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Predicting the Incidence Rate of Tuberculosis in Western Iran Using Time Series Models Before and After COVID-19

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Abstract

Background: Understanding the temporal variation and forecasting the incidence rate of smear-positive tuberculosis may be very helpful in promoting tuberculosis (TB) control initiatives. Therefore, predicting the incidence rate of TB before and after coronavirus disease 2019 (COVID-19) was the aim of this study.

Methods: This retrospective study was carried out utilizing data from Iran's National TB Control Program and the monthly TB incidence statistics from April 2005 to March 2021 in Kurdistan Province. There were 192 time points in total cases that were registered each month. Autoregressive Integrated Moving Average (ARIMA) models and interrupted time series were used in the study.

Results: The findings demonstrated that TB incidence was declining before the COVID-19 pandemic. However, despite the COVID-19 pandemic, the number of TB diagnoses has unexpectedly declined. During the 26 months of the pandemic, 8 cases of total TB cases, 6 cases of pulmonary TB cases, and 3 cases of extrapulmonary TB cases were detected, while predicted an average number of TB cases during the 26 months of the pandemic is 15 cases per 100,000 for total TB cases, 10 cases per 100,000 for pulmonary TB cases, and 3 cases per 100,000 people for extrapulmonary TB.

Conclusion: Our results show that TB patient detection in the Kurdistan region has become significantly more challenging because of the COVID-19 epidemic. In the event that the pandemic persists or recurs in the future, guidelines should be developed to protect these essential services.

Keywords: Tuberculosis, Predicting, Time Series Models, COVID-19 Pandemic

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Introduction

Tuberculosis (TB) usually affects the lungs, although it can affect almost any organ in the body and it is believed that 2 billion people worldwide are thought to be asymptomatically infected with mycobacterium TB and are at risk of developing active TB in the future (1). Also, 5% to 10% of those who are infected will get this sickness. Although TB can affect other organs, its primary effect is on the lungs (2). Humans are usually exposed to mycobacterium TB through the respiratory system; pulmonary TB affects around 80% of cases (3). Although several methods of treatment have been developed for TB, the disease is still a serious public health concern globally, particularly in poor nations such as Iran (4). About 10 million individuals worldwide have TB each year, which makes it the ninth most prevalent disease in the world (5). The World Health Organization estimates that the number of deaths associated with TB in 2021 was 1.4 million, more than twice the number of deaths related to human immunodeficiency virus/acquired immunodeficiency syndrome (0.65 million) (6). The General Department of TB and Leprosy reported in 2021

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↑What is "already known" in this topic:
In recent years, the trend of tuberculosis has been gradually decreasing. Unfortunately, health programs were disrupted by the COVID-19 pandemic, and it is still unknown how this affected tuberculosis (TB).

→What this article adds:
This work clarified that the COVID-19 pandemic has disrupted the diagnosis of TB patients in the Kurdistan region. Based on the time series model, the COVID-19 pandemic has increased the incidence of TB and the number of TB cases will not decrease until 2026.

that there were 7299 cases of various TB kinds in Iran, with 3945 cases (4.6 cases per 100,000 individuals) being smear-positive. Furthermore, between 2017 and 2021, the overall TB incidence rate decreased from 10.5 per 100,000 patients to 8.5 (7). The coronavirus disease 2019 (COVID-19) pandemic had an adverse effect on the prevalence of the disease, diagnosis, and treatment of TB. The majority of nonemergency services were suspended, which caused a delay in the identification of new TB cases (8). Recent reports state that the COVID-19 outbreak has negatively impacted patient care and referral, which has led to a decrease in the diagnosis and follow-up of diseases (9). The number of persons who are infected and untreated has grown, as seen by the drop in new TB cases recorded in 2020 and 2021. As a result, there will be a little delay before TB mortality and prevalence increase (10). In the future years, mortality is predicted to rise by roughly 13% (8). Although the incidence of TB in Iran is decreasing, it shares geographical boundaries with nations that have a high TB prevalence (11). Iraq accounts for approximately 3% of all TB cases and is 1 of 7 countries in the Eastern Mediterranean Regional Office region with a high TB prevalence. Compared to Iran, Iraq has a higher incidence. While it has been used in Iraq since 1998, the Directly Observed Treatment Short Course (DOTS) approach has only been applied in the Kurdish areas since 2001(12). Knowing the current status of TB in Iran's Kurdistan province is crucial because of its proximity to Iraqi Kurdistan and the effects of the COVID-19 pandemic (13-15). Forecasting and determining out the seasonal and temporal patterns of TB incidence is helpful. Determining the incidence pattern makes it possible to forecast the extent of upcoming health issues and offer the required medical care (16). To our knowledge, no exact data exist on the prevalence of TB in Iran's Kurdistan region. Thus, the goal of this study was to use a time-series model to evaluate the trend of TB in this province both before and after COVID-19. Understanding the TB disease pattern and anticipating new cases can assist policymakers in supporting screening programs and the early detection of TB cases.

Methods

Study Area and Data Collection

This study retrospectively examined data on TB patients diagnosed between April 2005 and March 2021 who were enrolled in the Kurdistan Province Tuberculosis Registration System. All TB cases confirmed by a clinical or laboratory diagnosis in Iran have to be reported within 24 hours, after which they must be examined by experts from nearby centers for disease prevention and control. Considering the date of diagnosis entered into the system, we had information on 2956 TB cases. All TB cases identified during the specified period were included in the analysis using the complete enumeration sample method used in this investigation. To avoid bias in the number and cause of illness, as well as to ensure the formation and control of competing hazards, the history and cause of patients were precisely documented in cooperation with the Civil Registration Center of the Kurdistan Provincial Health Department.

Inclusion and Exclusion Criteria

Cases were considered to have a TB infection and included in the study if they met either of the following criteria: (1) a positive sputum acid-fast bacilli test, a positive sputum culture for TB, or imaging findings consistent with TB; or (2) completion of a full course of treatment for pulmonary or extrapulmonary TB. Cases were excluded if they met any of the following criteria: (1) presence of TB symptoms or a prior TB diagnosis before employment at the hospital, (2) resignation before the study period, (3) a diagnosis of latent TB infection (LTBI), or (4) medical records that were incomplete, missing key information, or contained ambiguous diagnostic data.

Definition of Variables and Their Calculations

The number of new TB cases (a "new case" of TB is defined by the TB Dictionary as a person who has never had treatment for TB or who has taken anti-TB medication for less than a month) was divided by the number of person-years (PYs) to get the TB incidence rates. The incidence of TB (total patients, pulmonary TB, and extrapulmonary TB) was also computed per 100,000 people from April 2005 to March 2026. In the first case, the incidence rate of the disease was calculated using the data found between April 2005 and March 2020. In the second instance, the incidence rate for 2022–2026 was estimated using data that had already been found.

Construction of the Statistical Model Used

Trends in TB disease were predicted using time series models. Model identification, parameter estimation, model diagnostics, and forecasting were all included in the Box-Jenkins methodology. Time series of the data were shown for the period 2008–2017 to identify the various time series components in the data. The data were replotted after being log-transformed. The Augmented Dickey-Fuller (ADF) test was used to evaluate and validate stationarity in the modified data. With the ADF test P ≤ 5% level of significance, the series was considered stable. Also for evaluating the COVID-19 pandemic's effects on the TB disease (pulmonary, extrapulmonary, and overall TB cases), the TB disease trend from April 2005 to March 2021 was examined using interrupt time series models and accounting for data autocorrelation (17). The equation of order for the autoregressive model is as follows:

$$Outcome_{jt} = \beta_0 + \beta_1 \cdot time_t + \beta_2 \cdot level_j + \beta_3 \cdot trend_{jt} + \varepsilon_{jt}$$

The best model was chosen based on the model with the lowest RMSE and AICC index value. Finally, the test was used to verify the residual correlation of the chosen model. The time series model was fitted for 2 modes: one mode included all TB data, and the other mode included TB data from before the COVID-19 pandemic. In both cases, the expected values of TB patients—pulmonary TB, extrapulmonary TB, and the total number of patients—were predicted, and the difference between the average value predicted and detected during the COVID-19 pandemic was computed to ascertain the effect of COVID-19 on the progression of TB (18, 19).

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Statistical Software

Data were entered using Microsoft Excel 2013 (Microsoft Corp) and analyzed with R statistical software, Version 3.3.2 (R Foundation for Statistical Computing). The autoregressive integrated moving average(ARIMA) model, a time series modeling approach developed under the Box-Jenkins methodology, was employed for the analysis. A significance level of 0.05 was used to determine statistical significance.

Results

From April 2005 to March 2021, 2956 TB patients were identified in Kurdistan, of whom 1893 had pulmonary TB and 1063 had extrapulmonary TB. The best ARIMA model is shown seasonally and for each category of TB observations (pulmonary TB, extrapulmonary TB, and total TB cases) in Table 1.

The COVID-19 Pandemic's Effects on Diagnosis of the Number of TB Cases

An analysis of the TB data trend revealed that the COVID-19 pandemic had an impact on both the overall number of patients and pulmonary TB cases; overall patient diagnoses decreased by an average of 5.8 patients and pulmonary TB cases by 4.5 patients ($P < 0.05$). However, the number of extrapulmonary TB diagnoses remained unchanged, and the trend was uniform (Figure 1) (Table 2).

Use a Time Series Model to Predict the TB Incidence From Data Collected During the COVID-19 Pandemic Compared With Data Collected Prior to the Pandemic

Despite the data from the COVID-19 pandemic, predictions indicated that in the years that follow, there will be an average of 6 (95% CI (-2.19,16.41)), 5 (95% CI (-2.6,13.84)), and 2 (95% CI (-3.7,7.7)) cases of TB, pulmonary TB, and external TB each month (Figure 2). Additionally, Figure 3 shows the annual incidence of TB, which was determined using both identified and forecasted data.

Also, the estimate predicated on data collected prior to the COVID-19 pandemic indicated that the aggregate number of TB cases, including pulmonary and extrapulmonary cases, would be 15(95% CI (5.26,24.58)), 10(95% CI ((2.63,16.98)), and 3(95% CI (0.05,9.34)) cases per month on average in the years to come (Figure 4). In Figure 5, the annual incidence of TB has been calculated using the

Table 1. Analysis of ARIMA Models for Predicting Respiratory Diseases in Different Periods

Periods	Model	AICc	RMSE
Considering the Covid-19 period	ARIMA (2,1,3) (0,1,1) [12] Total	999.43	4.01
(entire of period)	ARIMA (1,1,2) (0,1,1) [12] Pulmonary TB	933.82	3.37
	ARIMA (0,1,1) (0,1,1) [12] Extrapulmonary TB	847.38	2.64
Before the Covid-19 period	ARIMA (2,0,2) (1,0,1) [12] Total	1058.11	4.22
	ARIMA (2,0,1) (1,0,1) [12] Pulmonary TB	979.54	3.47
	ARIMA (0,1,1) (0,1,1) [12] Extrapulmonary TB	847.38	2.64

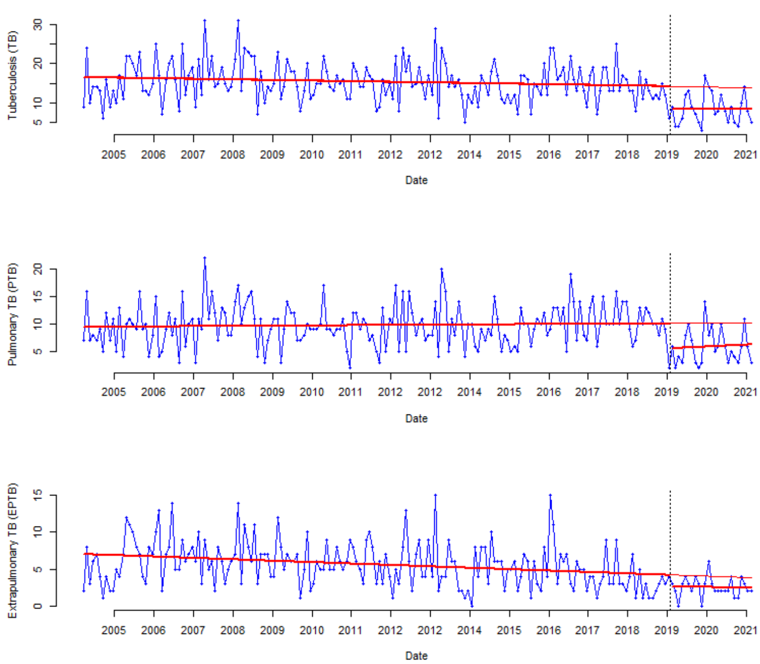

Figure 1. The impact of the COVID-19 pandemic on the diagnosis of the number of TB cases

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Table 2. Investigating the trend of the number of TB patients before and after the COVID-19 pandemic based on the Interrupt time series model

Interrupt time series		Estimate/95% CI	Std. Error	t-value	*P*-value
TB (TB)	(Intercept)	16.42 (14.92, 18.05)	0.76	21.64	0.0001
	Time	-0.01 (-0.03, 0.00)	0.007	-1.74	0.0830
	Level	-5.84 (-10.35, -1.34)	2.19	-2.66	0.0083
	Trend	0.02(-0.27, 0.30)	0.13	0.14	0.8876
Pulmonary TB (PTB)	(Intercept)	9.42 (8.36, 10.49)	0.52	18.04	0.0000
	Time	0.003 (-0.01, 0.01)	0.005	0.71	0.4747
	Level	-4.52 (-7.68, -1.37)	1.53	-2.95	0.0036
	Trend	0.02 (-0.18, 0.22)	0.09	0.24	0.8042
Extrapulmonary TB (EPTB)	(Intercept)	7.02 (6.02, 8.03)	0.48	14.41	<0.0001
	Time	-0.01 (-0.03, -0.01)	0.004	-3.40	0.0008
	Level	-1.52 (-4.37, 1.31)	1.37	-1.11	0.2682
	Trend	0.006 (-0.17, 0.19)	0.08	0.07	0.9380

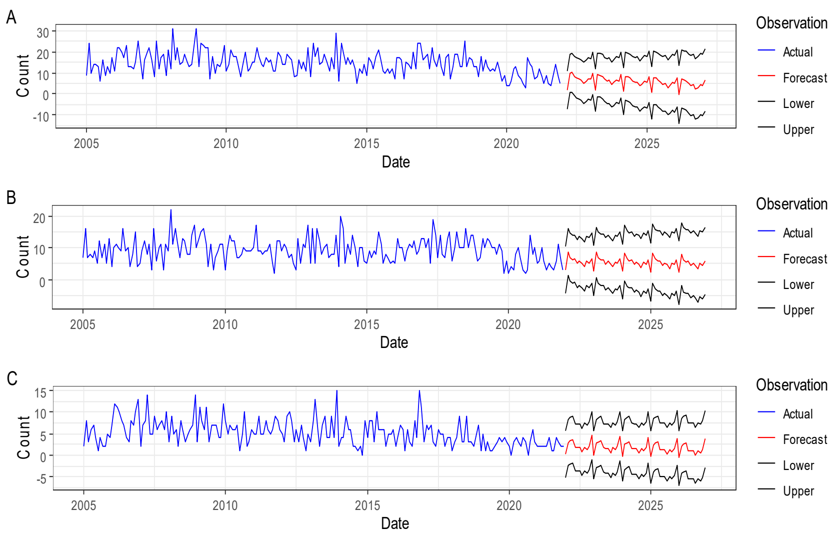

Figure 2. TB prediction based on total data (A: total patients, B: pulmonary TB, C: extrapulmonary TB)

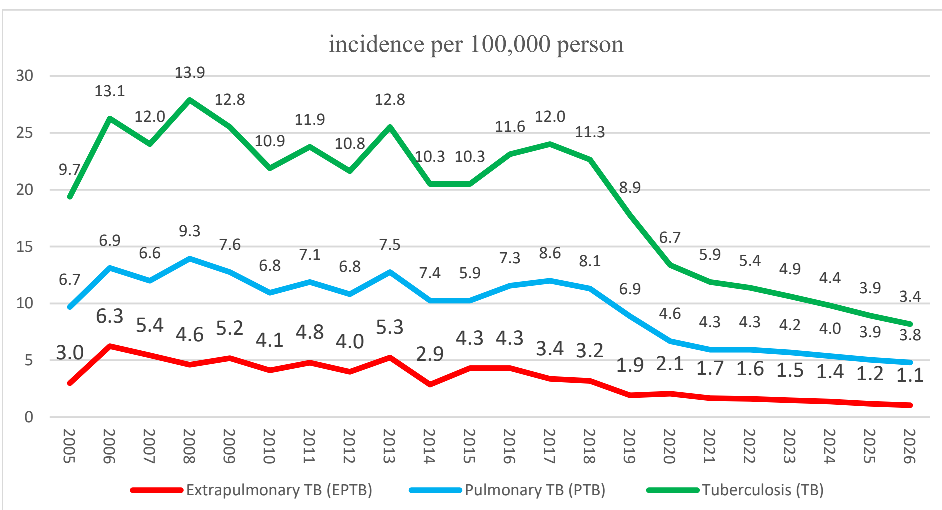

Figure 3. The annual incidence of TB in Kurdistan based on the identified and predicted data for the entire of period

identified and predicted data.

Discussion

According to our research, the COVID-19 pandemic has had an impact on the number of pulmonary and extra-pulmonary TB cases. The number of TB cases that were found was decreased by this epidemic. The COVID-19 pandemic has impacted all instances of TB; however, it has mostly targeted pulmonary TB. According to the estimated annual incidence of pulmonary TB independent of COVID-19, the number of TB cases per 100,000 people will decrease by 3.4 until 2026. According to the estimate incorporating the

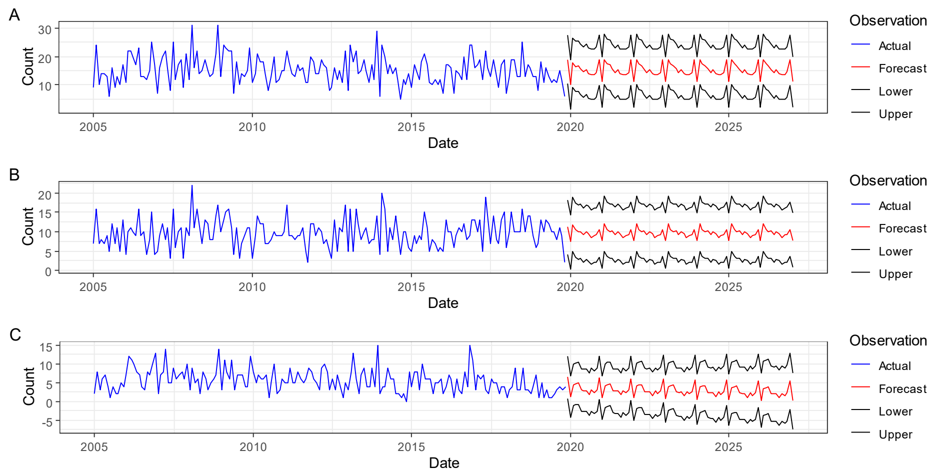

Figure 4. TB prediction before the COVID-19 pandemic (A: total patients, B: pulmonary TB, C: Extrapulmonary TB)

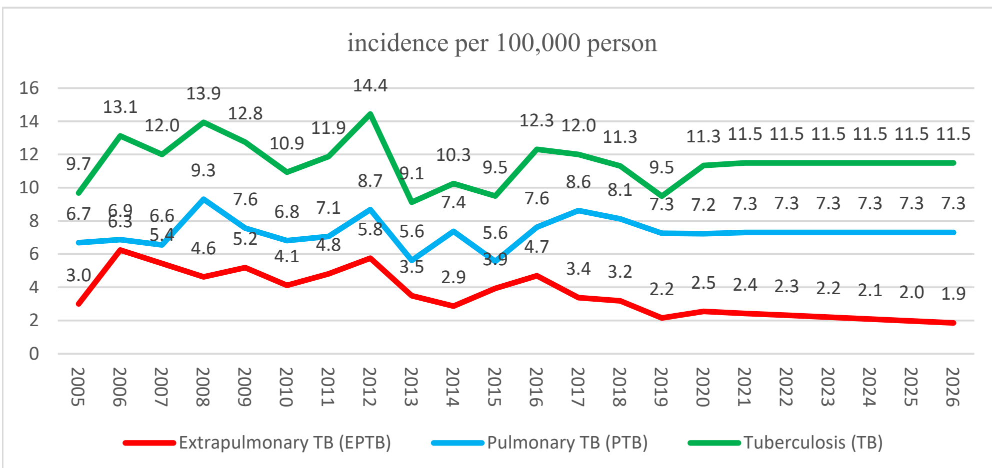

Figure 5. The annual incidence of TB in Kurdistan based on the identified and predicted data before the COVID-19 pandemic

effects of COVID-19, there will be 7.3 instances of pulmonary TB per 100,000 people in 2026. According to this model, the trend in TB incidence will not change until 2026.

Pulmonary TB cases have decreased as a result of COVID-19. The raised burden of health system and used facilities and health-workers in the COVID-19 pandemic damage to the diagnostic and treatment services of TB (20). The economic burden imposed on the health system and the increased workload of health workers affected TB control measures (21). There are many similarities between pathogenesis and clinical outcomes COVID-19 and TB (22). Although the lung is first infection organ in both TB and COVID-19, these diseases can involve other organs. The overlap of some symptoms of TB and COVID-19 caused the failure to diagnose TB during the COVID-19 pandemic (23). The COVID-19 pandemic caused a decrease in testing and health information about TB due to the limitation of TB services and the lack refer TB patients to health services (24).

However, people's fear also prevented them from using health services and harmed their treatment (25). COVID-19 delayed health care seeking. A fear of COVID-19 may cause for delay health care seeking. The diagnostic methods such as computed tomography scan were used to identify COVID-19 due to similarity of the symptoms of COVID-19 and TB (26). Postponing health care seeking due to the COVID-19 disease and not diagnosing TB in people can worsen the condition and increase the risk of transmission of TB disease (27). The lack of diagnosis and a high bacterial load for a long time increases the risk of transmission in close contacts (28). Although the risk of tuberculosis (TB) is recognized worldwide (28), underdiagnosis and underreporting can compromise the effectiveness of future control programs. Ineffective TB control represents a significant barrier to achieving the global targets for TB elimination and eradication by 2030. Delay in early diagnosis and treatment of new cases will increase the mortality of infected people. Longer delays lead to an increase in TB deaths. Drug-resistant TB is caused by improper therapy and delayed TB diagnosis (29). Although knowing the issues during the COVID-19 pandemic, TB can be detected and treated to reduce complications. By identifying the issue, the system can become more resilient to similar situations.

The prediction of TB cases with impact of COVID-19 showed that trend TB until 2026 is stable. The COVID-19 and TB are airborne infectious diseases and affect the lungs in the first attack. The symptoms of these two diseases are similar, making it challenging to differentiate between them, including fever, dyspnea, and cough (30).

The number of detected cases of pulmonary TB was decreased because there are similar clinical and symptoms between COVID-19 and TB. Several factors may have influenced the trend of tuberculosis (TB) during the COVID-19 pandemic: (1) Reactivation of latent pulmonary TB due to weakened immune function in individuals infected with COVID-19. Since approximately one-third of the global population has latent TB infection, immune suppression may trigger progression to active disease. (2) Vulnerable populations, including people living with HIV, immigrants, and refugees, were disproportionately affected. Poverty and reduced access to antiretroviral therapy during the pandemic may have contributed to an increased TB incidence (31). (3) Certain treatments for severe COVID-19, as well as lung damage caused by severe infection, may have facilitated the activation of opportunistic infections, increasing susceptibility to TB (32). (4) Disruptions in routine vaccination programs, including those for the BCG vaccine, may have negatively impacted TB prevention efforts in infants (32). We must consider how the COVID-19 pandemic has influenced the trend of tuberculosis. TB programming that does not have a significant pandemic impact COVID-19 may cause the program's efforts to eradicate tuberculosis to fail. Policymakers must modify TB eradication plans in light of the COVID-19 pandemic's effects.

This study had several limitations. We used ecological data and the quality of the data may be affected by data collection bias.

Conclusion

Our research indicates that TB cases have been affected by the COVID-19 pandemic. Forecasting models that account for COVID-19's impact on TB programs suggest that the number of TB cases is unlikely to decline until 2026. It is essential for policymakers to consider the effects of COVID-19 on TB control efforts, as neglecting these impacts could result in significant setbacks. This study underscores the urgency of reinforcing TB prevention measures and strengthening the resilience of health systems to withstand global health crises. Learning from this experience is crucial to ensure that TB prevention efforts are maintained and adapted in the face of future pandemics or other major disruptions.

Authors' Contributions

All authors contributed in designing, developing, and implementing the study.

Ethical Considerations

The Research Ethics Committee of Kurdistan University of Medical Sciences approved this study (Ethics code: IR.MUK.REC.1403.036). As this study utilized publicly available secondary data, individual consent to participate was not required.

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Conflict of Interests

The authors declare that they have no competing interests.

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