG	1.22 (0.96, 1.89)	1.00 (0.71, 1.72)	0.365
Unknown	4	13	
TP	70.3 (68.9, 75.5)	75.4 (63.3, 78.6)	0.57
Unknown	4	13	
UA	300 (255, 430)	296 (225, 398)	0.815

Table 3 (Continued)

Characteristic	Co-infected (N = 12)	Multi-infected (N = 27)	p
Unknown	4	13	
UREA	5.10 (3.89, 5.29)	4.45 (3.40, 5.62)	0.714
Unknown	4	13	

4. Discussion

As from prior knowledge, this is the first study to report the coinfection of *Tropheryma whipplei* (TW) and *Mycobacterium tuberculosis* (MTB) in Heilongjiang Province, China. This study was attempted to identify distinct clinical characteristics in these cases compared to other diseases. However, this study did not find significant differences from descriptions in existing literature. Therefore, this study has provided a descriptive analysis to serve as a reference for further understanding TW infections.

China's first reported case of MTB and TW co-infection was documented in 2021 in Shanghai [14]. The patient exhibited fever, cough, and respiratory distress, but notably did not present with sputum production or fatigue. In our study of 39 patients, regarding admission symptoms, cough, sputum production, and shortness of breath were the predominant respiratory symptoms, underscoring the respiratory nature of the disease in our patient population. However, the relatively low incidence of fever and fatigue suggests that these symptoms may not serve as reliable indicators of disease severity or progression in this context. Biochemical analysis revealed that most patients had elevated serum globulin levels and a low serum albumin/globulin ratio, which may indicate an underlying infectious disease. Unfortunately, these symptoms and biochemical findings are nonspecific, and without considering NGS testing, TW infection might easily be overlooked. To underscore the importance of NGS in aiding the diagnosis of TW infection, this study conducted a search of CNKI and PubMed for reported cases of TW infection in China (see supplementary). From January 1, 2007, to September 3, 2024, a total of 109 cases of TW infection were reported, with 103 cases using NGS for auxiliary diagnosis.

Referencing the study by Lai et al., this study compared the admission biochemical results of the Co-Infected and Multi-Infected groups and found differences in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels [15]. The finding was consistent with the results of Lai et al.'s study, although their results did not reach statistical significance. Along with the previously mentioned decrease in the albumin/globulin ratio, this emphasizes the necessity of closely monitoring and managing liver function in patients with multiple infections.

There are still some limitations in this study. In previous suggestions, Zong et al. proposed that NGS reports should include quality control measures, such as noting whether other samples in the same batch tested positive for the pathogen, to rule out false positives due to laboratory contamination [16]. All samples in our study underwent strict adherence to standard operating procedures for experimentation and quality control. Although it was suggested to add batch-specific results to further verify the reliability of the positive results, the research did not annotate each sample with the results of other samples in the batch. This is because the existing quality control measures have already ensured the reliability of the experimental results, and additional annotations could complicate the report unnecessarily. Furthermore, given the study design and sample size, implementing such a measure would present certain challenges in this study.

5. Conclusion

In conclusion, this study presents the first documented cases of TW and MTB co-infection in Heilongjiang Province, China. Although no significant clinical distinctions from mono-infections were identified, this descriptive analysis offers foundational data that may enhance clinical awareness and contribute to a deeper understanding of TW co-infection dynamics, underscoring the need for further investigation.

Disclosure statement

The authors declare no conflict of interest.

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