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TANAFFOS

Comparative Analysis of Clinical, Laboratory, and Imaging Profiles in Tuberculosis Patients Pre- and Post-COVID-19 Pandemic

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Background: While the COVID-19 pandemic has understandably dominated global attention, Tuberculosis (TB) remains a persistent and formidable global health threat. Acknowledging the impact of COVID-19 on immune function and the decreased referrals of TB patients to medical clinics during the pandemic, we sought to assess the clinical and paraclinical characteristics of TB patients in two distinct periods: pre-pandemic and pandemic periods.

Materials and Methods: We retrospectively identified 105 TB patients from the year preceding the pandemic and, during the pandemic, selected 72 TB patients with a positive history of COVID-19. A comprehensive analysis of various features, including age, gender, fever, cough, hemoptysis, and different imaging and laboratory parameters, was conducted and compared between the two groups.

Results: Post-pandemic TB patients exhibited a higher prevalence of hemoptysis, chest pain, and elevated erythrocyte sedimentation rate (ESR) levels, with P-values of 0.014, 0.006, and <0.001, respectively. Furthermore, our findings indicated an increased incidence of bilateral imaging features in COVID-19 TB patients (P= 0.02).

Conclusion: Given the potential effects of COVID-19 on immune function and the diagnostic challenges posed by overlapping clinical manifestations, clinicians should maintain a high index of suspicion for tuberculosis (TB) in patients with COVID-19, particularly those presenting with atypical or complex symptoms.

Keywords: Tuberculosis; COVID-19; Pandemic

INTRODUCTION

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, is a respiratory infection often presenting in its latent form but can sporadically progress to an active infection. (1-3) Triggers for active TB encompass immunosuppression, chronic obstructive pulmonary disease (COPD), advanced age, comorbidities, and others (4), with evidence suggesting COVID-19-related immunosuppression may act as a catalyst (1). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induces acute respiratory distress syndrome as a secondary effect of COVID-19, with a higher mortality rate than TB during the pandemic (5).

Diagnosing both TB and COVID-19 involves a diverse range of clinical features, laboratory, and imaging modalities. While many missed TB diagnoses can be attributed to COVID-19 (1), the pandemic's full impact on TB diagnostic findings remains uncertain.

TB is initially suspected in patients exhibiting relevant clinical manifestations, such as a persistent cough (>2-3 weeks), fever, night sweats, and weight loss, particularly in

regions endemic for TB (6). Initial diagnostic steps include chest radiography (CXR), which may reveal focal infiltration (upper or lower lobes, unilateral or bilateral) or/and pleural effusions. (7-9) Although chest CT scans offer higher sensitivity for subtle parenchymal lung changes, they are not essential for TB diagnosis and are primarily used during outbreaks (10). Laboratory confirmation involves sputum acid-fast bacilli (AFP) smear, mycobacterial culture, and molecular tests (such as nucleic acid amplification (NAA) tests and Xpert MTB/RIF assay (11-14).

COVID-19 presents a broad clinical spectrum from mild (minimal pneumonia) to critical illness (exhibiting hypoxia, respiratory failure, shock, or multi-organ dysfunction) (15, 16). Severe and critical forms are associated with comorbidities, advanced age, and physical inactivity. (17, 18) Initial presentations often include cough, myalgia, and headache, sometimes accompanied by diarrhea, sore throat, and alterations in smell or taste. Laboratory abnormalities may include lymphopenia (<1500/µL), thrombocytopenia, elevated lactate dehydrogenase, elevated liver enzymes, and inflammatory markers (19-21). CXR may appear normal in early or mild cases, with common abnormalities being consolidation and ground-glass opacities (22, 23). Although chest CT scan findings are more sensitive, they lack specificity for COVID-19 and are primarily reserved for hospitalized patients, revealing ground-glass opacities (with or without consolidation), pleural/interlobar septal thickening, and air bronchograms (24, 25).

The rising incidence of COVID-19/TB coinfection during the COVID-19 pandemic, coupled with the enduring effects of COVID-19, underscores the need to understand their distinct diagnostic features. Moreover, the delayed referrals of TB patients to medical clinics during the pandemic may also influence these findings. This study addresses this diagnostic challenge by comparing the clinical and paraclinical profiles of TB patients before and during the COVID-19 pandemic.

MATERIALS AND METHODS

Study Design

This retrospective, descriptive-analytical, single-centered study was conducted at Bou-Ali Hospital in Zahedan, Iran. The study included the evaluation of medical records for 105 TB patients from the pre-COVID-19 period (2018-2019) and 72 TB patients with a positive COVID-19 Real-time PCR history from 2019-2022. Inclusion criteria comprised individuals aged 15 and above, no known immunocompromised state, presence of imaging at the time of diagnosis, complete documentation, and absence of any other established diagnosis. The exclusion criteria were concurrent TB-COVID-19 disease, presence of an immunodeficiency, significant use of immunosuppressive medications, or an immunosuppressed state secondary to other causes.

The following parameters were examined and compared across the two groups: documented clinical features and physical examination findings, white blood cell, hemoglobin, and platelet counts, inflammatory markers (Erythrocyte Sedimentation Rate and C-reactive protein (assessed with a semi-quantitative measure that categorizes levels as follows: negative (no detectable CRP in blood, suggesting the absence of significant inflammation), +1: mild inflammation, +2: moderate inflammation, +3: severe inflammation)), imaging findings, pulmonary or extrapulmonary status, duration from symptom onset to seeking medical attention, duration of hospitalization, and confirmatory tests for TB (positive results in AFB smear, PCR, GeneXpert, or culture).

Clinical features and physical exams included fever, chills, cough, hemoptysis, dyspnea, sputum production, and chest pain. The imaging findings included cavitation, pulmonary or/and extra-pulmonary involvement in both CXR and lung CT scan modalities.

Statistical Analysis

Population analysis in the two groups was performed using SPSS V.26 (IBM, Armonk, New York, USA). Descriptive comparisons utilized Chi-Squared tests, while independent t-tests were employed for quantitative comparisons. Mann-Whitney U-tests were conducted to evaluate central tendencies in each group when the dependent variable was continuous.

Ethical Consideration

The Ethical Committee of Zahedan University of Medical Sciences approved this study under the code: IR.ZAUMS.REC.1401.344, adhering to the principles of the Declaration of Helsinki. Written informed consent, as appropriate, was obtained from each participant.

RESULTS

Out of the initial 186 patients, 9 were excluded due to other diagnoses such as hepatitis C, chronic corticosteroid use, Hodgkin lymphoma, bladder cancer, and chronic lymphocytic leukemia (CLL). The remaining 177 TB patients, comprising 105 pre-COVID-19 and 72 post-COVID-19 patients, were all aged over 15, with mean ages of 56.49±21.40 and 58.31±19.04 years, respectively. Among them, 89 were male, and 88 were female.

Statistical analysis revealed significant differences in clinical findings, specifically chest pain and hemoptysis (P-values of 0.006 and 0.014, respectively). However, there were no statistically significant differences in laboratory data except for elevated ESR levels, with a P-value of less than 0.001. Radiologically, bilateral pulmonary involvement demonstrated a significant difference (P-value<0.02). Notably, the presence of cavitary lesions on imaging and intra- and extra-pulmonary involvement was not significantly influenced by a previous COVID-19 infection. The duration from symptom onset to medical attention and the duration of hospitalization also did not exhibit any significant differences. Detailed results are presented in Table 1.

As per protocol, all COVID-19 patients admitted to our hospital receive steroids as part of their treatment. Severe cases received Remdesivir, but mild-to-moderate cases only received supportive treatments. Tocilizumab, another drug associated with COVID-19 treatment that increases the risk of TB infections, was a scarce medication back then, which we did not have access to.

Table 1. Comparison of the two TB populations with and without a prior COVID-19 infection

	Categories		Pre-COVID-19	Post-COVID-19	P-Value
	Total Patients		105	72	
	Average Age		56.49 ± 21.4	58.31 ± 19.0	0.561
Gender, N (%)	Male		52 (49.5)	37 (51.3)	0.771
	Female		53 (50.5)	35 (48.7)	
	Fever		77 (73.3)	48 (66.7)	0.259
	Cough		84 (80)	61 (84.7)	0.330
	Hemoptysis		12 (11.4)	17 (23.6)	0.014
Clinical Features, N (%)	Dyspnea		64 (60.9)	53 (73.6)	0.034
	Chest Pain		15 (14.3)	21 (29.2)	0.006
	Sputum production		60 (57.1)	43 (59.7)	0.683
	Weight Loss		57 (54.3)	39 (54.2)	0.985
	Loss of Consciousness		9 (8.6)	13 (18.0)	0.033
	Average WBC (x1000)		10.56 ± 5.9	10.01 ± 6.25	0.767
	Average Segment %[1]		73.11 ± 13.2	76.73 ± 12.5	0.033
	Average Hb (g/dL)		11.30 ± 2.2	11.53 ± 1.8	0.326
	Average Plt (x1000/µL)		326.62 ± 138.6	296.85 ± 136.9	0.441
Laboratory Findings	CRP	0	11	11	0.742
		+1	8	5	
		+2	23	13	
		+3	61	38	
	Average ESR (mm/hr)		69.32 ± 32.3	36.58 ± 33.5	<0.001
	Bilateral		63 (60)	55 (76.4)	0.02
Imaging Features, N (%)	Cavitation		32 (30.5)	32 (44.4)	0.057
	Pulmonary involvement		77 (73.3)	55 (76.4)	
	Extra-pulmonary involvement		11 (10.5)	5 (6.9)	0.612
	Pulmonary and Extra-pulmonary involvement		17 (16.2)	12 (16.7)	
Start of symptoms to medical attention (Days)[2]			97.18 ± 161.2	103.58 ± 151.5	0.434
Duration of Hospitalization (Days)[3]			12.95 ± 8.3	13.80 ± 13.4	0.611

[1] The average percentage of band neutrophils and segmented neutrophils.
[2] The average number of days the patients were hospitalized.
[3] The average number of days between patients' symptom onset and their seeking medical attention.

DISCUSSION

In this investigation of 177 TB patients before and after the onset of the COVID-19 pandemic, we observed significant effects of prior COVID-19 infection on ESR levels, chest pain, hemoptysis, and the extent of pulmonary involvement. These results suggest that a preceding COVID-19 infection may exacerbate the progression of TB, leading to a more complex presentation. Despite finding no statistically significant changes in other studied categories, their clinical relevance remains crucial.

The global TB/COVID-19 study group conducted a comprehensive investigation on a global cohort with co-infections of COVID-19 and TB, identifying fever, dyspnea, and dry cough as prevalent symptoms. They reported a higher occurrence of co-infections in men with drug-susceptible pulmonary TB. Their CT imaging revealed both typical and atypical ground-glass opacities, sometimes coexisting with cavitary and infiltrative TB features (26). Despite the exclusion of patients with concurrent infections, dyspnea, dry cough, and fever were more frequently observed in our study, although none of these differences reached statistical significance. Notably, 53 out of 72 patients who developed TB after a COVID-19 infection exhibited dyspnea, 48 had fever, and 61 had cough. Imaging in our study also revealed bilateral pulmonary involvement. It is crucial to emphasize that our study focuses on the impact of a prior COVID-19 infection on subsequent TB infections, distinguishing it from the co-infection focus of the global TB/COVID-19 study group (26). The most significant changes between the clinical features were the occurrence of chest pain, hemoptysis, dyspnea, and loss of consciousness, most of which imply a more acute occurrence of symptoms. Among the paraclinical findings, ESR levels, bilateral pulmonary abnormalities on chest radiography, and mean segmental neutrophil counts were significantly different in the post-COVID-19 era. Comparatively, and in contrast to expectations, post-COVID patients had lower ESR levels compared to the pre-COVID era. All findings indicate a more insidious progression of the disease leading up to the acute onset of symptoms.

Tadolini et al. conducted a study on a cohort of 49 cases with both COVID-19 and TB infections, exploring the sequelae of this dual condition. They suggested that TB treatment might trigger a resurgence of COVID-19 infection and that high-resolution CT imaging could aid in identifying pre-existing TB. This implies the potential for bidirectional co-infections between TB and COVID-19 (27). In contrast, our study did not evaluate pre-existing TB reactivation triggered by a COVID-19 infection or vice versa. The significance of prior infection was not compared.

A study from Turkey reported two cases of simultaneous TB and COVID-19 infections, examining various comorbidities, symptoms (especially fever and sputum production), and laboratory tests. They noted that fever, nodular CT findings, and bilateral involvement were common in both cases (28). Consistently, our study revealed statistically significant bilateral lung involvement on imaging in TB patients with a prior history of COVID-19 infection.

In a study by Yang et al., symptomatic patterns of TB and COVID-19 were described separately in Wuhan and Zhejiang. They reported fever and cough as predominant COVID-19 symptoms (>80% each) in Wuhan, with shortness of breath and myalgia in 31% and 11%, respectively. They did not explore hemoptysis or evaluate co-infections of the two conditions. Imaging comparisons indicated that TB reactivation presents with more widespread lung involvement, resembling COVID-19 (29). Similarly, our findings highlight the statistical significance of bilateral lung involvement in TB patients with a prior history of COVID-19 infection, reinforcing the resemblance between the two conditions.

Limitations and Implications

While our study provides valuable insights, it is essential to acknowledge its limitations. The retrospective nature of the study and the exclusion of concurrent infections may limit the generalizability of our findings. Additionally, the absence of evaluation for pre-existing TB

complicates the comprehensive understanding of the bidirectional interactions between TB and COVID-19. Nevertheless, our results underscore the importance of considering a history of COVID-19 in TB patients, especially when encountering symptoms such as chest pain, hemoptysis, and elevated ESR levels, as these may indicate a more intricate clinical course.

The most notable limitation in our study was the inability to ascertain whether patients in the post-pandemic group had a latent TB infection, hindering a thorough evaluation of the impact of a COVID-19 infection on TB reactivation. Other limitations include the relatively small sample size and the discrepancy in the number of patients between the two groups. Further research is warranted to explore the intricate relationships between these two infectious diseases.

All patients admitted for COVID-19 to our institution during COVID-19 received steroids as part of their treatment unless contraindications existed. The long-term effects of steroids in suppressing the immune system, as well as the tapering process, could have exacerbated the patients' TB infections or increased their rate. Additionally, Remdesivir, used as our primary COVID-19 treatment, is not associated with increased TB infections. Tocilizumab, a monoclonal antibody used in COVID-19 treatment, was also used during this time, but given its scarcity in our region, it was not part of the treatment regimen for our patients.

CONCLUSION

In conclusion, our study underscores that prior COVID-19 infections might complicate TB infections. With overlapping clinical presentations and similar imaging features, coupled with the prevailing emphasis on managing COVID-19, there is a critical need for clinicians to remain vigilant about TB. Recognition of the intricate interactions between these infections is crucial for accurate diagnosis and effective management, particularly given the potential for bidirectional co-infections. As the medical community navigates the challenges posed by dual infectious threats, a comprehensive understanding of the interplay between TB and COVID-19 becomes essential for optimizing patient care and public health efforts.

Data Availability Statement

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

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Conflict of Interest

The authors have no conflicts of interest to declare.

REFERENCES

1. Shariq M, Sheikh JA, Quadir N, Sharma N, Hasnain SE, Ehtesham NZ. COVID-19 and tuberculosis: the double whammy of respiratory pathogens. ***Eur Respir Rev*** 2022;31(164):210264.
2. Organization WH. Global Tuberculosis Report 2021. In: WHO G, editor. 2021.
3. Chakaya J, Khan M, Ntoumi F, Aklillu E, Fatima R, Mwaba P, et al. Global Tuberculosis Report 2020 - Reflections on the Global TB burden, treatment and prevention efforts. ***Int J Infect Dis*** 2021;113 Suppl 1(Suppl 1):S7-S12.
4. Yilmaz E, Küçük S. The evaluation of the relationship between COVID-19 and autoimmune responses with a cross-sectional trial using medical records. ***J Infect Dev Ctries*** 2023;17(6):782-90.
5. Sironi M, Hasnain SE, Rosenthal B, Phan T, Luciani F, Shaw MA, et al. SARS-CoV-2 and COVID-19: A genetic, epidemiological, and evolutionary perspective. ***Infect Genet Evol*** 2020;84:104384.
6. Lewinsohn DM, Leonard MK, LoBue PA, Cohn DL, Daley CL, Desmond E, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines:

Diagnosis of Tuberculosis in Adults and Children. ***Clin Infect Dis*** 2017;64(2):111-5.

7. Meyer M, Clarke P, O'Regan AW. Utility of the lateral chest radiograph in the evaluation of patients with a positive tuberculin skin test result. ***Chest*** 2003;124(5):1824-7.
8. Daley CL, Gotway MB, Jasmer RM. Radiographic manifestations of tuberculosis: a primer for clinicians. San Francisco: Francis J. Curry National Tuberculosis Center; 2003.
9. Restrepo CS, Katre R, Mumbower A. Imaging Manifestations of Thoracic Tuberculosis. ***Radiol Clin North Am*** 2016;54(3):453-73.
10. Lee SW, Jang YS, Park CM, Kang HY, Koh WJ, Yim JJ, et al. The role of chest CT scanning in TB outbreak investigation. Chest 2010;137(5):1057-64.
11. Drug-Resistant Tuberculosis: A Survival Guide for Clinicians. 3rd edition ed: California Department of Public Health, Curry International TB Center. 2022.
12. Prevention CfDCa. Drug Susceptibility Testing: Centers for Disease Control and Prevention; 2012 [Available from: https://www.cdc.gov/tb/topic/laboratory/drug_testing.htm
13. Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, Dendukuri N. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. ***Cochrane Database Syst Rev*** 2014;2014(1):CD009593.
14. Boehme CC, Nabeta P, Hillemann D, Nicol MP, Shenai S, Krapp F, et al. Rapid molecular detection of tuberculosis and rifampin resistance. ***N Engl J Med*** 2010;363(11):1005-15.
15. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. ***Lancet*** 2020;395(10223):497-506.
16. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. ***JAMA*** 2020;323(11):1061-9.
17. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. ***Lancet*** 2020;395(10229):1054-62.
18. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. ***JAMA*** 2020;323(20):2052-9.
19. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. ***JAMA Intern Med*** 2020;180(7):934-43.
20. Del Valle DM, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, Wang B, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. ***Nat Med*** 2020;26(10):1636-43.
21. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. ***BMJ*** 2020;369:m1966.
22. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. ***Lancet Infect Dis*** 2020;20(4):425-34.
23. Wong HYF, Lam HYS, Fong AH, Leung ST, Chin TW, Lo CSY, et al. Frequency and Distribution of Chest Radiographic Findings in Patients Positive for COVID-19. ***Radiology*** 2020;296(2):E72-E78.
24. Byrne D, Neill SBO, Müller NL, Müller CIS, Walsh JP, Jalal S, et al. RSNA Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19: Interobserver Agreement Between Chest Radiologists. ***Can Assoc Radiol J*** 2021;72(1):159-66.
25. Bao C, Liu X, Zhang H, Li Y, Liu J. Coronavirus Disease 2019 (COVID-19) CT Findings: A Systematic Review and Meta-analysis. ***J Am Coll Radiol*** 2020;17(6):701-9.
26. TB/COVID-19 Global Study Group. Tuberculosis and COVID-19 co-infection: description of the global cohort. ***Eur Respir J*** 2022;59(3):2102538.
27. Tadolini M, Codecasa LR, García-García JM, Blanc FX, Borisov S, Alffenaar JW, et al. Active tuberculosis, sequelae and COVID-19 co-infection: first cohort of 49 cases. ***Eur Respir J*** 2020;56(1):2001398.
28. Can Sarınoğlu R, Sili U, Eryuksel E, Olgun Yildizeli S, Cimsit C, Karahasan Yagci A. Tuberculosis and COVID-19: An overlapping situation during pandemic. ***J Infect Dev Ctries*** 2020;14(7):721-5.
29. Yang H, Lu S. COVID-19 and Tuberculosis. ***J Transl Int Med*** 2020;8(2):59-65.