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MAJOR ARTICLE

Impact of *Strongyloides stercoralis* Coinfection on Disease Severity and Treatment Outcomes in Pulmonary Tuberculosis

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Background. This study investigates how *Strongyloides stercoralis* (Ss) infection impacts pulmonary tuberculosis (PTB) treatment outcomes, disease severity, and bacterial burdens in PTB patients with Ss coinfection.

Methods. We used chest x-rays and sputum smear grades to assess lung conditions and bacterial loads in 483 PTB patients. Ss infection was confirmed by seropositivity, and cytokine and profibrotic factor levels were analyzed using multiplex enzyme-linked immunosorbent assay. Treatment outcomes were categorized as favorable (cure without recurrence) or unfavorable (treatment failure or TB recurrence) during treatment or within 12 months postcure.

Results. PTB patients coinfected with Ss had significantly higher bacterial loads, increased risk of bilateral lung lesions, and greater likelihood of cavitary disease compared with those without Ss infection. The coinfected individuals exhibit significantly increased levels of cytokines (interleukin [IL]-4, IL-5, IL-13, interferon [IFN]-α, and IFN-β) and profibrotic factors (vascular endothelial growth factor, epidermal growth factor [EGF], fibroblast growth factor 2 [FGF-2], and PDGF-AB/BB [platelet-derived growth factor]) and significantly diminished levels of cytokines (IFN-γ and IL-2).

Conclusions. This study underscores the exacerbating impact of Ss coinfection on PTB severity and treatment outcomes, emphasizing the need for integrated management strategies for affected patients.

Keywords. cytokines; helminth infections; pulmonary tuberculosis; *Strongyloides stercoralis*; TB treatment outcome.

Pulmonary tuberculosis (PTB) remains a leading global cause of death, with 1.5 million reported fatalities worldwide [1]. Similarly, an estimated 1.5 billion people, or 24% of the global population, are affected with helminth infections, making helminths some of the most prevalent infections globally [2]. Among the diverse helminth infections, *Strongyloides stercoralis* (Ss), a soil-transmitted helminth affecting around 600 million individuals, stands out [3]. The significant overlap in geographical distribution between *Mycobacterium tuberculosis* (Mtb) and helminth infections adds complexity to the existing public health challenge [4, 5]. Despite epidemiological associations suggesting an increased TB risk with helminth infections [6, 7], clear data on their impact on bacterial burdens, PTB severity, and treatment outcomes are lacking.

Control of Mtb relies on the host's innate and adaptive immune responses [8]. Helminths manipulate host immunity by triggering intricate immune-regulatory circuits and inducing substantial helper type 2 (Th2) responses [9]. Immune alteration favors the survival, multiplication, and dissemination of Mtb, resulting in active TB and associated sequelae [10, 11]. Although cytokines play a critical role in the immune response to TB, the impact of Ss coinfection on cytokine responses in TB has not been explored in detail. Thus, understanding the influence of helminth coinfection in TB disease is crucial, as immunological responses to helminths could impact the control of TB disease and treatment outcomes [12].

Our study hypothesizes that coinfection with helminths might increase the disease severity and pathogenesis of TB due to altered immune responses. Testing this hypothesis can guide research aimed at understanding the interactions between these 2 infections and their implications for treatment and public health strategies. Addressing this knowledge gap, our study aimed to compare bacterial burdens, disease severity, and TB treatment outcomes in PTB individuals with or without Ss coinfection. This research not only holds significance for unraveling the intricate dynamics within

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coinfected individuals but also has the potential to guide strategies for enhanced diagnosis, treatment, and disease control, particularly in regions where TB and intestinal helminths commonly coexist.

METHODS

Ethics Statement

The study received approval from the ethics committees of the National Institute for Research in Tuberculosis (NIRT) and the Prof. M. Viswanathan Diabetes Research Center (ECR/51/INST/TN/2013/MVDRC/01). Informed written consent was obtained from all participants, and study procedures adhered to institutional ethical committee guidelines.

Study Population and Data Variables

The study involved participants from Chennai, South India, enrolled in the prospective Effect of Diabetes on Tuberculosis Severity (EDOT) study from February 2014 to August 2018. Adult individuals aged 20 to 75 with new positive sputum smears and culture were recruited in this study. Individuals with PTB were diagnosed by positive solid cultures in Lowenstein-Jensen medium. Chest x-rays were used to determine cavitary disease as well as unilateral vs bilateral involvement. Chest x-rays were read by 2 independent radiologists. Smear grade was used to determine bacterial burdens and classified as 1+, 2+, and 3+. The laboratory investigators were blinded to the chest x-ray and bacteriology results. Those with previous TB episodes, prior TB treatment, drug-resistant TB, positive HIV status, immune suppression medications, pregnancy, and lactation were excluded from this study, and reasons for excluding them were immunosuppressive medications (eg, corticosteroids, biologics, chemotherapy) and that HIV can alter immune responses, complicating the interpretation of immunology studies by confounding results. Pregnant individuals were excluded due to immune changes during pregnancy that may lead to relative immune compromise, affecting study outcomes; also, these are priority populations at increased risk for reactivation of latent tuberculosis and conversion to active pulmonary TB. All recruited pulmonary TB patients received anti-TB treatment through Directly Observed Treatment Short course (DOTS) therapy as per WHO recommendations and were monitored by the National Tuberculosis Elimination Program (NTEP). Follow-up extended to 6 months of treatment and 1 year post–treatment completion, involving a total of 483 culture-confirmed PTB individuals, with 74 positive for *S. stercoralis* infection and 409 negative. Treatment completion without loss to follow-up was another inclusion criterion for the study. Treatment outcomes were defined as favorable or unfavorable. Favorable treatment outcome (cure) was defined as negative results of sputum cultures at months 5 and 6 of treatment without recurrent disease during follow-up. Unfavorable treatment outcomes included treatment failure, defined as positive sputum culture results at month 5 or 6, all-cause mortality, or recurrent TB within 12 months after initial cure. These participants did not receive any treatment for helminth infection.

Diagnostic Procedures

Diagnosis of Ss infection utilized the presence of immunoglobulin G antibodies to the recombinant NIE (31-kDa recombinant antigen) antigen, comprising a sensitivity of 97% and specificity of 95% [13]. Filarial infection exclusion was confirmed through negative tests for circulating filarial antigen (TropBio Og4C3 assay). We did not perform stool examinations and relied only on seropositivity as a diagnostic for Ss infection as per the study protocol.

Multiplex Assays for Cytokines and Profibrotic Factors

Circulating plasma cytokine and profibrotic factor levels were measured in a subset of Ss+/PTB+ (n = 74) and Ss-/PTB+ (n = 409) individuals using the multiplex Luminex assay (Bio-Rad Laboratories, Inc.). The analytes measured were cytokines (IFN-γ, IL-2, TNF-α, IL-4, IL-5, IL-13, IFN-α, IFN- β) and profibrotic factors (vascular endothelial growth factor [VEGF], EGF [epidermal growth factor], FGF-2 [fibroblast growth factor 2], and PDGF-AB BB [platelet-derived growth factor]) in PTB individuals with or without Ss infection. The experiment was carried out according to the manufacturer's instructions (R&D systems). The standard ranges of each cytokine were as follows: IFN-γ 49.18–11 950 pg/mL, TNF-α 8.89–2160 pg/mL, IL-2 31.11–7560 pg/mL, IL-4 15.72–3820 pg/mL, IL-5 6.5–1580 pg/mL, IL-13 367.78–89 370 pg/mL, IFN-α 5.31–1290 pg/mL, and IFN-β 16.3–3960 pg/mL.

Statistical Analysis

Before analysis, the data were thoroughly checked for completeness and consistency. Continuous variables were examined for normality using the Shapiro-Wilks test and were found not to be normal. The data were then presented using frequency, percentage, median, and quartiles. Differences in continuous variables between the Ss+ and Ss- groups were examined using the Wilcoxon rank-sum test, while the relationships between groups and factors such as sputum smear grade, bilateral lung lesion, cavitary lesion, and tuberculosis treatment failure and relapse were examined using the Pearson chi-square test. Generalized linear models with binomial regression and log-link functions were used to identify key factors. Prevalence ratios (PRs) and adjusted prevalence ratios (aPRs) were calculated along with the corresponding 95% CIs. Covariates with significant PRs, such as sex, smoking status, and anemia, were taken into account when adjusting for aPR. The data analysis was performed using STATA software, version 15.0 (StataCorp, College Station, TX, USA), with all *P* values considered 2-sided and statistical significance set at the .05 α level.

RESULTS

Demographics of the Study Population

The study comprised 483 individuals diagnosed with pulmonary tuberculosis, among whom 74 were positive for Ss infection (Ss+) and 409 were negative (Ss-). The median age (interquartile range [IQR]) was 44 (36–51.5) years for Ss+ and 45 (36–52) years for Ss-. While no significant differences were observed in age, body mass index (BMI), alcohol use, socioeconomic status, geographical location, or HbA1c levels, significant differences were noted in gender (male), smoking, and anemia between Ss+ and Ss- individuals (Table 1).

S. stercoralis Is Associated With Increased Radiographic TB Disease Severity and Greater Bacterial Burdens

Ss+ was associated with an increased risk of bilateral lung lesions (PR, 4.09; 95% CI, 2.57–6.49; $P < .001$) and cavitation (PR, 4.96;

Table 1. Demographics and Clinical Characteristics of the Study Population by *Strongyloides stercoralis* Coinfection

Variable	Overall (n = 483)	Ss- (n = 409)	Ss+ (n = 74)	*P* Value[a]
Age, median (IQR), y	45.0 (36.0–52.0)	45.0 (36.0–52.0)	44.0 (36.0–51.5)	.426
Age classification, No. (%)				.376
Up to 35 y	112 (23.2)	97 (23.7)	15 (20.3)	
36–45 y	136 (28.2)	109 (26.7)	27 (36.5)	
46–55 y	153 (31.7)	133 (32.5)	20 (27.0)	
>55 y	82 (17.0)	70 (17.1)	12 (16.2)	
Gender, No. (%)				.009
Female	139 (28.8)	127 (31.1)	12 (16.2)	
Male	344 (71.2)	282 (68.9)	62 (83.8)	
Body mass index, median (IQR), kg/m^2	20.03 (17.50–23.30)	20.00 (17.42–23.37)	20.69 (18.22–23.00)	.539
Body mass index classification, No. (%)				.591
Normal (18.5–22.9 kg/m^2)	190 (39.3)	156 (38.1)	34 (45.9)	
Undernourished (<18.5 kg/m^2)	154 (31.9)	134 (32.8)	20 (27.0)	
Overweight (23.0–24.9 kg/m^2)	91 (18.8)	77 (18.8)	14 (18.9)	
Obesity (≥25 kg/m^2)	48 (9.9)	42 (10.3)	6 (8.1)	
HbA1c%, median (IQR)	6.80 (5.80–10.40)	6.80 (5.80–10.30)	6.80 (5.80–10.95)	.738
Diabetes mellitus (HbA1c%), No. (%)				.425
No DM (<5.7%)	94 (19.5)	83 (20.3)	11 (14.9)	
Pre-DM (5.7%–6.4%)	127 (26.3)	104 (25.4)	23 (31.1)	
DM (≥6.5%)	262 (54.2)	222 (54.3)	40 (54.1)	
Smoking status, No. (%)				<.001
Nonsmoker	139 (28.8)	133 (32.5)	6 (8.1)	
Smoker	125 (25.9)	71 (17.4)	54 (73.0)	
Unknown	219 (45.3)	205 (50.1)	14 (18.9)	
Alcohol status, No. (%)				.614
Nonalcoholic	249 (51.6)	214 (52.3)	35 (47.3)	
Alcoholic	75 (15.5)	61 (14.9)	14 (18.9)	
Unknown	159 (32.9)	134 (32.8)	25 (33.8)	
Household income <5000 INR/mo, %	17.8	18.2	17.1	.3911
Anemia, median (IQR), g/dL	12.40 (11.10–13.90)	12.60 (11.20–14.00)	11.65 (10.93–12.73)	<.001
Anemia (female: <12 g/dL & male: <13 g/dL) classification, No. (%)				<.001
No anemia	223 (46.2)	206 (50.4)	17 (23.0)	
Anemia	260 (53.8)	203 (49.6)	57 (77.0)	
Cavitary lung lesions, No. (%)				<.001
No cavitary lung lesions	305 (63.1)	286 (69.9)	19 (25.7)	
Cavitary lung lesions	178 (36.9)	123 (30.1)	55 (74.3)	
Bilateral lung lesions, No. (%)				<.001
No bilateral lung lesions	306 (63.4)	284 (69.4)	22 (29.7)	
Bilateral lung lesions	177 (36.6)	125 (30.6)	52 (70.3)	
AFB smear testing, No. (%)				<.001
Smear negative	312 (64.6)	294 (71.9)	18 (24.3)	
Smear positive	171 (35.4)	115 (28.1)	56 (75.7)	
TB treatment outcome, No. (%)				.019
Favorable outcome	404 (83.6)	349 (85.3)	55 (74.3)	
Rx failure/relapse	79 (16.4)	60 (14.7)	19 (25.7)	

[a]Wilcoxon rank-sum test; Pearson's chi-square test.

Abbreviations: AFB, acid fast bacillus; DM, diabetes mellitus; INR, Indian rupee; IQR, interquartile range; TB, tuberculosis.

95% CI, 3.04–8.08; $P < .001$). After adjusting for confounding variables, Ss+ remained significantly associated with higher risk of bilateral lung lesions (aPR, 2.70; 95% CI, 1.61–4.52; $P < .001$) and cavitation (aPR, 3.33; 95% CI, 1.95–5.68; $P < .001$), indicating increased TB disease severity in Ss+ individuals. Ss+ was associated with an elevated risk of smear grade (PR, 5.68; 95% CI, 3.45–9.34; $P < .001$). Furthermore, Ss+ remained significantly associated with increased smear grade after adjusting for confounding variables (aPR, 3.83; 95% CI, 2.22–6.63; $P < .001$), indicating higher bacterial burdens in PTB patients with Ss+ infection (Table 2).

S. stercoralis Is Associated With Altered Levels of Cytokines and Profibrotic Factors in PTB

To assess the impact of coincident Ss infection on cytokines and profibrotic factors in PTB individuals, we measured the plasma levels of cytokines (interferon [IFN]-γ, tumor necrosis factor [TNF]–α, interleukin [IL]-2, IL-4, IL-5, IL-13, IFN-α, IFN-β) and profibrotic factors (VEGF, EGF, FGF-2, PDGF-AB BB) in PTB individuals with or without Ss infection. The circulating levels of TNF-α were not significantly different between PTB Ss+ and PTB Ss- individuals. However, cytokines IFN-α (gemoetric mean [GM] of 27.16 pg/mL vs 21.75 pg/mL;

Table 2. Association of Ss Infection With Bacterial Burden, Disease Severity, and Treatment Failure/Relapse in PTB

Outcome Variable	SsI/PTB PR (95% CI)	*P* Value	SsI aPR (95% CI)	*P* Value
Bacterial burden				
Sputum smear grade	5.68 [3.45–9.34]	<.001	3.83 [2.22–6.63]	<.001
Disease severity				
Bilateral lung lesions	4.09 [2.57–6.49]	<.001	2.70 [1.61–4.52]	<.001
Cavitary lung lesions	4.96 [3.04–8.08]	<.001	3.33 [1.95–5.68]	<.001
TB treatment failure/relapse	1.77 [1.11–2.81]	.016	1.65 [0.98–2.79]	.060

The aPR models were adjusted for gender, smoking status, and anemia, as these factors showed a significant PR.

Abbreviations: aPR, adjusted prevalence ratio; PR, prevalence ratio; PTB, pulmonary tuberculosis; Ss, *Strongyloides stercoralis*; SsI, *Strongyloides stercoralis* infection; TB, tuberculosis.

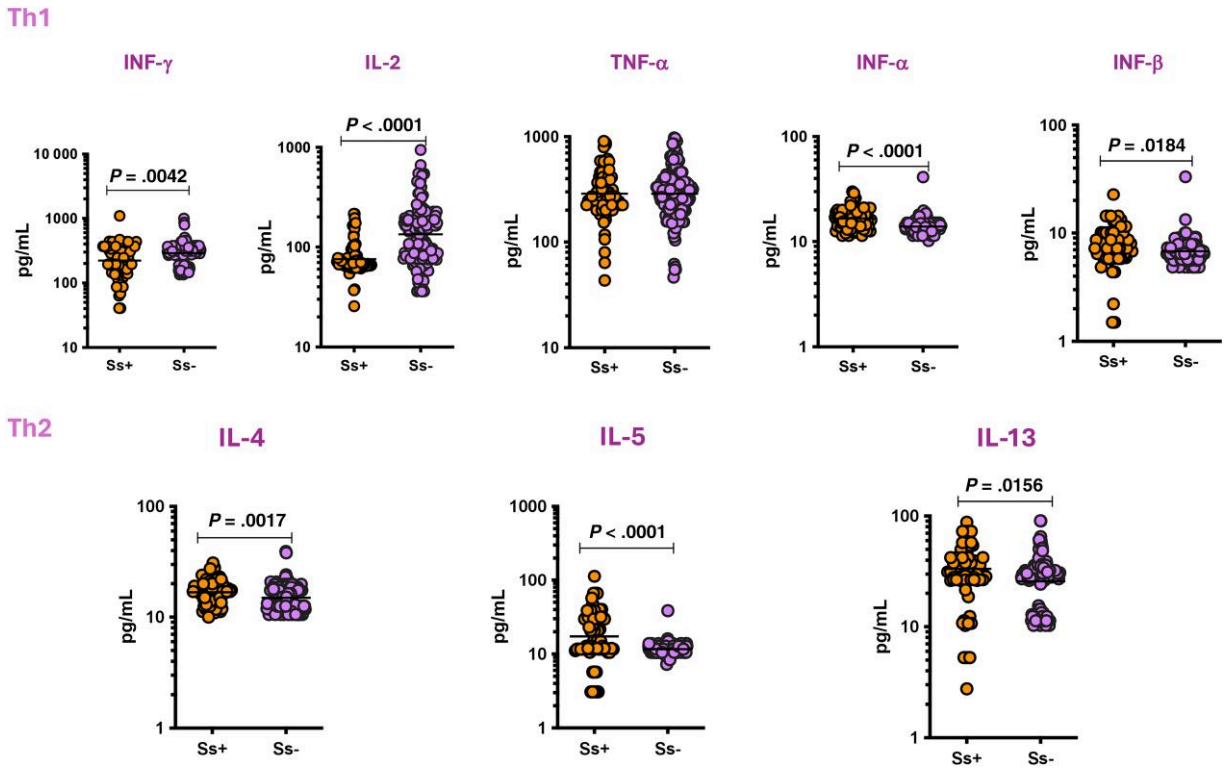

Figure 1. Cytokine levels in Ss+ & Ss- individuals with PTB. The plasma levels of cytokines (IFN-γ, TNF-α, IL-2, IFN-α, IFN-β, IL-4, IL-5, and IL-13) were measured by multiplex enzyme-linked immunosorbent assay in Ss+ & PTB (n = 74) and Ss- & PTB (n = 409) individuals. The results are shown as scatter plots, with each circle representing a single individual and the bar representing the GM. *P* values were calculated using a Mann-Whitney test with Holm's correction for multiple comparisons. Abbreviations: GM, gemoetric mean; IFN, interferon; IL, interleukin; PTB, pulmonary tuberculosis; SS, *Strongyloides stercoralis*; TNF, tumor necrosis factor.

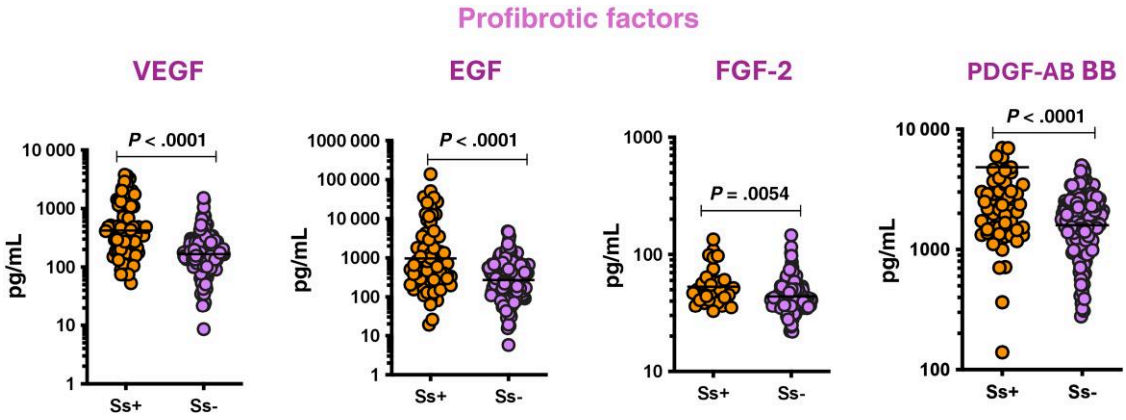

Figure 2. Cytokine levels in Ss+ & Ss- individuals with PTB. The plasma levels of profibrotic factors (VEGF, EGF, FGF-2, and PDGF-AB BB) were measured by multiplex enzyme-linked immunosorbent assay in Ss+ & PTB (n = 74) and Ss- & PTB (n = 409) individuals. The results are shown as scatter plots, with each circle representing a single individual and the bar representing the GM. *P* values were calculated using a Mann-Whitney test with Holm's correction for multiple comparisons. Abbreviations: EGF, ; FGF-2, ; GM, ; PDGF-AB BB, ; PTB, pulmonary tuberculosis; SS, *Strongyloides stercoralis*; VEGF, vascular endothelial growth factor.

$P < .0001$), IFN-β (GM of 27.16 pg/mL vs 21.75 pg/mL; $P = .0184$), IL-4 (GM of 14.04 pg/mL vs 10.91 pg/mL; $P = .0017$), IL-5 (GM of 14.04 pg/mL vs 10.91 pg/mL; $P < .0001$), and IL-13 (GM of 14.04 pg/mL vs 10.91 pg/mL; $P = .0156$) (Figure 1) and profibrotic factors VEGF (GM of 14.04 pg/mL vs 10.91 pg/mL; $P < .0001$), EGF (GM of 14.04 pg/mL vs 10.91 pg/mL; $P < .0001$), FGF2 (GM of 14.04 pg/mL vs 10.91 pg/mL; $P = .0054$), and PDGF-AB BB (GM of 14.04 pg/mL vs 10.91 pg/mL; $P < .0001$) (Figure 2) were significantly elevated in PTB Ss+ individuals in comparison with PTB Ss- individuals. In contrast, the circulating plasma levels of cytokines IFN-γ (GM of 10.37 pg/mL vs 12.04 pg/mL; $P = .0042$) and IL-2 (GM of 10.37 pg/mL vs 12.04 pg/mL; $P < .0001$) (Figure 1) were significantly diminished in PTB Ss + individuals when compared with PTB Ss- individuals. Thus, Ss+ is associated with altered levels of cytokines and heightened levels of profibrotic factors in PTB individuals. Our findings imply that the dominance of Th2 responses in the presence of helminths might suppress Th1 responses, potentially leading to an inadequate immune response against TB; also, profibrotic factors play a crucial role in the pathology of TB–helminth coinfections, contributing to lung fibrosis and complicating disease management.

S. stercoralis Is Associated With Increased Risk of Unfavorable TB Treatment Outcomes

Univariate analysis revealed that Ss+ was associated with an increased risk of unfavorable treatment outcomes (PR, 1.77; 95% CI, 1.11–2.81; $P = .016$). Similarly, Ss+ remained significantly associated with unfavorable treatment outcomes after adjusting for confounding variables (aPR, 1.65; 95% CI, 0.98–2.79; $P = .060$); after adjusting for confounders, the aPR of 1.65 was no longer statistically significant, but the *P* value of .06 was close to the threshold for significance, indicating a risk of treatment failure or TB recurrence in PTB patients with Ss+ infection (Table 2).

DISCUSSION

Identifying risk factors associated with TB disease severity, bacterial burdens, and treatment outcomes is crucial for public health interventions. Undernutrition, HIV infection, alcohol use, smoking, and diabetes are widely recognized risk factors for unfavorable treatment outcomes in PTB [13–15]. Elevated bacterial burdens and increased cavitary disease are linked to higher transmission rates and poorer treatment outcomes [16, 17]. Therefore, elucidating these risk factors provides valuable insights for targeted interventions to improve TB management.

Previous studies investigating the association between helminth infections and TB disease severity have encountered methodological limitations, such as small sample sizes and inconsistent case definitions [12]. While some studies have suggested a potential link between helminth infections and increased disease involvement in TB-affected lung zones [18], findings from other research on *Mycobacterium leprae* have indicated a more severe presentation of leprosy in helminth-infected individuals [19]. However, conflicting evidence exists, with some studies reporting an association between helminth coinfection and lower sputum smear grades in TB patients [20]. In contrast, our previous study clearly demonstrated that Ss infection is associated with higher bacterial burden and exacerbated disease severity in PTB individuals in a different cohort [21]. The inconsistent findings in the literature underscore the need for robust, well-designed studies with larger sample sizes and standardized methodologies to elucidate the relationship between helminth infections and TB disease severity.

Existing studies, including our previous work, have established that helminth infections can significantly affect both innate and adaptive immune responses to mycobacterial antigens, even in cases of latent TB [7, 22–26]. Specifically, concurrent infections with filaria have been shown to markedly suppress protective responses to mycobacteria, notably Th1 and Th17 responses, as well as TLR-mediated immune reactions in latent TB, indicating a potential pathway through which helminth infections may facilitate the progression to active TB [22, 23]. Infections with helminths like *Strongyloides stercoralis* (Ss) and *Schistosomes* are known to amplify regulatory T-cell responses, thereby suppressing Th1 responses in latent TB [7]. Coinfections with helminths have also been associated with reduced monocyte activation, increased M2 macrophage polarization, diminished monocyte functionality, and lower T-cell activation in individuals with latent TB infection (LTBI), with these altered functions being partly reversible through anthelmintic treatment [24]. Furthermore, Ss infection has been linked to changes in systemic cytokine levels and other proinflammatory indicators in individuals with coinfections [25]. Treatment with anthelmintics has also been observed to alter systemic and TB antigen–stimulated cytokine profiles in individuals coinfected with Ss and LTBI [26].

Our research builds upon previous discoveries, confirming the impact of Ss infection on the modulation of systemic cytokines and profibrotic factor responses in PTB. Helminth infections are known for their extensive influence on immune responses, altering type 1, type 2, and type 17 cytokines, alongside other pro-inflammatory reactions in coinfected individuals [27–29]. This immune response modulation by helminths leads to advanced, more severe forms of active TB and therapeutic challenges [30]. *Mtb* infection induces type I IFN expression in human and mouse models. Additionally, the discovery of IFN-related gene signatures in patients with active TB disease has created significant momentum behind investigation of the innate immune pathways and pathophysiological consequences of type I IFN expression during *Mtb* infection [31, 32]. VEGF has been associated with pleural inflammation and fibrosis, with altered endothelial functions observed in PTB patients. Studies by Ferrian et al. have indicated that individuals with smear-positive and culture-positive TB exhibit elevated levels of VEGF compared with those who are smear-negative and culture-negative [33]. Additionally, systemic VEGF levels have been noted to rise more significantly in PTB patients with cavitations and bilateral disease involvement [34]. In our study, we noted a marked increase in cytokines (IL-4, IL-5, IL-13, IFN-α, and IFN-β) and profibrotic factors (VEGF, EGF, FGF-2, and PDGF-AB BB) and a notable decrease in cytokines (IFN-γ and IL-2) in PTB patients with concurrent Ss infection. This pattern suggests that Ss infection leads to a suppression of type 1 cytokine responses while elevating type 2 cytokine, type 1 interferon, and growth factor responses, thereby providing a potential biological explanation for the heightened disease severity observed in PTB patients with Ss coinfection.

In this study, several factors known to influence disease severity and bacterial burdens, including age, gender, BMI, diabetes mellitus (DM), smoking status, anemia, and alcohol use, were carefully controlled for. Importantly, the study groups were well matched at baseline, with no significant differences observed in age, alcohol consumption, BMI, or DM between the Ss+ and Ss- groups. However, notable differences were observed in gender, smoking, and anemia between the 2 groups. Despite these baseline differences, the significant association of Ss infection with PTB remained evident. This baseline comparability is essential as it ensures that any observed variations in clinical, hematological, and immunological parameters can be attributed to the presence or absence of helminth infections, rather than preexisting discrepancies in the study populations.

The findings of this study provide valuable insights into the association between Ss+ infection and disease severity, bacterial burdens, and treatment outcomes in individuals with PTB. Our analysis revealed several noteworthy observations that warrant further discussion. First, our results indicate that PTB patients coinfected with Ss+ exhibit more severe disease manifestations compared with those without Ss infection. Specifically, Ss+ individuals demonstrated a higher prevalence of bilateral lung lesions and cavitation, both of which are indicative of advanced TB disease. These findings align with previous studies suggesting that helminth infections can exacerbate TB disease severity by modulating the host immune response and promoting tissue damage.

Furthermore, our analysis revealed a significant association between Ss+ infection and increased bacterial burdens in PTB patients. Higher smear grades, indicative of greater bacterial load, were consistently observed among individuals with Ss+ infection. This suggests that Ss+ coinfection may contribute to enhanced Mtb replication and dissemination within the host, potentially leading to more severe disease progression and increased transmission rates. Importantly, our study also highlights the impact of Ss+ infection on treatment outcomes in PTB. We found that individuals coinfected with Ss+ were at a significantly higher risk of experiencing unfavorable treatment outcomes, including treatment failure or TB recurrence. This underscores the importance of considering helminth infections in the management of TB by instituting routine helminth infection screening at TB diagnosis, as coinfection may impede treatment efficacy and contribute to prolonged disease duration and increased risk of transmission.

Our study suffers from the limitations of not performing stool examinations and relying only on seropositivity as a diagnostic for Ss infection. Additionally, it is important to note that it remains uncertain whether any seropositive participants had previously been treated with ivermectin. Nevertheless, our data

provide an important advance in the understanding of the effect of multiple infections within the same individual in terms of pathology and bacteriology. The observed associations between Ss+ infection and disease severity, bacterial burdens, and treatment outcomes underscore the need for integrated approaches to TB management that address coexisting helminth infections. Strategies aimed at controlling helminth infections, such as mass drug administration, deworming campaigns, and improved sanitation, may complement existing TB control efforts and help mitigate the impact of coinfections on TB outcomes to align with the End TB strategy.

Overall, our findings contribute to a better understanding of the complex interactions between helminth infections and TB and emphasize the importance of considering coinfections in TB control strategies. Further research is needed to elucidate the exact mechanism of cytokine modulation in TB immunopathogenesis and explore potential therapeutic strategies targeting helminth infection to improve TB management and outcomes in coinfected individuals. Our study finds that including *S. stercoralis* screening in TB patients and promoting the integration of deworming into national TB control programs are practical, actionable solutions.

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Author contributions. S.B. and N.P.K. designed the study. S.M., A.N., and K.M. conducted experiments. N.P.K., A.N., and S.S. acquired data. N.P.K., K.T., and S.M. analyzed data. S.B., H.K., S.N., V.V., and S.S. contributed reagents and revised subsequent drafts of the manuscript. V.V. and S.H. were responsible for the enrollment of the participants and contributed to the acquisition and interpretation of clinical data. S.B., N.P.K. and S.M. wrote the manuscript. All authors read and approved the final manuscript.

Data availability. All the reported data are available within the manuscript.

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Potential conflicts of interest. All other authors report no potential conflicts.

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