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ORIGINAL ARTICLE

Medical and Social Risk Factors for Progression of Latent Tuberculosis Infection to Active Tuberculosis in Children Living in Household Contacts in Uzbekistan: A Prospective Study

Adzhablaeva-Dinara Namazovna[1,*], Parpieva-Nargiza Nusratovna[2], Chelnokova-Olga Germanovna[3]

Abstract

Introduction: Latent tuberculosis infection (LTBI) is characterized by a sustained immune response to *Mycobacterium tuberculosis* antigens without clinical, radiographic, or microbiological evidence of active disease. The aim of this study was to assess medical and social risk factors for progression of latent tuberculosis infection (LTBI) to active pulmonary tuberculosis in children with household TB contact.

Materials and methods: A prospective study (2022–2024) involved 120 children aged 4–12 with LTBI. Two groups were formed: children who developed active TB (LTBI-to-TB group) and those who remained latent. Inclusion required consent. Clinical, immunological (IL-2, IgM), and social factors were analyzed. Risk was evaluated via relative risk (RR) and 95% confidence intervals.

Results: Progression to active TB was linked to bacillary TB contact (RR=6.5), maternal TB (RR=5.2), anemia (RR=3.8), ≥5 ARI episodes/year (RR=26.0), ineffective BCG (RR=3.0), single-parent homes (RR=11.0), territorial TB (RR=4.5), helminthiasis (RR=10.0), chickenpox (RR=5.0), genitourinary diseases (RR=8.0), ENT pathology (RR=5.7), isoniazid monotherapy (RR=2.7), COVID-19 or HIV exposure (RR=8.0), IL-2 ≥311.1 ng/ml, and IgM ≥1.18 IU/ml.

Discussions: Immunological and social factors increase LTBI progression risk. High-risk children need tailored monitoring.

Keywords:Latent tuberculosis; Tuberculosis; Risk factors; Child; Contact tracing; Immunological biomarkers

Factores de riesgo médicos y sociales para la progresión de la infección tuberculosa latente a tuberculosis activa en niños en contacto intradomiciliario en Uzbekistán: un estudio prospectivo

Resumen

Introducción: La infección tuberculosa latente (ITBL) se caracteriza por una respuesta inmunitaria sostenida a antígenos de Mycobacterium tuberculosis sin evidencia clínica, radiográfica ni microbiológica de enfermedad activa. El objetivo de este estudio fue evaluar los factores de riesgo médicos y sociales para la progresión de la infección tuberculosa latente (ITBL) a tuberculosis pulmonar activa en niños con contacto domiciliario con TB.

Materiales y métodos: Estudio prospectivo (2022-2024) en el que participaron 120 niños de 4 a 12 años con ITBL. Se formaron dos grupos: niños que desarrollaron tuberculosis activa (grupo ITBL a tuberculosis) y aquellos que permanecieron latentes. La inclusión requirió consentimiento informado. Se analizaron factores clínicos, inmunológicos (IL-2, IgM) y sociales. El riesgo se evaluó mediante el riesgo relativo (RR) y sus intervalos de confianza del 95%.

Resultados: La progresión a TB activa se relacionó con el contacto con TB bacilar (RR = 6,5), TB materna (RR = 5,2), anemia (RR = 3,8), ≥5 episodios de IRA/año (RR = 26,0), BCG ineficaz (RR = 3,0), hogares monoparentales (RR = 11,0), TB territorial (RR = 4,5), helmintiasis (RR = 10,0), varicela (RR = 5,0), enfermedades genitourinarias (RR = 8,0), patología otorrinolaringológica (RR = 5,7), monoterapia con isoniazida (RR = 2,7), exposición a COVID-19 o VIH (RR = 8,0), IL-2 ≥311,1 ng/ml e IgM ≥1,18 UI/ml.

Discusión: Los factores inmunológicos y sociales aumentan el riesgo de progresión de la ITBL. Los niños de alto riesgo necesitan un seguimiento personalizado.

Palabras clave: Tuberculosis latente; Tuberculosis; Factores de riesgo; Niño; Rastreo de contactos; Biomarcadores inmunológicos

1 Samarkand State Medical University, Department of Phthisiology and Pulmonology, Samarkand, Uzbekistan. https://orcid.org/0000- 0002-0613-5526

2 Republican Specialized Scientific-Practical Medical Center of Phthisiology and Pulmonology, Tashkent, Uzbekistan. https://orcid.org/0000-0001-8218-4760

3 Department of Phthisiology, Yaroslavl State Medical University, Yaroslavl, Russia. https://orcid.org/0000-0003-0840-1151

* Autor para correspondencia:
Correo electrónico: dinarasammi@mail.ru

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Introduction

Latent tuberculosis infection (LTBI) is characterized by a sustained immune response to *Mycobacterium tuberculosis* antigens without clinical, radiographic, or microbiological evidence of active disease[1,5]. In pediatric settings, accurately predicting the progression from LTBI to localized tuberculosis (TB), most commonly pulmonary TB, is essential for timely preventive interventions[1,3]. Children exposed to household TB cases represent a particularly vulnerable group, where early risk assessment is critical to avoid progression to active TB[2,3].

Previous research has highlighted the role of various epidemiological, medical, and social factors in influencing LTBI progression in children[1,2,4]. Prolonged exposure to infectious TB cases, especially those with multidrug-resistant (MDR) strains, significantly elevates this risk, particularly within household environments where contact is frequent and prolonged[3,7].

Additional factors, such as the index case's adherence to anti-TB therapy, vaccination status, and living conditions, further influence outcomes[2,8]. Although BCG vaccination is broadly applied, its protective efficacy can vary, especially in immunocompromised or malnourished children[1,4].

Recently, immunological biomarkers have gained attention for their potential to differentiate between latent and active TB infection. Among them, interleukin-2 (IL-2) has shown promise as a discriminative marker between LTBI and active disease in pediatric populations[6,9]. Several studies have supported its diagnostic utility in this context[6,10,11].

Despite global efforts to reduce TB incidence, there is limited evidence on effective prevention strategies tailored to children living in TB-affected households[7,8]. In many primary care settings, the role of general practitioners is often limited to referrals, which may delay critical interventions[1,2].

Given the persistently high pediatric TB burden in Uzbekistan, this study aimed to assess and analyze the medical, immunological, and social risk factors contributing to the progression of LTBI into localized pulmonary TB among children residing in household contact environments.

Materials and Methods

A prospective cohort study was conducted from 2022 to 2024, in accordance with the International STROBE standard[1]. The study was conducted at the Samarkand Regional Center of Phthisiology and Pulmonology and the City Tuberculosis Dispensary in Uzbekistan. This study focused on children diagnosed with latent tuberculosis infection (LTBI) who resided in household TB contact settings. The total observation period ranged from 12 to 24 months, during which the risk of progression from LTBI to localized pulmonary tuberculosis was analyzed. Two comparative groups were formed: Group I included 40 children (aged 4–12 years) who developed localized pulmonary TB within 1–2 years of LTBI. Group II included 80 children (aged 4–12 years) with confirmed LTBI who did not develop TB within the 12–24 months follow-up period.

The inclusion criteria for Group I were as follows: children aged 4–12 years with a confirmed diagnosis of LTBI, followed by a diagnosis of localized pulmonary tuberculosis within 1–2 years, and informed consent from parents or guardians.

The inclusion criteria for Group II were the same age range and confirmed LTBI without evidence of TB development during the observation period, and informed consent was obtained.

The exclusion criteria were as follows: children aged < 4 or > 12 years and refusal to participate by the child or parents/guardians.

The process of participant selection and follow-up is presented in Figure 1 (STROBE flowchart).

This study collected clinical, laboratory, instrumental, immunological, and epidemiological data at baseline. Detailed anamnesis included sex, age, TB diagnosis, vaccination status, symptom duration, exposure to the TB index case, family structure, and preventive therapy history. Objective clinical evaluation included anthropometry and signs suggestive of TB by means of palpation, percussion, and auscultation.

LTBI was assessed via the tuberculin skin test (PPD-L, 2 TU) and Diaskintest® (recombinant TB allergen) performed simultaneously on both forearms [2]. Interferon-Gamma Release Assay (QuantiFERON®-TB Gold) was used to detect cellular immune response to ESAT-6 and CFP-10 antigens[3]. Cytokine levels (IL-2, IL-4, and IFN-γ) were measured in serum samples using enzyme-linked immunosorbent assay (ELISA) kits ("Vector-Best", Novosibirsk, Russia).

Immunological assessment was performed on a subset of participants because some parents partially refused to consent to this component of the study. Additionally, the capacity to conduct immunological analyses became available at our institution only in 2023, which limited the number of children included in this part of the study.

Chest imaging included X-ray, computed tomography (CT), and multislice spiral CT (MSCT) using the "Insitum 32" (USA) scanner with a slice thickness of 0.5–1.0 mm. MSCT was performed during deep inspiration with breath-hold in children aged ≥7 years.

Throughout the longitudinal follow-up of the children included in the study, regular monitoring of clinical and laboratory parameters, as well as the epidemiological situation in the household, was performed. Final disinfection not performed" refers to households in which terminal disinfection of living spaces was not carried out after the hospitalization or death of the infectious TB index case, as required by the National Tuberculosis Control Program. The follow-up period was 24 months long. Of the total participants, six children (5.0% of

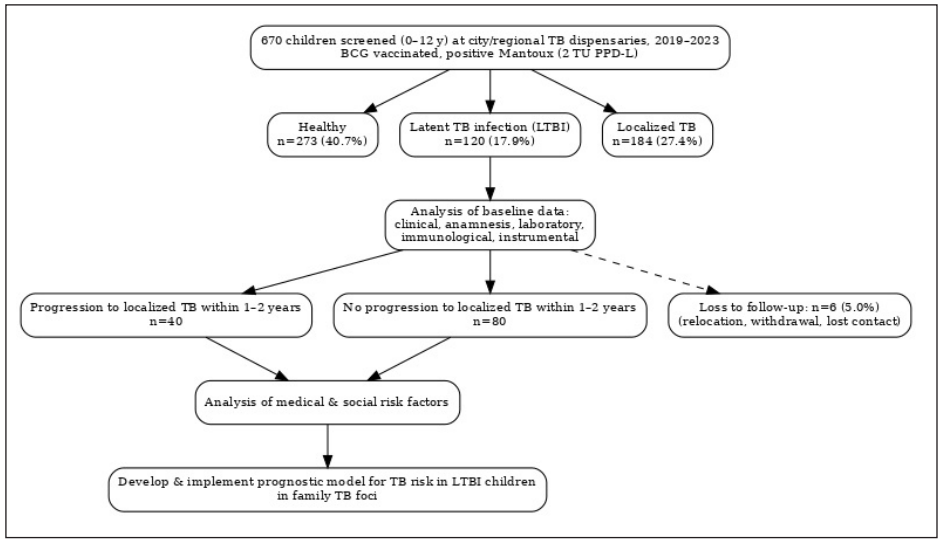

Figure 1. STROBE flowchart illustrating participant recruitment, inclusion, follow-up, and analysis

the cohort) were lost to subsequent analysis due to relocation, parental withdrawal of consent, or loss of contact. These cases were classified as censored data. Survival analysis methods were applied to account for these cases, including Kaplan–Meier curves and Cox proportional hazards models, which incorporated censored observations. Both completed and censored follow-up data were included in the main statistical analysis, minimizing the risk of systematic bias and ensuring an accurate estimation of the time to event (LTBI progression).

Statistical analyses were performed using SPSS Statistics version 29.0.2. Student's t-test was used for normally distributed variables, and Mann–Whitney U, Kruskal–Wallis H, and Pearson's χ^2 tests for non-parametric and categorical data. Binary outcome comparisons included relative risk (RR) and odds ratios (OR) with 95% confidence intervals (CI). A p-value <0.05 was considered statistically significant.

ROC analysis was performed to determine the threshold values of the quantitative predictors and their diagnostic utility. The quality of the predictive model was evaluated using sensitivity, specificity, and Area Under Curve (AUC), a numerical indicator of the area under the ROC curve, which reflects the model's discriminative power.

The study protocol was in accordance with the ethical standards of the Helsinki Declaration[4]. Written informed consent was obtained from the parents or legal guardians of all participants. The study was approved by the Ethics Committee of Samarkand State Medical University (Protocol No. 35, dated December 1, 2021).

Results

A total of 120 children were included in the study. Group 1 (LTBI progressing to localized TB) included 40 children (mean age 7.80 ± 2.64 years), and Group 2 (LTBI without progression) included 80 children (mean age 7.85 ± 2.57 years).

Among children in Group 1, localized TB was diagnosed based on respiratory and systemic symptoms. Verification was performed by the Central Medical Control Commission in accordance with the national classification. The majority (70%) had intrathoracic lymph node TB, 25.0% had primary pulmonary TB complex, and 5.0% had miliary TB ($p < 0.001$). The infiltrative stage was observed in all patients, and complications were rare (2.5%).

The Diaskintest papule size increased significantly over 12 – 24 months in Group 1 (from 17.3 ± 0.4 mm to 22.5 ± 0.3 mm), whereas it decreased in Group 2 (from 20.9 ± 0.4 mm to 12.9 ± 0.5 mm).

Drug susceptibility testing showed that 70.9% of mycobacterial isolates from children in Group 1 were drug-sensitive, compared to 83.3% in Group 2 ($p > 0.05$). Multidrug-resistant tuberculosis (MDR-TB) was detected in 19.4% and 5.6% of Group 1 and Group 2 children, respectively ($p > 0.05$), while extensively drug-resistant tuberculosis (XDR-TB) was observed in 6.5% and 5.6%, respectively.

The level of interleukin-2 (IL-2) was significantly lower in Group 1 (children with LTBI progression) than in Group 2 (259.1 ± 173.7 vs. 317.1 ± 174.1 IU/mL, $p < 0.0001$). ROC curve analysis determined a threshold IL-2 value of < 251.1 IU/mL, with a sensitivity and specificity of 78.9% and 72.3%, respectively (AUC = 0.775). IL-2 levels below this threshold are associated with an increased risk of progression from latent to active tuberculosis.

Discussion

We identified a multifactorial set of risk factors, including medical, social, immunological, and environmental factors, that contribute to the progression of latent tuberculosis infection (LTBI) to localized tuberculosis (TB) in children living in household contact settings. These findings emphasize the necessity of a

Table 1. Epidemiological and Contact Risk Factors Associated with LTBI Progression

Characteristic of the Source of Infection	Group 1: LTBI → TB (n=40)	Group 2: LTBI only (n=80)	p-value	χ^2	OR (95% CI)
Bacterial excretion					
BK+	31 (77.5%)	36 (45.0%)	< 0.001	11.42	4.21 (1.78–9.98)
BK–	9 (22.5%)	44 (55.0%)	< 0.05	11.42	0.24 (0.10–0.56)
Source of infection					
Mother	22 (55.0%)	18 (22.5%)	< 0.001	12.68	4.21 (1.86–9.51)
Father	11 (27.5%)	15 (18.8%)	> 0.05	1.20	1.64 (0.67–4.01)
One relative	1 (2.5%)	43 (53.8%)	< 0.001	30.16	0.02 (0.003–0.17)
Two or more relatives	6 (15.0%)	4 (5.0%)	> 0.05	3.49	3.353 (0.89–12.66)
Drug susceptibility/resistance					
Drug sensitive TB	22 (70.9%)	30 (83.3%)	> 0.05	1.47	0.49 (0.15-1.58)
MDR-TB	6 (19.4%)	2 (5.6%)	> 0.05	3.02	4.08 (0.76-21.93)
XDR-TB	2 (6.5%)	2 (5.6%)	> 0.05	0.02	1.17 (0.16-8.85)

Note: Values are presented as *n (%)*, BK – *Mycobacterium tuberculosis* detected by microscopy or culture;OR – Odds Ratio; CI – Confidence Interval; p < 0.05 considered statistically significant.

Table 2. Social Risk Factors for Progression of LTBI to Localized TB

Social Risk Factor	Group 1: LTBI → TB (n=40)	Group 2: LTBI only (n=80)	p-value	χ^2	OR (95% CI)
Single-parent family	11 (27.5%)	2 (2.5%)	< 0.05	9.80	14.79 (1.81–121.14)
Large family	11 (27.5%)	6 (7.5%)	< 0.05	5.54	4.68 (1.19–18.34)
Parental smoking	21 (52.5%)	18 (22.5%)	< 0.05	7.68	3.81 (1.45–10.02)
Child not enrolled in organized in school	15 (37.5%)	12 (15.0%)	< 0.05	5.23	3.40 (1.16–10.00)
Low-income family	32 (80.0%)	18 (22.5%)	< 0.05	26.47	13.78 (4.71–40.28)
Unstable parental employment	7 (17.5%)	2 (2.5%)	< 0.05	7.46	12.091 (1.39–104.85)

Note: Values are presented as *n (%)*, OR – Odds Ratio; CI – Confidence Interval; p<0.05 considered statistically significant.

Table 3. Biological risk factors in children with and without LTBI progression

Biological History Factor	Group 1: LTBI → TB (n=40)	Group 2: LTBI only (n=80)	p-value	χ^2	OR (95% CI)
Family history of tuberculosis	11 (27.5%)	6 (7.5%)	< 0.05	5.54	4.67 (1.19–18.34)
Early complementary feeding (< 4 mo.)	23 (57.5%)	8 (10.0%)	< 0.001	20.18	12.18 (3.64–40.77)
ARVI in the first year of life	30 (75.0%)	12 (15.0%)	< 0.001	29.09	17.00 (5.52–52.36)
Anemia in the first year of life	29 (72.5%)	6 (7.5%)	< 0.001	35.21	32.515 (8.30–127.45)
History of allergic diseases	9 (22.5%)	4 (5.0%)	< 0.05	5.17	5.52 (1.11–27.43)
≥5 ARVI episodes per year	26 (65.0%)	2 (2.5%)	< 0.001	58.23	72.43 (15.42–340.11)

Note: Values are presented as *n (%)*, ARVI – acute respiratory viral infection; OR – Odds Ratio; CI – Confidence Interval; p<0.05 considered statistically significant

comprehensive, multidimensional approach to TB prevention in pediatric populations, extending beyond mere pathogen exposure to incorporate the social determinants of health[2,4,7].

A key practical implication is the proposed predictive model that integrates immunological biomarkers, such as interleukin-2 (IL-2) and immunoglobulin M (IgM). The relatively high area under the curve (AUC) value for IL-2 (0.775) suggests its potential utility as a biomarker for the early identification of children at increased risk of TB progression. This finding aligns with international evidence and supports the incorporation of IL-2-based assays into screening strategies for pediatric LTBI[6,8,9,11].

Our study revealed significantly higher immunoglobulin M (IgM) levels in children with LTBI progression than in those without progression. This finding seems to contradict some published reports, which indicate an increase in IgG and a decrease in the IgM/IgG ratio during the transition from latent to active tuberculosis. Several factors may explain these discrepancies.

First, elevated IgM levels in our pediatric cohort may reflect an early humoral immune response phase, in which IgM is produced before class switching to IgG. This temporal aspect is particularly relevant in children, whose immune responses may differ from those of adults.

Second, methodological differences, such as the timing of sample collection relative to disease stage and assay sensitivity, may affect IgM measurements, potentially contributing to divergent results across studies.

Additionally, interpreting IgM levels in conjunction with other immunological markers, such as IL-2, provides a more comprehensive picture of immune dynamics during LTBI progression. Our findings underscore the complexity of immune responses in tuberculosis and highlight the need for the development of multifaceted biomarker panels.

Further longitudinal research is necessary to clarify the role of IgM and its interplay with other immune factors in the progression of pediatric TB.

Despite these strengths, this study had several methodological limitations that should be acknowledged. The research was conducted solely in the Samarkand region of Uzbekistan, which may limit the generalizability of the results. Furthermore, some variables, particularly those concerning maternal health during pregnancy, relied on retrospective recall, potentially introducing reporting bias. Nevertheless, the prospective design and rigorous statistical analyses enhanced the reliability of the observed associations.

Our analysis of mycobacterial drug susceptibility revealed that 70.9% of isolates from children with LTBI progression were drug-sensitive compared to 83.3% in those without progression ($p > 0.05$). Multidrug-resistant TB (MDR-TB) was detected in 19.4% of progressing cases and 5.6% of non-progressors. The prevalence of extensively drug-resistant TB (XDR-TB) did not significantly differ between the groups. Although these differences did not reach statistical significance, likely due to the limited sample size, there was a clinically relevant trend toward higher drug resistance among children experiencing disease progression. These findings highlight the importance of monitoring drug resistance in TB preventive programs, particularly given the potential limitations of isoniazid monotherapy in the presence of resistant strains. Individualized preventive treatment regimens based on susceptibility profiles may be necessary to reduce the risk of progression and curb the emergence of resistance.

Notably, our results align with the global literature emphasizing the impact of malnutrition, immunodeficiency, household overcrowding, and parental unemployment or smoking on childhood TB risk[4,7]. The novelty of this study lies in the concurrent evaluation of immunological biomarkers and sociodemographic factors, offering an integrative perspective rarely addressed in previous research.

Childhood malnutrition and immunosuppression are critical factors that exacerbate susceptibility to TB progression. Malnutrition impairs cell-mediated immunity, reducing the host's ability to contain latent infections, consistent with our findings and global evidence[4,7]. Immunosuppressive conditions, whether due to coexisting diseases or environmental stressors, further compromise immune responses, facilitating the transition from latent infection to active disease.

Table 4. Impact of Vaccination, Final Disinfection, and Preventive Chemotherapy on LTBI Progression

Factor	Group 1: LTBI → TB (n=40)	Group 2: LTBI only (n=80)	p-value	χ^2	OR (95% CI)
Low BCG efficacy (1–4 mm)	16 (40.0%)	10 (12.5%)	< 0.001	7.81	4.67 (1.51-14.46)
Final disinfection not performed	24 (60.0%)	14 (17.5%)	< 0.001	15.22	7.07 (2.52–19.85)
Isoniazid+ Rifapentine, 3 months (3HR)	4 (10.0%)	39 (48.7%)	< 0.001	17.42	0.12 (0.04-0.36)
Isoniazid +Rifapentine, 1 month (1HR)	6 (15.0%)	11 (13.8%)	> 0.05	0.85	1.11 (0.38-3.38)
Isoniazid in monotherapy, 6 months (6H)	24 (60.0%)	18 (22.5%)	< 0.001	16.48	5.17 (2.27-11.75)
Levofloxacin, 6 months (6Lfx)	6 (15.0%)	12 (15.0%)	> 0.05	0.07	1.00 (0.35-2.90)

Note: Values are presented as *n (%)*, Final disinfection not performed refers to the absence of terminal disinfection measures in the household after TB case detection, OR – Odds Ratio; CI – Confidence Interval; $p<0.05$ considered statistically significant.

Table 5. Impact of Additional Epidemiological Factors on the Progression of LTBI to Localized TB

Epidemiological Factor	Group 1: LTBI → TB (n=40)	Group 2: LTBI only (n=80)	p-value	χ^2	OR (95% CI)
COVID-19 (Mother infected)	13 (32.5%)	8 (10.0%)	< 0.05	6.05	4.33 (1.27-14.78)
COVID-19 (Father infected)	8 (20.0%)	2 (2.5%)	< 0.05	6.14	9.75 (1.16-82.11)
HIV (Father infected)	8 (20.0%)	2 (2.5%)	< 0.05	6.14	9.75 (1.16-82.11)
TB Source in school	9 (22.5%)	4 (5.0%)	< 0.05	5.17	5.52 (1.11-27.43)
Residing in former TB hotspot	8 (20.0%)	2 (2.5%)	< 0.05	6.14	9.75 (1.16-82.11)

Note: Values are presented as *n (%)*, ARVI – acute respiratory viral infection; OR – Odds Ratio; CI – Confidence Interval; $p<0.05$ considered statistically significant.

Furthermore, isoniazid monotherapy, the standard prophylactic treatment for LTBI, may paradoxically represent a risk factor for disease progression if the treatment is incomplete or if resistant mycobacterial strains are present. Our cohort demonstrated a notable prevalence of MDR-TB strains (19.4% of progressing cases), underscoring the need for careful monitoring of drug susceptibility during preventive therapy. The emergence of resistance necessitates vigilant surveillance and may require modification of prophylactic regimens to mitigate the risk of progression[3,14,17].

In this study, isoniazid monotherapy, although the standard regimen for LTBI prophylaxis, was paradoxically associated with an increased risk of progression to active TB in children, particularly when treatment adherence was suboptimal or in the presence of drug-resistant mycobacterial strains. This finding aligns with the existing literature, suggesting that monotherapy may be insufficient to prevent progression in the context of resistant strains or incomplete treatment courses[18]. The selection pressure imposed by isoniazid alone can favor the emergence of multidrug-resistant strains, thereby compromising its prophylactic efficacy. Comparatively, combination regimens, such as isoniazid with rifapentine, have demonstrated improved outcomes in reducing progression risk, highlighting the need to tailor preventive therapy based on drug susceptibility profiles and patient adherence[18]. These observations emphasize the importance of individualized preventive approaches and routine drug susceptibility testing in TB control programs.

Moreover, the presence of COVID-19 infection in either parent indicates a high likelihood that the child, sharing the household environment, was exposed to SARS-CoV-2 and may have experienced mild or asymptomatic infection. Such exposure may modulate the child's immune system, potentially diminishing immunological responsiveness and thereby facilitating the progression from latent infection to active TB. This immunological interaction underscores the importance of incorporating parental COVID-19 history into risk assessments for TB progression among pediatric household contacts[14–17].

Interestingly, unlike IL-2, interferon-gamma (IFN-γ) did not demonstrate diagnostic significance in this cohort, which differs from some previous reports[6,10,13]. Potential explanations include immunological age-dependent variations, assay sensitivity, and unique epidemiological features of the studied population. Further research is required to elucidate these discrepancies.

The relatively high area under the curve (AUC = 0.775) confirms the potential of IL-2 as a biomarker for the early identification of children at an increased risk of TB progression. Our findings indicate that lower IL-2 levels (< 251.1 IU/mL) serve as a significant risk factor for progression from latent infection to active tuberculosis. This aligns with the existing literature reporting decreased IL-2 production in patients who progress to active TB, reflecting impaired cell-mediated immunity[6,8,9,11]. Therefore, measuring IL-2 levels and applying this threshold can be useful for risk stratification and targeted preventive interventions in pediatric LTBI.

Table 6. Influence of Somatic Comorbidities on the Progression of Latent TB Infection (LTBI) to Localized TB in Children

Somatic Condition	Group 1: LTBI → TB (n=40)	Group 2: LTBI only (n=80)	p-value	χ^2	OR (95% CI)
Urinary tract diseases	8 (20.0)	2 (2.5)	< 0.05	6.14	9.75 (1.16-82.11)
ENT pathology	5 (12.5)	8 (10.0)	> 0.05	0.13	1.29 (0.32-5.19)
Anemia	15 (37.5)	8 (10.0)	< 0.05	8.35	5.40 (1.60-18.21)
Chickenpox	10 (25.0)	4 (5.0)	< 0.05	6.28	6.33 (1.29-31.12)
Helminthic invasion	10 (25.0)	2 (2.5)	< 0.001	8.53	13.00 (1.58-107.23)
ARVI (acute respiratory infections)	21 (52.5)	12 (15.0)	< 0.001	12.58	6.26 (2.16-18.20)

Note: Values are presented as n (%), ARVI – acute respiratory viral infection; OR – Odds Ratio; CI – Confidence Interval; p<0.05 considered statistically significant, ENT – ear, nose, throat; ARVI – acute respiratory viral infection.

Table 7. Immunological Markers and Their Diagnostic Performance in LTBI Progression

Indicator	Group 1: LTBI → TB (Mean ± SD)	Group 2 LTBI only (Mean ± SD)	p-value	Threshold Value	AUC	Sensitivity (%)	Specificity (%)
IL-2 (IU /mL)	259.1 ± 173.7	317.1 ± 174.1	< 0.0001	< 251.1	0.775	78.9	72.3
IFN-γ (IU /mL)	21173 ± 9578	22875 ± 10833	>0.05	< 20,874.2	0.238	0.0	100.0
IgM (IU/mL)	1.24 ± 0.23	1.08 ± 0.07	<0.0001	< 1.18	0.674	65.8	66.0
IFN-γ / IL-2 ratio	66.55 ± 0.25	88.58 ± 0.08	>0.05	< 63.22	0.536	61.2	54.2

Note: Values are presented as mean ± SD, IL-2 – interleukin-2; INF-γ – interferon gamma; IgM – immunoglobulin M; INF-γ/IL-2 – ratio of interferon gamma to interleukin-2, AUC – area under curve; Se – sensitivity; Sp – specificity. Thresholds defined by ROC analysis, p < 0.05 was considered statistically significant.

In our study, the level of interleukin-2 (IL-2) was significantly lower in children with LTBI progression than in those without progression (259.1 ± 173.7 vs. 317.1 ± 174.1 IU/mL, $p < 0.0001$). ROC curve analysis identified a threshold IL-2 value below 251.1 IU/mL, which is associated with a substantially increased risk of progression from latent infection to active tuberculosis (AUC = 0.775, sensitivity 78.9%, specificity 72.3%). Thus, an IL-2 level below 251.1 IU/mL may be considered a significant prognostic marker for LTBI progression.

Although isoniazid monotherapy remains the standard prophylactic treatment for LTBI, our data revealed an association between isoniazid monotherapy and an increased risk of progression to active tuberculosis. This may be explained by suboptimal adherence and the presence of drug-resistant mycobacterial strains, which reduce the effectiveness of the monotherapy. The selective pressure exerted by isoniazid alone can promote the emergence of multidrug-resistant TB (MDR-TB), thereby compromising prophylactic efficacy. These findings are consistent with those of published studies showing that combination regimens, such as isoniazid with rifapentine, achieve better prevention outcomes and reduce the risk of progression[18]. Our results emphasize the importance of individualized preventive therapy guided by drug susceptibility testing and close monitoring of treatment adherence.

Our study also highlights the complex interplay between immunological markers and sociodemographic factors in LTBI progression. The combination of lower IL-2 levels with adverse social determinants, such as malnutrition, household overcrowding, and unstable parental employment, indicates the need for a comprehensive multidisciplinary approach to pediatric TB prevention. Future strategies should integrate immunological screening with social and environmental interventions to effectively reduce the risk of TB progression.

Future studies should validate this predictive model across diverse epidemiological settings and evaluate its feasibility for implementation in routine primary care. Additional interventional trials focusing on maternal health, nutritional support, and optimized preventive chemotherapy are warranted to establish causality and inform the national TB control policies.

In conclusion, this study enriches the evidence base for LTBI progression in children by providing a predictive framework grounded in both biomedical and social risk factors. These findings advocate for a shift toward personalized, risk-adapted TB prevention strategies in high-burden, resource-limited contexts.

Ethical Considerations

Protection of persons and animals. This study involved human participants and was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/). The research protocol was approved by the Ethics Committee of Samarkand State Medical University (Protocol No. 35, dated December 1, 2021).

Protection of vulnerable populations. The study population included children aged 4–12 years, who are considered a vulnerable group. Written informed consent was obtained from the parents or legal guardians of all participants before their inclusion in the study.

Confidentiality. The authors affirm that all data were collected and analyzed in compliance with the institutional protocols for confidentiality. Written informed consent was obtained from the guardians of all participants. The Methods section includes information on ethical approval and consent procedures.

Privacy. All personal data were anonymized to protect the participants' identities. No names, initials, or identifiable information were used in the manuscript or the tables. Written consent for participation and data use was obtained from the parents or guardians. No patient photographs were used in this study.

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Conflict of Interests. The authors have no conflict of interest to declare.

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