frontiers | Frontiers in Tropical Diseases

TYPE Brief Research Report
PUBLISHED 20 August 2024
DOI 10.3389/fitd.2024.1412871

OPEN ACCESS

EDITED BY
Radha Gopalaswamy,
National Institute of Research in Tuberculosis (ICMR), India

REVIEWED BY
Selvakumar Subbian,
The State University of New Jersey, United States
Parvinder Kaur,
Foundation for Neglected Disease Research (FNDR), India

*CORRESPONDENCE
Andrea Gori
andrea.gori@unimi.it

RECEIVED 05 April 2024
ACCEPTED 01 August 2024
PUBLISHED 20 August 2024

CITATION
Genovese C, Colaneri M, Pagano S, Schiuma M, Galli L, Fama F, Antinori S, Gori A and Torre A (2024) Assessing the prevalence of schistosomiasis and strongyloidiasis in a tuberculosis clinic: the TB-TROPIcare study. *Front. Trop. Dis* 5:1412871.
doi: 10.3389/fitd.2024.1412871

Assessing the prevalence of schistosomiasis and strongyloidiasis in a tuberculosis clinic: the TB-TROPIcare study

Camilla Genovese[1,2], Marta Colaneri[1,3], Simone Pagano[1,2], Marco Schiuma[1], Lucia Galli[1,2], Federico Fama[1,2], Spinello Antinori[1,2], Andrea Gori[1,2,3]* and Alessandro Torre[1]

[1]Department of Infectious Diseases, ASST Fatebenefratelli Sacco University Hospital, Milan, Italy, [2]Department of Biomedical and Clinical Sciences, Università degli Studi di Milano, L. Sacco Hospital, Milan, Italy, [3]Centre for Multidisciplinary Research in Health Science (MACH), Università degli Studi di Milano, Milan, Italy

Introduction: In recent years, Europe has experienced a significant flux of migrants, often hailing from regions endemic for schistosomiasis and strongyloidiasis, diseases frequently overshadowed by tuberculosis (TB) in healthcare priorities. While TB remains a prevalent concern among this population, chronic schistosomiasis and strongyloidiasis are frequently neglected. Motivated by this observation, we aimed to investigate the prevalence of schistosomiasis and strongyloidiasis in patients attending our TB outpatient clinic.

Methods: We conducted a retrospective, observational study spanning from June 2020 to January 2024, focusing on patients attending the TB outpatient clinic of Luigi Sacco Hospital of Milan, Italy. Serology tests were performed in patients with a history suggestive of exposure to either *Schistosoma* spp. or *Strongyloides stercoralis*.

Results: Among the 228 patients included in the study, 84 (36.8%) individuals were born in Italy, one came from Spain, 80 (35.1%) from strongyloidiasis moderate or high endemic countries and 63 (27.6%) from areas endemic for schistosomiasis and strongyloidiasis. Of these patients, 160 (70.2%) were diagnosed with tuberculosis disease, while 68 (29.8%) had tuberculosis infection. The prevalence of schistosomiasis was 26.7%, while that of strongyloidiasis was 7.8%. Notably, 3 patients tested positive for both infections.

Conclusion: Our study highlights the often-underestimated prevalence of schistosomiasis and strongyloidiasis among migrants accessing healthcare for TB, underscoring the importance of increased awareness and targeted screening within this population.

KEYWORDS

neglected tropical diseases, tuberculosis, helminthiases, schistosomiasis, strongyloidiasis, prevalence

Background

Neglected tropical diseases (NTDs), including schistosomiasis and strongyloidiasis, have gained attention due to increased migration to Europe from endemic regions. Despite being considered rare in high-income countries, *Schistosoma* spp. infections affect nearly 780 million people worldwide, and *Strongyloides stercoralis* infections surpass 600 million people globally (1, 2). Other than the burden associated with the acute infections caused by these two microorganisms, chronic infections by *Schistosoma* spp. and *Strongyloides stercoralis* are associated with significant morbidity and mortality, highlighting the importance of gaining deeper knowledge about the prevalence of these conditions. Specifically, chronic schistosomiasis might be complicated by liver cirrhosis, kidney disease, bladder cancer, and infertility (3–5), while chronic strongyloidiasis can cause urticaria, diarrhea and asthma. Severe complications of strongyloidiasis usually affect immunocompromised individuals and include hyper- and disseminated- infections, which are life-threatening (6, 7).

Schistosomiasis is caused by 5 *Schistosoma* spp. species, *Schistosoma haematobium*, *Schistosoma mansoni*, *Schistosoma. japonicum*, *Schistosoma intercalatum* and *Schistosoma mekongi*, each endemic to different regions, predominantly in Africa, Asia (e.g., China, Cambodia, Laos, Philippines), and South America (e.g., Brazil, Venezuela) (8). Similarly, *Strongyloides stercoralis* is widespread in Africa, Asia, South America and in some Eastern European countries (9).

With increasing migration rates to Europe, the number of individuals at risk of these infections is rising. In fact, a recent systematic review by Asundi et al. reported a seroprevalence of 12.2% for strongyloidiasis and of 18.4% for schistosomiasis in migrants who reside in countries with low endemicities (10). Moreover, while these infections are often imported by tourists or migrants from endemic regions, in Italy, cases of strongyloidiasis have been reported in individuals born before 1952 (11), and autochthonous schistosomiasis cases have emerged in Corsica, France, in recent years (12). Epidemiological studies in Italy reveal in migrants varying prevalence rates of strongyloidiasis, ranging from 4.5% to 17%, and schistosomiasis ranging from 6% to 27% (11, 13–15). However, the actual burden may be underestimated, particularly among migrants, due to prioritization of other conditions such as tuberculosis (TB) or HIV.

The Italian Society of Tropical Medicine and Global Health (SIMET) has issued recommendations for managing these infections in non-endemic countries, advocating for screening in individuals born or residing in endemic areas. Specifically, screening of schistosomiasis and strongyloidiasis should be performed in all individuals who were born or have resided for a cumulative period of at least one year in areas endemic for either one of these two conditions (16, 17).

However, implementing screening programs is challenging, especially among hard-to-reach populations like asylum seekers and refugees (18, 19). Screening and prevention activities can therefore be performed in specific contexts: at the arrival in the hosting country or in reception centers and shelters. In these settings, though, resources are often limited and reserved to assess conditions which are considered more urgent, both from a clinical and a public health point of view. Since TB remains a prevalent condition among migrants, requiring months of treatment and several follow up appointments, TB outpatient clinics offer a unique opportunity for schistosomiasis and strongyloidiasis screening.

Motivated by these challenges, our study aimed to assess the prevalence of schistosomiasis and strongyloidiasis in our TB outpatient clinic.

Methods

We conducted a retrospective, monocentric, observational study including patients who attended the TB outpatient clinic of Luigi Sacco Hospital of Milan, Italy, from June 2020 to January 2024.

Objectives

The primary objective of the study was to evaluate the prevalence of strongyloidiasis and schistosomiasis among patients attending the TB outpatient clinic who underwent serological testing for *Schistosoma* spp. and *Strongyloides stercoralis*.

The secondary objectives of the study were to delineate the demographic and clinical characteristics of patients who tested positive for the strongyloidiasis and schistosomiasis serological tests, and to discern variances between patients who tested positive *vs* negative on the strongyloidiasis and schistosomiasis serological examinations.

Patients and setting

All patients aged more than 18 years evaluated at the TB outpatient clinic at Luigi Sacco Hospital were consecutively included in the study. Patients attending the TB outpatient clinic typically have either a TB disease (TBD, also known as active TB disease) or TB infection (TBI, also known as latent TB infection) (20). They are routinely referred to the clinic when diagnosed with either of the two abovementioned conditions in other settings (e.g., from the Infectious Diseases Inpatient Department or other hospitals which do not have outpatient department dedicated to TB patients).

Schistosomiasis and strongyloidiasis screening and management

During their initial evaluation, patients underwent routine microbiological and biochemical screening (e.g. full blood count, liver and renal function tests, C-reactive protein, erythrocyte sedimentation rate, serologies for HIV, hepatitis B and C and syphilis), accounting for around 3 mL of plasma and 8.5 mL of serum. Individuals at risk of past exposure to *Schistosoma* spp. or *Strongyloides stercoralis* underwent NovaTec Immunodiagnostica

GmBh® enzyme-linked immunosorbent assay (ELISA) for the qualitative detection of serum IgG antibodies against *Schistosoma mansoni* and *Strongyloides stercoralis* (16, 17, 21).

Stool and urine microscopy parasitological tests were subsequently performed in those testing positive at serology. Specifically, urine collection was performed for every patient who tested positive for *Schistosoma* specific IgG and came from countries at risk for *Schistosoma haematobium* infection. Patients were given a plastic jar to collect their 24h-urine sample, which was then sent to the Microbiology laboratory of Luigi Sacco Hospital. Urine samples were centrifugated before realizing a microscopy exam (at 40x and 100x) for the detection of *Schistosoma haematobium* eggs. Instead, patients who tested positive for schistosomiasis or strongyloidiasis were asked to collect three Para-Pak® PLUS Ecofix stool samples produced in different days. Stool samples were also sent to Microbiology laboratory for microscopic examination (at 40x and 100x). Additionally, three other stool samples produced in different days were collected from patients who tested positive for strongyloidiasis and sent within 24 hours to the microbiology laboratory for specific stool culture.

Treatment with praziquantel or ivermectin was proposed to all patients with a probable schistosomiasis or strongyloidiasis (defined as a positive serology and a positive history of stay in an endemic country 3 months prior presentation) (16, 17, 21). Praziquantel, which required in-hospital administration, was given with food at the dosage of 40 mg/kg in a single dose for patients coming from countries endemic for *Schistosoma mansoni*, *Schistosoma haematobium* and *Schistosoma intercalatum*, while patients coming from countries endemic for *Schistosoma japonicum* and *Schistosoma mekongi* were administered 60 mg/kg divided in two subsequent doses (16). Ivermectin was given at the dosage of 200 mgc/kg in two consecutive days (22).

Definitions

Individuals at risk for schistosomiasis were defined as individuals born or who have resided for at least one cumulative year in schistosomiasis-endemic countries. Individuals at risk for strongyloidiasis were defined as individuals born or who have resided for at least one cumulative year in countries with moderate to high endemicity for *Strongyloides stercoralis*, as well as individuals born or who have resided in Italy before 1952.

The endemic countries for strongyloidiasis and the high-risk countries for schistosomiasis were defined based on national and international recommendations (16, 17, 21).

Demographic and clinical data, including comorbidities and coinfections, were collected. Investigated comorbidities included liver diseases (e.g., cirrhosis and steatohepatitis). rheumatologic diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, sarcoidosis, psoriatic arthritis), diabetes mellitus (type 1 and type 2), cancer (both hematological and solid organ cancers), endocrine diseases, lung diseases (e.g., chronic obstructive pulmonary disease, asthma, bronchiectasis, interstitial lung diseases), coronary heart disease, chronic kidney disease (stage III to V), neurologic diseases (e.g., history of hemorrhagic or ischemic stroke, demyelinating diseases, peripheral neuropathies). Treatment with steroids was defined as patients receiving ≥ 15 mg of prednisone (or equivalent) for at least one month. Tobacco use was defined as ongoing tobacco use. Intravenous drug use was defined as ongoing intravenous drug use. Alcohol use was defined as at least 14 drinks per week, or at least 7 drinks per week for women and >65 years old. Eosinophilia was defined as eosinophils count greater than 500 cells/mm^3.

Statistical analysis

Categorical data are presented as absolute frequencies and proportions. Continuous variables are presented as mean and standard deviation. Prevalence of positive serologies was calculated as the ratio between patients with a positive serology for either *Schistosoma* spp. or *Strongyloides stercoralis* over the total patient who were tested and is presented with a 95% confidence interval (CI). Concerning the secondary objectives, categorical variables were compared with Fisher exact tests, while continuous with Mann Whitney tests. Statistical significance threshold was set at 0.05. Analyses were performed in R-Studio software (v. 4.2.3).

Ethics committee

The study was notified on March 20th 2024, to the Ethics Committee Lombardia 1 with number CET-133-2024, in accordance with local regulations. The study was conducted in accordance with local legislation and national requirements. All participants signed informed written consent for clinical and biological data collection as part of the Infectious Diseases Outpatient Department Registry of Luigi Sacco Hospital, which was approved by Ethics Committee Lombardia 1.

Results

A total of 228 patients attended the TB outpatient clinic from June 2020 to January 2024.

The overall characteristics of patients attending the TB outpatient clinic are reported in Table 1. The median age of the patients attending the TB outpatient clinic was 46 years [IQR 35, 61]. One hundred-sixty individuals (70.2%) were diagnosed with TBD, while 68 (29.8%) had TBI.

While 84 (36.8%) individuals were born in Italy, 144 patients originated from foreign countries. Indeed, 80 (35.1%) patients originated from strongyloidiasis moderate- or high-endemic countries, and 63 (27.6%) patients were born in areas endemic for schistosomiasis and strongyloidiasis. Only one patient came from a foreign country which is not considered endemic for schistosomiasis and strongyloidiasis (Spain). The median length of stay in Italy for patients coming from foreign countries was 144 months [IQR 48, 240].

Strongyloidiasis screening was suggested for 170 patients attending the clinic. Of these, 153 (90%) were tested for strongyloidiasis serology. Of the 63 patients originating countries

TABLE 1 Characteristics of the included patients.

		Serologies not performed (n=75)	Strongyloides stercoralis serology only (n=97)	Schistosoma spp. and Strongyloides stercoralis serologies (n=56)	Total (n=228)	p-value
Age (median [IQR])		53 [38.5, 65.0]	44 [34, 63]	43 [33, 52]	46 [35, 61]	<0.005
Male (%)		41 (54.7)	51 (52.6)	33 (58.9)	125 (54.8)	0.748
Ethnicity, n (%)	*African* *Latin* *Asian* *Caucasian* *Indian*	0 (0.0) 5 (6.7) 1 (1.3) 69 (92.0) 0 (0.0)	12 (12.4) 32 (33.0) 5 (5.2) 25 (25.8) 23 (23.7)	26 (46.4) 6 (10.7) 23 (41.1) 0 (0.0) 1 (1.8)	38 (16.7) 43 (18.9) 29 (12.7) 94 (41.2) 24 (10.5)	< 0.0001
***Schistosoma* spp. endemic country, n (%)**		2 (2.7)	5 (5.2)	56 (100.0)	63 (27.6)	< 0.0001
***Strongyloides stercoralis* endemic country, n (%)**	*Moderate* *High*	7 (10.4) 5 (6.7)	27 (40.3) 48 (49.5)	33 (49.3) 23 (41.1)	67 (29.3) 76 (33.3)	
Months spent in Italy for non-Italian patients (median [IQR])		72 [36, 144]	144 [54, 240]	138 [69, 240]	144 [48, 240]	0.358
Months spent in country of origin for non-Italian patients (median [IQR])		324 [204, 372]	300 [262, 396]	342 [274, 438]	324 [260, 408]	0.309
BMI (mean (sd))		24.1 (4.9)	23.6 (4.5)	21.2 (3.5)	23.2 (4.5)	0.0005
Liver disease, n (%)		8 (10.7)	12 (12.4)	6 (10.7)	26 (11.4)	0.925
Rheumatologic disease, n (%)		12 (16.0)	11 (11.3)	4 (7.1)	27 (11.8)	0.294
Diabetes mellitus, n (%)		10 (13.3)	16 (16.5)	6 (10.7)	32 (14.0)	0.598
Steroid treatment, n (%)		5 (6.7)	14 (14.4)	3 (5.4)	22 (9.6)	0.106
HBV infection, n (%)	*Occult* *Chronic*	6 (8.0) 2 (2.7)	7 (7.2) 5 (5.2)	10 (17.9) 3 (5.4)	23 (10.1) 10 (4.4)	0.083 0.673
HCV infection, n (%)		3 (4.0)	2 (2.1)	0 (0.0)	5 (2.2)	0.300
Cancer, n (%)		6 (8.0)	2 (2.1)	0 (0.0)	8 (3.5)	0.028
Endocrine disease, n (%)		5 (6.7)	6 (6.2)	5 (8.9)	16 (7.0)	0.806
Lung disease, n (%)		5 (6.7)	6 (6.2)	1 (1.8)	12 (5.3)	0.402
Coronary heart disease, n (%)		0 (0.0)	3 (3.1)	1 (1.8)	4 (1.8)	0.309
Chronic kidney disease, n (%)		1 (1.3)	0 (0.0)	3 (5.4)	4 (1.8)	0.049
Neurologic disease, n (%)		2 (2.7)	5 (5.2)	1 (1.8)	8 (3.5)	0.491
Tobacco use, n (%)		25 (33.3)	20 (20.6)	19 (33.9)	64 (28.1)	0.098
Alcohol consumption, n (%)		11 (14.7)	12 (12.4)	4 (7.1)	27 (11.8)	0.410
Intravenous drug use, n (%)		3 (4.0)	5 (5.2)	3 (5.4)	11 (4.8)	0.919
HIV status positive, n (%) **CD4+ T count at diagnosis (mean (sd))**		6 (8.0) 229.1 (221.9)	9 (9.3) 220.9 (251.1)	6 (10.7) 202 (155.5)	21 (9.2) 218.2 (207.4)	0.868 0.974
TB status, n (%)	*Infection* *Disease*	35 (46.7) 40 (53.3)	20 (20.6) 77 (79.4)	13 (23.2) 43 (76.8)	68 (29.8) 160 (70.2)	0.0004
Pulmonary TBD, n (%)		25 (33.3)	50 (51.5)	30 (53.6)	105 (46.1)	0.025
Extrapulmonary TBD, n (%)		18 (24.0)	46 (47.4)	25 (44.6)	89 (39.0)	0.004
TB treatment status, n (%)	*Completed* *Ongoing*	48 (64.0) 19 (25.3)	66 (68.0) 27 (27.8)	38 (67.9) 15 (26.8)	152 (66.7) 61 (26.8)	0.836 0.934

(Continued)

TABLE 1 Continued

		Serologies not performed (n=75)	Strongyloides stercoralis serology only (n=97)	Schistosoma spp. and Strongyloides stercoralis serologies (n=56)	Total (n=228)	p-value
Death, n (%)		3 (4.0)	1 (1.0)	0 (0.0)	4 (1.8)	0.174
LTFU, n (%)		5 (6.7)	3 (3.1)	3 (5.4)	11 (4.8)	0.542

IQR, interquartile range; sd, standard deviation; BMI, body mass index (expressed as kg/m^2); HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; TB, tuberculosis; TBD, tuberculosis disease; LTFU, lost to follow up.
Extra-pulmonary TB cases were lymph node, abdominal, or ocular TB. Some patients had both pulmonary and extra-pulmonary TB locations of infection. With lost to follow-up, we mean patients who did not attend programmed consultations because they either moved to another city/country or were incarcerated.

also endemic for schistosomiasis, 56 (88.8%) were tested for schistosomiasis. In the group of patients tested for strongyloidiasis serology, 22 were Italian and either had a history of stay in an endemic country or were born before 1952.

Among 56 patients tested for schistosomiasis serology, 15 patients were positive resulting in a prevalence of 26.7% [95% CI 16.9-39.9]. The most represented countries were China with 5 positive patients (33.3%) and Egypt with 2 positive patients (13.3%) (Figure 1). The median age was 43 years [IQR 32.5, 46] and notably, only 40% were males. The median length of stay in the original country was 324 months [IQR 239, 348]. Patients who resulted positive to schistosomiasis serology had a longer length of stay in Italy compared with those who tested negative to schistosomiasis serology, however not in a significant way (168 months [IQR 78, 234] vs 132 months [IQR 60, 240], respectively). Table 2 shows the characteristics of patients who were tested for schistosomiasis serology. No significant differences were observed between patients who tested positive with respect to those with a negative serology.

Concerning strongyloidiasis, of the 153 screened patients, 12 resulted positive for serology, resulting in a prevalence of 7.8% [95% CI 4.5-13.2]. Of those testing positive, the majority came from Bangladesh (25%) followed by Philippines (16.7%) and Peru (16.7%) (Figure 1). Of note, none of the screened Italian patients resulted positive to serology. The median age of patients who tested positive was 41.5 [IQR 31,48], half of them were men. The median length of stay in the country of origin was comparable between the patients who resulted positive (324 months [IQR 254.5, 420]) and the patients who resulted negative (324 months [IQR 264, 405]) to *Strongyloides stercoralis* serology. The median time spent in Italy was longer, but not significantly, in patients with a positive serology compared with those with a negative

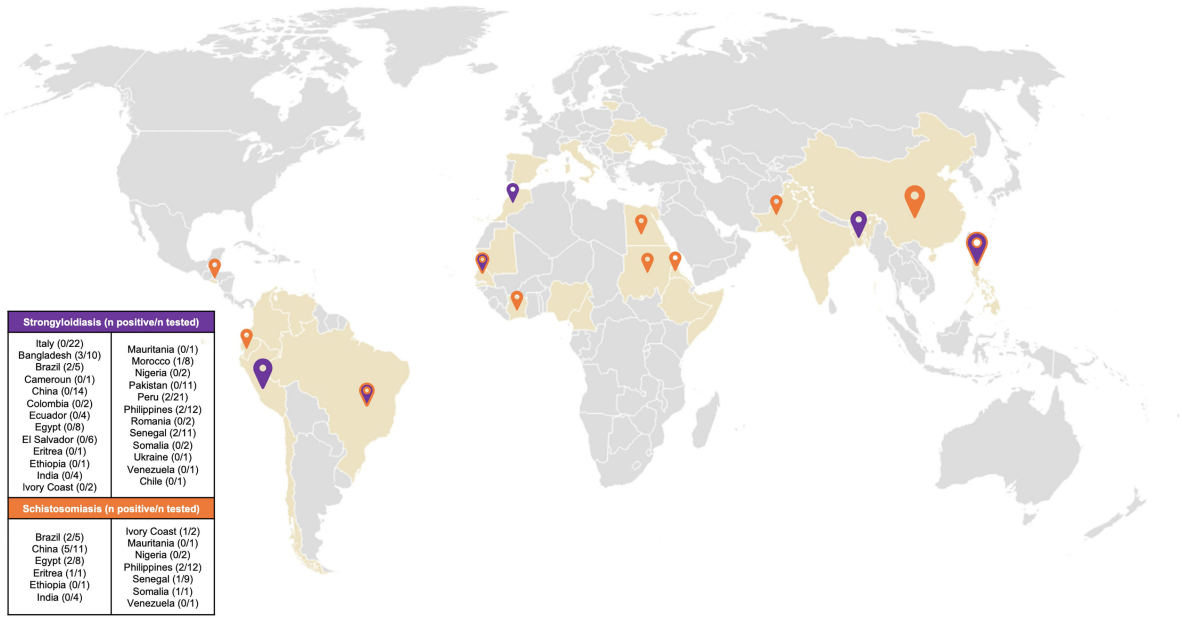

FIGURE 1
Map of country of origin of patients resulted positive to screening. Coloured countries are the countries of origin of all the patients attending the TB outpatient clinic. Orange pin: Country of origin of patients who resulted positive to *Schistosoma* spp screening. Purple pin: Country of origin of patients who resulted positive to *Strongyloides stercoralis* screening. Purple/orange pin: Country of origin of patients who resulted positive to *Schistosoma* spp. and/or *Strongyloides stercoralis* screening. Size of pins is proportional to the number of patients who tested positive to screening.

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TABLE 2 Characteristics of the patients who were tested for Schistosoma spp. serology.

Variable		Schistosoma spp. serology negative (n=41)	Schistosoma spp. serology ppositive (n=15)	Total (n=56)	p-value
Age (median [IQR])		44 [33, 55]	43 [32.5, 46.0]	43 [33, 52]	0.487
Male (%)		27 (65.9)	6 (40.0)	33 (58.9)	0.151
Ethnicity, n (%)	*African* *Latin* *Asian* *Caucasian* *Indian*	20 (48.8) 4 (9.8) 16 (39) 0 (0.0) 1 (2.4)	6 (40.0) 2 (13.3) 7 (46.7) 0 (0.0) 0 (0.0)	26 (46.4) 6 (10.7) 23 (41.1) 0 (0.0) 1 (1.8)	
Months spent in Italy (median [IQR])		132 [60, 240]	168 [78, 234]	138 [69, 240]	0.774
Months spent in country of origin (median [IQR])		348 [276, 468]	324 [239, 348]	342 [274, 438]	0.182
BMI (mean (sd))		21.1 (3.8)	21.6 (2.6)	21.2 (3.5)	0.622
Liver disease, n (%)		3 (7.3)	3 (20.0)	6 (10.7)	0.383
Rheumatologic disease, n (%)		3 (7.3)	1 (6.7)	4 (7.1)	1.000
Diabetes mellitus, n (%)		5 (12.2)	1 (6.7)	6 (10.7)	0.916
Steroid treatment, n (%)		3 (7.3)	0 (0.0)	3 (5.4)	0.684
HBV infection, n (%)	*Occult* *Chronic*	9 (22.0) 2 (4.9)	1 (6.7) 1 (6.7)	10 (17.9) 3 (5.4)	0.353 1.000
HCV infection, n (%)		0 (0.0)	0 (0.0)	0 (0.0)	
Cancer, n (%)		0 (0.0)	0 (0.0)	0 (0.0)	
Endocrine disease, n (%)		3 (7.3)	2 (13.3)	5 (8.9)	0.864
Lung disease, n (%)		1 (2.4)	0 (0.0)	1 (1.8)	1.000
Coronary heart disease, n (%)		1 (2.4)	0 (0.0)	1 (1.8)	1.000
Chronic kidney disease, n (%)		3 (7.3)	0 (0.0)	3 (5.4)	0.684
Neurologic disease, n (%)		0 (0.0)	1 (6.7)	1 (1.8)	0.596
Tobacco use, n (%)		14 (34.1)	5 (33.3)	19 (33.9)	1.000
Alcohol consumption, n (%)		3 (7.3)	1 (6.7)	4 (7.1)	1.000
Intravenous drug use, n (%)		2 (4.9)	1 (6.7)	3 (5.4)	1.000
TB status, n (%)	*Infection* *Disease*	8 (19.5) 33 (80.5)	5 (33.3) 10 (66.7)	13 (23.2) 43 (76.8)	0.466
Pulmonary TBD, n (%)		24 (58.5)	6 (40.0)	30 (53.6)	0.352
Extrapulmonary TBD, n (%)		19 (46.3)	6 (40.0)	25 (44.6)	0.905
TB treatment status, n (%)	*Completed* *Ongoing*	29 (70.7) 12 (29.3)	9 (60.0) 3 (20.0)	38 (67.9) 15 (26.8)	0.661 0.724
Death, n (%)		0 (0.0)	0 (0.0)	0 (0.0)	
LTFU, n (%)		0 (0.0)	3 (20.0)	3 (5.4)	0.023

IQR, interquartile range; sd, standard deviation; BMI, body mass index (expressed as kg/m^2); HBV, hepatitis B virus; HCV, hepatitis C virus; TB, tuberculosis; TBD, tuberculosis disease; LTFU, lost to follow up.

Extra-pulmonary TB cases were lymph node, abdominal, or ocular TB. Some patients had both pulmonary and extra-pulmonary TB locations of infection. With lost to follow-up, we mean patients who did not attend programmed consultations because they either moved to another city/country or were incarcerated.

serology (168 months [IQR 67.5, 231] vs 144 months [IQR 60, 240], respectively). Similarly to schistosomiasis, no significant differences were observed between the patients who tested positive compared to those who tested negative to *Strongyloides stercoralis* serology, as reported by Table 3.

Only 3 patients tested positive for both schistosomiasis and strongyloidiasis serologies, two of them came from Brazil and one from Sudan.

A stool microscopy parasitological test was performed for 8 of the 15 patients who tested positive for schistosomiasis serology and for all

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TABLE 3 Characteristics of the patients who were tested for Strongyloides stercoralis serology.

Variable		Strongyloides stercoralis serology negative (n=141)	Strongyloides stercoralis serology positive (n=12)	Total (n=153)	p-value
Age (median [IQR])		44 [34, 56]	41.5 [31, 48]	44 [34, 56]	0.417
Male (%)		78 (55.3)	6 (50.0)	84 (54.9)	0.957
Ethnicity, n (%)	*African* *Latin* *Asian* *Caucasian* *Indian*	35 (24.8) 34 (24.1) 26 (18.4) 25 (17.7) 21 (14.9)	3 (25.0) 4 (33.3) 2 (16.7) 0 (0.0) 3 (25.0)	38 (24.8) 38 (24.8) 28 (18.3) 25 (16.3) 24 (15.7)	0.517
Months spent in Italy for non-Italian patients (median [IQR])		144 [60, 240]	168 [67.5, 231.0]	144 [60, 240]	0.952
Months spent in country of origin for non-Italian patients (median [IQR])		324 [264, 405]	324 [254.5, 420.0]	324 [264, 411]	0.958
BMI (mean (sd))		22.7 (4.4)	23.6 (3.3)	22.7 (4.3)	0.477
Liver disease, n (%)		15 (10.6)	3 (25.0)	18 (11.8)	0.309
Rheumatologic disease, n (%)		13 (9.2)	2 (16.7)	15 (9.8)	0.743
Diabetes mellitus, n (%)		20 (14.2)	2 (16.7)	22 (14.4)	1.000
Steroid treatment, n (%)		14 (9.9)	3 (25.0)	17 (11.1)	0.264
HBV infection, n (%)	*Occult* *Chronic*	14 (9.9) 7 (5.0)	3 (25.0) 1 (8.3)	17 (11.1) 8 (5.2)	0.264 1.000
HCV infection, n (%)		2 (1.4)	0 (0.0)	2 (1.3)	1.000
Cancer, n (%)		2 (1.4)	0 (0.0)	2 (1.3)	1.000
Endocrine disease, n (%)		9 (6.4)	2 (16.7)	11 (7.2)	0.458
Lung disease, n (%)		7 (5.0)	0 (0.0)	7 (4.6)	0.943
Coronary heart disease, n (%)		3 (2.1)	1 (8.3)	4 (2.6)	0.725
Chronic kidney disease, n (%)		2 (1.4)	1 (8.3)	3 (2.0)	0.565
Neurologic disease, n (%)		5 (3.5)	1 (8.3)	6 (3.9)	0.963
Tobacco use, n (%)		36 (25.5)	3 (25.0)	39 (25.5)	1.000
Alcohol consumption, n (%)		14 (9.9)	2 (16.7)	16 (10.5)	0.809
Intravenous drug use, n (%)		7 (5.0)	1 (8.3)	8 (5.2)	1.000
TB status, n (%)	*Infection* *Disease*	30 (21.3) 111 (78.7)	3 (25.0) 9 (75.0)	33 (21.6) 120 (78.4)	1.000
Pulmonary TBD, n (%)		75 (53.2)	5 (41.7)	80 (52.3)	0.641
Extrapulmonary TBD, n (%)		65 (46.1)	6 (50.0)	71 (46.4)	1.000
TB treatment status, n (%)	*Completed* *Ongoing*	97 (68.8) 38 (27.0)	7 (58.3) 4 (33.3)	104 (68.0) 42 (27.5)	0.672 0.889
Death, n (%)		1 (0.7)	0 (0.0)	1 (0.7)	1.000
LTFU, n (%)		5 (3.5)	1 (8.3)	6 (3.9)	0.963

IQR, interquartile range; sd, standard deviation; BMI, body mass index (expressed as kg/m^2); HBV, hepatitis B virus; HCV, hepatitis C virus; TB, tuberculosis; TBD, tuberculosis disease; LTFU, lost to follow up.

Extra-pulmonary TB cases were lymph node, abdominal, or ocular TB. Some patients had both pulmonary and extra-pulmonary TB locations of infection. With lost to follow-up, we mean patients who did not attend programmed consultations because they either moved to another city/country or were incarcerated.

the patients who tested positive for strongyloidiasis serology. Urinary microscopy examination was performed in 8 patients who tested positive for schistosomiasis. Only one patient from Bangladesh had a positive stool microscopy examination for *Strongyloides stercoralis* and one patient originating from Sudan had a positive urinary parasitological test for *Schistosoma haematobium*.

Blood tests showed eosinophilia in 11 (7.2%) of the screened patients. Of these, 3 tested positive for *Schistosoma* spp. serology

and 3 tested positive for *Strongyloides stercoralis* serology. None of these patients tested positive for both infections. When asked for the presence of specific symptoms of schistosomiasis or strongyloidiasis, none of the patients who tested positive to either *Schistosoma* spp. or *Strongyloides stercoralis* serology showed any manifestation of disease at multiple physical examinations.

Ivermectin was administered to all patients who tested positive on serological screening for strongyloidiasis. Meanwhile, praziquantel was administered to 5 (33.3%) of the patients who tested positive for schistosomiasis, and none reported previous praziquantel treatment. No side effects were reported. The primary reason for withholding praziquantel from most patients was the known drug interaction between rifampin and praziquantel. Consequently, praziquantel was only offered to patients who completed their antitubercular treatment.

Discussion

Our study aimed to assess the prevalence of two NTDs, schistosomiasis and strongyloidiasis, among patients attending the TB clinic at Luigi Sacco Hospital in Milan, Northern Italy. Additionally, we aimed to characterize the demographics and clinical features of patients testing positive for these infections, and to compare the characteristics of patients with positive and negative test results. TB remains a primary healthcare concern for marginalized populations, including asylum seekers, undocumented migrants, and refugees, often originating from regions endemic for schistosomiasis and strongyloidiasis. On one hand, TB is closely associated to conditions of immunosuppression and malnutrition (23), commonly observed in underserved populations (24). On the other hand, TB disease itself has been linked to the development of immunosuppression (25). The necessity for TBI screening in patients undergoing immunosuppressive therapies is well recognized across various healthcare settings. Given the potential for chronic strongyloidiasis to progress to disseminated infections under immunosuppressed conditions, it is prudent to consider screening for this condition in patients attending TB outpatient clinics, whether for TBD or TBI.

Schistosomiasis has not been linked to immunosuppression. However, chronic infection may remain asymptomatic for years while establishing unreversible lesions which can lead to liver cirrhosis, bladder cancer or infertility. Delay in the schistosomiasis diagnosis has often been described and was associated both with difficulties in accessing healthcare and poor awareness of physicians in non-endemic countries (26, 27).

In our cohort, the prevalence of schistosomiasis was 26.7% [95% CI 16.9-39.9], slightly higher compared to the prevalence in migrants of 18.4% proposed by Asundi et al., in their recent systematic review (10). This could be explained by the small sample size of our study. In Italy, studies have reported significant variations in the prevalence of these diseases among patients arriving from endemic regions, with rates ranging from 6% to 27.6% (13, 15). Notably, while the majority of imported schistosomiasis cases worldwide originate from Sub-Saharan Africa (28), our cohort exhibited a different distribution, with only 26% of positive cases originating from this region, primarily from Sudan, Senegal, and Eritrea. This unexpected finding could be attributed to comparable patient numbers across various countries of origin, as indicated by Italian migration reports (29). Interestingly, the median length of stay in Italy for patients testing positive for schistosomiasis in our study was higher (median: 168 months; IQR: 78-234) compared to a previously reported median of 110 months for asymptomatic patients in a multicenter study (27). This discrepancy may reflect increased awareness and screening efforts targeting recently arrived migrants in recent years. Furthermore, the median age of our cohort was notably higher (43 years) compared to the referenced study (27 years) (27), highlighting the importance of attention to individuals who have resided in Italy for a longer period and may have had limited access to healthcare services for an extended duration.

Concerning the prevalence of strongyloidiasis, our result was lower compared with the prevalence in migrants proposed by Asundi (10) and Buonfrate et al. (11) but was consistent with the one obtained by another multicentric study conducted in Italy (13). Interestingly, while Buonfrate et al. found a 1-8% seroprevalence of strongyloidiasis in Italians born before 1952, we identified none in our population (11). Nevertheless, despite this difference, screening is warranted in this kind of patients based on different prevalence studies (30, 31) and considering the risk of developing complicated forms of strongyloidiasis following immunosuppression. Interestingly, a significant proportion of patients born in Italy before 1952 sought treatment at our clinic for TBI, often as part of pre-immunosuppressive therapy screening protocols (e.g., prior to corticosteroids or immunomodulating agents). In our population, almost 10% of patients who were screened for strongyloidiasis had a positive history for rheumatologic conditions, while 11% were undergoing a steroid treatment. This underscores the importance of extending strongyloidiasis screening beyond Infectious Diseases wards to other clinical settings, such as Rheumatology and Hematology departments.

Three patients tested positive for both parasitic infections. While we recognize the possibility of false positive results in either test, in the absence of positive parasitological tests, the decision to treat these patients was based on adherence to current recommendations (16, 17, 21). Backing this approach of testing and treating patients, a recent study by Roure et al. proposed a significant disparity in healthcare costs between adopting a "test-and-treat" strategy compared to a "watchful wait" approach, particularly among long-term migrants (32).

Our study carries some limitations. Firstly, we were unable to obtain additional data regarding the progression of symptoms associated with these conditions. Although thorough physical examinations were conducted during each visit, it is possible that certain nonspecific symptoms may have been underreported due to language or cultural barriers. Secondly, we did not assess the response to antiparasitic treatment. Unfortunately, follow-up of these patients after completion of TB treatment can be challenging, as patients

travel frequently or have unstable employment situations that are not conducive to regular outpatient clinic visits. Lastly, our sample size is limited. However, it's important to note that we are examining two conditions that are not endemic in Italy, within a specific population. Studies at regional or national level are needed to comprehensively assess the prevalence of these overlooked conditions.

Conclusion

In conclusion, our study underlines the frequently underestimated prevalence of schistosomiasis and strongyloidiasis among patients seeking healthcare for tuberculosis. These findings emphasize the critical need for increased awareness and targeted screening efforts across various healthcare settings. While specialized departments such as Infectious Diseases outpatient clinics play a pivotal role, extending screening protocols to include other departments like Hematology, Rheumatology, as well as primary healthcare settings, is essential to effectively address these often-overlooked conditions within this vulnerable population.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Comitato EticoTerritoriale LOMBARDIA 1. The studies were conducted inaccordance with the local legislation and institutional requirements.Written informed consent for participation was not required from theparticipants or the participants' legal guardians/ next of kin inaccordance with the national legislation and institutional requirements.

Author contributions

CG: Conceptualization, Writing – original draft, Writing – review & editing, Investigation. MC: Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. SP: Conceptualization, Writing – original draft, Writing – review & editing. MS: Investigation, Writing – review & editing, Conceptualization. LG: Investigation, Writing – review & editing. FF: Writing – review & editing, Investigation. SA: Supervision, Validation, Writing – review & editing. AG: Writing – review & editing, Supervision, Validation. AT: Conceptualization, Investigation, Writing – review & editing, Supervision, Validation.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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