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Childhood Tuberculosis Following Household Exposure: Risk Factors and Clinical Outcomes from a Retrospective Cohort

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Abstract

Background: Tuberculosis (TB) remains a major cause of morbidity and mortality, with children primarily infected through close contact with adults. Data on household transmission in children in Türkiye are limited.

Objective: This study aimed to determine the prevalence of latent t.u.berculosis infection (LTBI) and active TB disease among pediatric household contacts of adults with pulmonary multidrug-resistant (MDR) or drug-susceptible (DS) TB and identify risk factors associated with TB infection.

Methods: This retrospective study included children (0–18 years) exposed to adult pulmonary TB at a tertiary center (2018–2024). Demographic, clinical, and diagnostic data were collected. Pediatric cases were classified as latent or active TB, and index case resistance as MDR or DS. The risk factors for active TB were evaluated.

Results: A total of 124 household contacts were evaluated. The median age of the contacts was 111 months (IQR 47-151), and 65 (52.4%) were female. Bacillus Calmette-Guérin (BCG) coverage was 92.7%. LTBI was detected in 7 (5.6%) and active TB in 11 (8.8%) children. The absence of BCG vaccination ($p = 0.027$) and longer time to presentation ($p = 0.002$) were significantly associated with TB. Exposure to an MDR-TB index case significantly increased TB risk (42.9% vs 6.9%, $p = 0.016$). On multivariate analysis, MDR-TB contact (OR: 8.5; 95% CI: 1.39–52.4) and lack of BCG vaccination (OR: 6.3; 95% CI: 1.09–36.2) were independent predictors of disease.

Conclusion: A substantial proportion of pediatric household contacts of TB patients developed infection or disease, with delayed evaluation, MDR-TB exposure, and absence of BCG vaccination significantly increasing the risk of progression.

Keywords Pediatric tuberculosis · Household contact · Multidrug-resistant tuberculosis · Tuberculosis risk factors

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INTRODUCTION

Tuberculosis (TB) is a disease caused by *Mycobacterium tuberculosis* (Mtb) and is one of the leading causes of morbidity and mortality among all age groups. According to the World Health Organization's (WHO) 2024 Global Tuberculosis Report, TB affects more than 10 million people annually, and this number has been increasing since 2021 (1). Children and adolescents under the age of 15 account for approximately 11% of the global TB burden; therefore, 1.1 million children contract TB each year, with nearly half of them being under the age of five (2). According to the report published in 2023, based on 2020 data, the total number of TB cases reported in Türkiye was approximately 9,000, of which 4.4% were children under 15 years of age. The same report indicated that among new cases subjected to drug susceptibility testing, the rate of multidrug-resistant tuberculosis (MDR-TB) was 2.2% (3). TB transmission to children usually occurs through prolonged and close contact with adults who have pulmonary tuberculosis. After exposure, children are at the highest risk of developing the disease within the first two years, with the risk being particularly high in children under the age of five (4). The WHO recommends contact screening, preventive treatment for high-risk individuals, drug susceptibility testing, and the treatment of all diagnosed TB cases as key strategies. Effective TB control heavily relies on contact screening and the treatment of TB cases arising from contact (5). There is limited information from Türkiye regarding the frequency of TB infection in children who have been in close contact with adults diagnosed with TB. This study primarily aimed to assess the rates of latent TB infection (LTBI) and active TB disease in pediatric household contacts of adults with either multidrug-resistant (MDR) or drug-sensitive (DS) TB. A secondary aim was to explore the risk factors associated with TB infection development in these children.

METHODOLOGY

Setting and Patients

This study was a cross-sectional retrospective cohort study. Patients aged 0-18 years who were household contacts of an adult diagnosed with pulmonary TB and presented to the pediatric infectious disease outpatient clinic of a tertiary center between January 2018 and December 2024 were consecutively included (n = 135). A total of 135 child household contacts of 71 adult TB index cases were evaluated. Following the exclusion of 11 contacts due to incomplete data, 124 (7 MDR TB and 117 DS TB) were included in the final analysis (Figure 1).

Study Groups and Definitions

In this study, after evaluating all contacts, they were divided into case groups according to the following diagnoses. The definitions of the case groups are as follows:

The household contacts group refers to individuals living in the same household as an adult tuberculosis (TB) index case and having close, long-term exposure to the infected person.

Multidrug-resistant TB (MDR-TB) contacts are individuals who are exposed to an MDR-TB index case in their household.

Drug-susceptible TB (DS-TB) contacts are household contacts exposed to a DS-TB index case.

The latent TB infection (LTBI) group comprises household contacts who have a positive tuberculin skin test (TST) and an interferon-gamma release assay (IGRA) result without active TB disease.

The TB disease group refers to household contacts with a clinical or microbiological diagnosis of active TB disease.

The non-TB group consisted of household contacts who had not developed active TB disease, excluding those with latent tuberculosis infection (LTBI).

Pediatric household contacts of MDR-TB and DS-TB index cases were evaluated to assess the risk of developing active TB. However, a comparative analysis between the drug-resistant and drug-susceptible groups could not be performed due to the presence of only one index case with drug-resistant TB that did not meet the MDR-TB classification criteria.

In Bacillus Calmette-Guérin (BCG) vaccinated children, a TST result >15 mm was considered positive, whereas a threshold of >10 mm was used for unvaccinated children and >5 mm for immunocompromised patients. Multidrug-resistant tuberculosis (MDR-TB) is defined as tuberculosis caused by strains of Mtb resistant to at least two major first-line anti-tuberculosis drugs, isoniazid (INH) and rifampin (R) (6).

Data Collection

Age, gender, underlying diseases, time of admission after the index case, BCG vaccine status, symptoms (fever, cough, night sweats, etc.), physical examination findings, posteroanterior (PA) and lateral chest X-rays, thoracic computed tomography (CT), and other radiologic imaging studies, tuberculin skin test (TST), interferon-gamma release assay (IGRA) results, and laboratory findings as follows: white blood cell (WBC) count, neutrophil (Neu) count, platelet (Plt) count, c-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Microbiological tests included acid-fast bacilli (AFB) screening, mycobacterial culture for detection of *Mycobacterium tuberculosis complex* (MTBC), and a polymerase chain reaction (PCR) test for Mtb on respiratory specimens. These specimens were collected and evaluated accordingly.

CULTURE AND PCR METHOD

Respiratory specimens (early morning gastric aspirate and sputum samples) were processed for both mycobacterial culture and molecular detection of Mtb.

For liquid culture, the specimens were decontaminated using the standard N-acetyl-L-cysteine–sodium hydroxide (NALC–NaOH) method and inoculated into mycobacteria growth indicator tubes (MGIT). Cultures were incubated and monitored using the BD BACTEC MGIT 960 system (Becton Dickinson, Sparks, MD, USA) for up to 42 days.

For solid culture, the samples were inoculated onto Löwenstein–Jensen medium and incubated at 35–37°C for up to 8 weeks. Colonies suggestive of MTBC were further evaluated using conventional biochemical or molecular methods.

For molecular testing, the MTBC nucleic acid (DNA) point-of-care test (POCT) based on the automated integrated gene sequencing (AIGS) real-time fluorescent PCR method (Hangzhou Lifereal Biotechnology Co., Ltd., Hangzhou, China) was used to perform a polymerase chain reaction (PCR) assay targeting specific genetic sequences of Mtb. The test was performed according to the manufacturer's protocol on the respiratory specimens. Molecular typing was conducted using the Truenat molecular platform (Molbio Diagnostics, Goa, India), while drug susceptibility and resistance profiling were performed using both the BD BACTEC MGIT 960 system (Becton Dickinson, Sparks, MD, USA) and the Truenat platform.

Statistical Analysis

Demographic and descriptive continuous variables with normal distribution are reported as the mean (standard deviation, SD), whereas non-normally distributed data are presented as median values (interquartile range, IQR). The median or mean values between the two groups were compared using the Mann–Whitney U test or Student's t-test depending on the sample distribution. In contrast, categorical variables were compared using the chi-square or Fisher's exact test as appropriate. A p value of ≤ 0.05 was considered statistically significant. Logistic regression analysis was conducted to examine the associations between the independent variables and the outcome.

Ethics Statement

This study adhered to the ethical standards outlined in the Declaration of Helsinki. Ethical approval was granted by the Research Ethics Committee of the Faculty of Medicine at Marmara University in Türkiye on April 6, 2014 (Approval No: 09.2024.615). Informed written consent was obtained from the parents or legal guardians of all participating children.

RESULTS

A total of 124 household contacts were evaluated. The median age of household contacts was 111 months (IQR 47-151 months), and 65 (52.4%) were female. The median time to presentation after exposure was 20 days (IQR: 10-90 days). A total of 12 out of 124 children (9.6%) in the study population had an underlying disease, with the most common being asthma (8 cases, 6.5%), followed by atrial septal defect (2 cases, 1.6%), hypothyroidism (1 case, 0.8%), and immunodeficiency (1 case, 0.8%). A total of 115 out of 124 (92.7%) children had received the BCG vaccination. The overall prevalence of LTBI was 5,6% (7 of 124) among the household contacts. Tuberculosis was detected in 11 (8.8%) TB-exposed children. Among these, eight were clinically diagnosed, while three (2.4%) had Mtb growth in the respiratory tract samples. Notably, in three children diagnosed with TB, the index case was MDR (Figure 1).

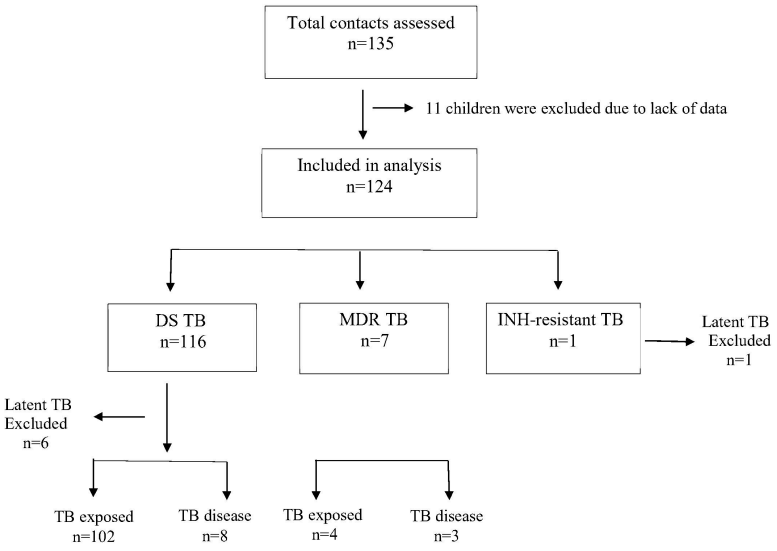

Figure 1. Flow chart showing distribution of pediatric household contacts in the MDR TB and DS TB groups

Index Case Features

The most common index case was a parent, accounting for 39% of cases (50 cases), followed by a grandparent (27 cases, 21%) and a sibling (21 cases, 16%). Additionally, Mtb growth was detected in the respiratory samples of all index cases contacted by 124 children. Multidrug-resistant (MDR) tuberculosis was detected in the index cases of seven contacts.

Comparison of Tuberculosis Disease Group is Non-Tuberculosis Disease Group

The median age of children in the TB disease group was 103 months (IQR: 47-154 months), which was lower than the mean age of those in the non-TB group (112 months, 10-162 months); however, the difference was not statistically significant. Additionally, the time to presentation after contact was significantly longer in children with TB (60 days, IQR 60–210) than in those without TB (15 days, IQR 10–36) (p = 0.002). The absence of BCG vaccination was significantly more common among children with TB (27.3%) than those without (4.7%) (p = 0.027). The characteristics of the children with and without TB disease are summarized in Table 1.

Table 1. Demographic, Clinical and Laboratory Characteristics of Pediatric Patients with and without Tuberculosis

Variables	No TB Disease (n = 106)	TB Disease (n = 11)	*P* Value
Age			
Months; median (25th-75th)	112 (IQR:47-154)	103 (IQR:10-162)	0.6*
Gender, n (%)			
Male	53 (50%)	2 (18.2%)	**0.042**†
Female	53 (50%)	9 (81.8%)	
BCG status, n (%)			
Vaccinated	101 (95.3%)	8 (72.7%)	**0.027**‡
Relation to Index Case, n (%)			
Parent	42 (39.6%)	6 (54.6%)	0.26†
Other	64 (60.4%)	5 (45.5%)	
Symptoms, n (%)			
Cough	27 (25.5%)	6 (54.5%)	0.051‡
Fever	2 (1.9%)	2 (18.2%)	**0.044**‡
Weight loss	4 (3.8%)	1 (9.1%)	0.4‡
Night sweats	6 (5.7%)	2 (18.2%)	0.16‡
Time to Admission after Contact with Index Case (days; median (25p-75p)**)**	15 (IQR:10-60)	60 (IQR:60-285)	**0.003***
Multiple Drug Resistance	4 (%3,8)	3 (%27.3)	**0.018**‡
Imaging, n(%)			
Chest X-ray pathology present	15 (14.2%)	8 (72.7%)	**<0.001**‡
Chest CT pathology present	6 (46.2%)	11 (100%)	**0.005**‡
Laboratory Values			
WBC (/µL), mean±sd	8244 ±3100	10690 ±3422	**0.016**++
Lym (/µL), median (25th-75th)	2900 (IQR:2300-4000)	3600 (IQR:3050-4500)	0.148*
Neu (/µL), median (25th-75th)	3500 (IQR:2550-4600)	3800 (IQR:2200-8800)	0.32*
Plt (x10^3/µL),median (25th-75th)	303 (IQR:258-343)	364 (IQR:326-458)	0.1*
CRP (mg/L) median (25th-75th)	0.8 (IQR:0.2-3.0)	39 (IQR:0.3-79)	0.051*
ESR (mm/h) median (25th-75th)	7 (IQR:4-11)	33 (IQR:28-77)	**<0.001***

a Mann–Whitney U test, ++: Student's t-test, †: Chi-square test, ‡: Fisher's exact test

CRP: c-reactive protein, CT: computed tomography, ESR: erythrocyte sedimentation rate, IQP: interquartile percentile, Neu: neutrophil cont, Plt: platelet cont, WBC: white blood cell co

Table 2. Radiological findings of the household contact children

Finding	No TB Disease (n = 106)	TB Disease (n = 11)
Chest X-ray Findings	**n %**	**n %**
No pathology	91(85.8%)	3 (27.3%)
Infiltration	12 (11.3%)	3 (27.3%)
Hilar lymphadenopathy	2 (1.8%)	3 (27.3%)
Cavity	0	2 (18%)
Miliary involvement	0	1 (9%)
Effusion	1 (0.9%)	0
Thorax CT Findings (n:24)	**(n=13)**	**(n=11)**
No pathology	7 (53.8%)	0
Parenchymal infiltration	3 (23%)	5 (45.4%)
Mediastinal lymphadenopathy	0	8 (72.7%)
Nodule	2 (15.3%)	7 (63.6%)
Atelectasis	2 (15.3%)	2 (18.1%)
Cavity	0	3 (27.2%)

CT:computed tomography, TB:tuberculosis

Regarding all symptoms, cough was the most common symptom observed among all children, occurring in 36 of 124 children (29%). When comparing symptoms between the children with TB and non-TB groups, fever was significantly more common in children with TB (18.2% vs. 1.9%) (p = 0.044). However, no significant differences were observed in terms of cough, weight loss, or night sweats.

The radiological imaging findings of the patients are presented in Table 2. Parenchymal infiltration was the most common finding, followed by mediastinal lymphadenopathy. Imaging studies also revealed that pathological findings on chest X-ray were observed in 72.7% of children with TB , compared to only 14.2% in those without TB (72.7% vs. 14.2%) (p < 0.001). Similarly, pathological findings on thoracic CT scans were observed in 100% of children with TB, whereas the rate was 46.2% in children without TB (p = 0.005).

Comparison of MDR Group v Non-MDR Group

Children exposed to drug-resistant tuberculosis (MDR-TB) had a lower median age (89 months [IQR: 21–139]) compared with those exposed to drug-sensitive (non-MDR) tuberculosis (111 months [IQR: 47–159]); however, this difference was not statistically significant (p = 0.4). Among children exposed to MDR-TB cases, 85.7% had a parent as the index case, whereas this proportion was only 38.8% in the DS-TB contact group. This difference was found to be statistically significant (p = 0.02). In children exposed to MDR-TB cases, 42.9% developed tuberculosis disease, whereas only 6.9 % of those exposed to DS-TB cases developed the disease (p = 0.016), indicating a significant statistical difference.

Identification of Independent Predictors of Tuberculosis Disease

To predict tuberculosis among household child contacts, a multivariate logistic regression model was constructed based on age, gender, BCG vaccination status, time from the index case to admission, and MDR-TB contact history. MDR-TB contact history and lack of BCG vaccination were identified as independent predictors. Having had contact with an MDR-TB case was associated with an increased risk of tuberculosis [odds ratio (OR): 8.545, 95% confidence interval (CI): 1.393–52.410; p = 0.020], while not having received BCG vaccination was associated with a higher risk of tuberculosis (OR: 6.321, 95% CI: 1.088–36.15; p: 0.040). Other variables, including age, gender, and time from the index case to admission, were not significantly associated with tuberculosis in the model.

Treatment

A total of 94 contacts (75%) received prophylaxis. Of these, 90 received INH for six months, while two were switched to a 4-month R regimen due to INH-induced liver toxicity, and one received R because of INH resistance. Among the children with contact with MDR-TB, three were closely monitored without receiving prophylaxis, one received prophylaxis based on the drug susceptibility of the index case, and three were diagnosed with TB disease. None of the patients who received prophylaxis developed TB disease during the follow-up period.

In our study, of the 11 patients diagnosed with TB, eight received standard TB treatment with isoniazid, rifampin, pyrazinamide, and ethambutol (HRZE), while three patients were treated with amikacin, moxifloxacin, cyclophorine, pyrazinamide, and linezolid based on the drug susceptibility of the source case.

DISCUSSION

Tuberculosis is treatable and preventable; however, it continues to be a leading cause of death in children. Early detection, source case identification, and treatment are crucial to prevent further infections. This study focused on children who were exposed to TB within household settings. It evaluates the risk factors for developing the disease and emphasizes the importance of early diagnosis, vaccination, and preventive treatment in reducing disease progression.

A significant finding of our study was the relatively high proportion (8.8%) of TB disease among children with household exposure, which is consistent with previous studies that report a risk range of 3.3%–5.5 % (7). In Türkiye, there is no comprehensive study or national dataset on contact screening in childhood. However, various clinical studies have reported the rate of TB infection among contact children. In a study by Durmuş et al., this rate was found to be 30% (8).

In our study, the unvaccinated status for BCG was significantly associated with an increased risk of developing tuberculosis, reinforcing the well-established protective effect of BCG vaccination in childhood (9). Colditz et al. (10) reported that the BCG vaccine provides an overall efficacy of approximately 50%–60% against childhood TB, with higher protection rates of around 70%–80% against severe forms such as TB meningitis and miliary TB. Similarly, Trunz et al. (11) analyzed 18 case-control studies and found efficacy rates of 73% for TB meningitis and 77% for miliary TB , confirming BCG's strong protective effect. Consistent with the WHO recommendations to vaccinate in countries with a high TB burden due to strong evidence of the protective effect of BCG against severe pediatric TB, our findings further emphasize the critical importance of BCG vaccination in preventing tuberculosis during early childhood, especially in high-risk populations (12).

The study revealed that children diagnosed with TB presented significantly later after exposure (60 days) compared with those without TB. This finding aligns with previous reports indicating that 83% of pediatric TB cases are diagnosed within the first 90 days following exposure, emphasizing the importance of close monitoring during this critical period (13). Delayed diagnosis has been identified as a key factor contributing to disease progression and worse clinical outcomes in pediatric TB, underscoring the need for early

detection and timely treatment to prevent disease advancement and transmission (14).

The clinical spectrum of TB in children is highly variable, ranging from asymptomatic cases to those presenting with subtle and nonspecific symptoms (15). Especially when diagnosed through contact tracing, children with active TB may be entirely asymptomatic (16). In our study, cough was identified as the most common symptom among children with TB, consistent with the findings of Marais et al. (17). In their study, 46% of children (n = 428) presenting with a persistent cough lasting more than 2 weeks were diagnosed with pulmonary TB . These results highlight persistent cough as an important clinical indicator of TB diagnosis in children. Although fever is generally considered an uncommon symptom of TB in children, low-grade and intermittent fever can still be present in pediatric TB cases (15). In our study, fever was significantly associated with TB disease, highlighting its importance as a clinical sign to consider during pediatric TB screening.

In our study, children exposed to MDR-TB had a significantly higher risk of developing active TB (42.9%) compared with those exposed to drug-susceptible TB (7.3%). Studies in the literature present conflicting data regarding the risk of TB among contacts of drug-susceptible and MDR-TB patients. For instance, a study by Becerra et al. found that contacts exposed to MDR-TB had a higher risk of TB infection compared to contacts of DS-TB cases but no significant difference in active disease development (18). Additionally, Teixeira et al. (19) reported no differences in infection or disease rates between the two groups. In contrast, the study by Javaid et al. (20) showed that 17.4% of MDR-TB contacts developed active TB, compared to 4.2% among contacts of DS-TB cases. Our findings may be explained by the fact that children exposed to MDR-TB cases were subjected to longer periods of infectiousness due to delayed diagnosis, prolonged treatment courses, and treatment non-adherence in these index cases. This extended exposure period increased the likelihood of transmission and progression to active tuberculosis among child contacts. Therefore, the higher rate of TB observed in the MDR-TB contact group may reflect this prolonged and more intense exposure, highlighting the need for targeted surveillance and preventive strategies in this high-risk group.

In this study, parental index cases were significantly more common in the MDR-TB group (85.7%) than in the DS-TB group (38.8%). This finding is consistent with the findings of Dayal et al. (21), who also reported a significantly higher proportion of infected children with parental index cases in the MDR-TB group than in the DS-TB group. In our setting, close and prolonged contact between children and parents may contribute to increased transmission risk in MDR-TB. However, this contrasts with the study by Seddon et al. (22) which found no association between the type of index case and TB infection. These differences may reflect variations in household structures and caregiving patterns across different populations. This finding underscores the critical role of parental MDR-TB exposure in childhood TB outcomes. It emphasizes the necessity of systematic screening and early diagnosis of household contacts for effective TB control in children.

Prophylactic treatment was administered to 75% of the exposed children, with INH being the most used agent. Importantly, none of the children who received prophylaxis developed TB during follow-up, reinforcing the effectiveness of preventive therapy in reducing disease progression. Consistent with our findings, previous studies have shown that preventive therapy significantly reduces the risk of TB among exposed children, with an overall effectiveness of 63% (13). However, given the increasing prevalence of drug-resistant TB, preventive therapy for MDR-TB remains controversial. There is general agreement that preventive therapy is warranted, especially for high-risk contacts such as immunocompromised individuals or very young children, but there is no consensus on what regimen(s) should be used (23).

Limitations

This study has a retrospective design, and some data may be incomplete. The small number of children exposed to MDR-TB limited comparisons between the groups. Being a single-center study also restricts the generalizability of the findings. Additionally, the follow-up duration varied among contacts, which may affect the accuracy of the disease progression rates. Molecular typing of the Mycobacterium tuberculosis strains was not performed, limiting confirmation of the transmission chains. Despite these limitations, the study offers valuable insights into TB exposure and risk factors in children, highlighting the need for larger, prospective studies.

CONCLUSION

Our study highlights the importance of early detection, vaccination, and prophylactic treatment in managing childhood TB exposure. This underscores the need for enhanced monitoring of MDR-TB contacts and timely medical evaluation after household exposure. Future research with larger cohorts and long-term follow-up is essential to better understand the well-known risk factors and refine the preventive strategies for pediatric TB.

Ethics Committee Approval	Ethical approval of this article was granted by the Research Ethics Committee of the Faculty of Medicine at Marmara University in Türkiye on April 6, 2014 (Approval No: 09.2024.615)
Informed Consent	Informed written consent was obtained from the parents or legal guardians of all participating children.
Peer Review	Externally peer-reviewed.
Author Contributions	Conception/Design of Study- S.Y., G.A., S.Ö.D. Data Acquisition- S.A.T., B.P., P.C.E., D.B.A., M.Ç.A. Data Analysis/Interpretation- G.A., E.K., S.Ö.D., A.D.İ.; Drafting Manuscript- S.Y., S.Ö.D., S.A.T., B.P, P.C.E., D.B.A., M.Ç.A.Ç;

Critical Revision of Manuscript- G.A., E.AK., S.Ö.D., A.D.I. ..; Final Approval and Accountability- G.A., S.Ö.D.,S.Y., S.A.T., A.D.I., B.P., P.C.E., D.B.A., M.Ç.A.Ç..

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