Original Article

Spatial Distribution of Smear-Positive Pulmonary Tuberculosis Incidence Rates in Iran: A Registry-Based Study (2018–2022)

Abstract

Background: Smear-positive pulmonary tuberculosis (SPPTB) is a significant public health concern in Iran. This registry-based study aimed to investigate the incidence rates of SPPTB in Iran from 2018 to 2022. **Methods:** The study analyzed SPPTB cases using the Spatial Lag Model to investigate the spatial distribution of SPPTB incidence rates, income inequality, and delayed diagnosis across the provinces of Iran and mapped the results using GIS maps. **Results:** The study found that SPPTB is prevalent among older individuals and males. The analysis identified significant spatial variation in the distribution of SPPTB incidence rates, income inequality, and delayed diagnosis across the provinces. The highest incidence rate of SPPTB was found in Sistan and Baluchestan Province and Golestan provinces. The study found a positive association between income inequalities, measured by the Gini index, and SPPTB incidence rates, indicating that provinces with higher income inequality may have higher incidence rates of SPPTB. The negative correlation with delayed diagnosis implies that predominantly, SPPTB cases are identified in the early months. **Conclusions:** The study highlights the need to address socioeconomic disparities in health outcomes and implement targeted interventions in areas with higher income inequality to reduce the burden of SPPTB in Iran. Despite decreased SPPTB incidence rates in Iran over the past decade, some regions, such as Sistan and Baluchestan, still have high incidence rates. The Iranian government has implemented policies and programs to reduce income inequality and delayed diagnosis within the country, which can contribute to reducing the burden of SPPTB.

Keywords: *Case notification rate, incidence rate, Iran, poverty, tuberculosis*

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Introduction

Tuberculosis (TB) is a major public health issue of global concern, with a high incidence reported worldwide. In 2021 alone, approximately 10.6 million cases and 1.6 million deaths were recorded due to TB. This infectious disease is caused by a bacterial infection that primarily affects the lungs but can also impact other organs.[1-3] The disease spreads through the air when an infected person coughs or sneezes, releasing TB bacteria into the air.[4] Smear-positive pulmonary tuberculosis (SPPTB) is a particularly concerning form of the disease as it is more infectious than other forms of TB and can spread easily from person to person.[5] SPPTB patients have a higher risk of transmitting the disease to others, and early diagnosis and treatment are essential for controlling the spread of the disease.

In the investigation of the factors influencing the TB incidence rate, it is crucial to recognize the potential role of social and economic factors. Moreover, delayed diagnosis stands out as a significant factor in the treatment of TB. The Gini coefficient can be employed to explore the effects of income inequality and poverty, while the impact of delayed diagnosis can be assessed by considering various variables.[6]

Poverty and income inequality are important determinants of TB incidence. Research has indicated that TB is more common among individuals in low-income communities, and poverty is a significant factor associated with the acquisition of the disease. Poor living conditions, inadequate nutrition, and limited access to healthcare services increase the likelihood of TB transmission and disease progression.[7] There is a correlation between the incidence of TB and the Gini index, which measures income inequality. Higher levels of income inequality are associated with higher TB incidence rates, even after controlling for

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other factors such as poverty and access to healthcare.[8] This may be due to the concentration of TB risk factors such as poor living conditions and limited access to healthcare services in low-income neighborhoods with high levels of income inequality.[9] Addressing these factors through poverty reduction programs, improved living conditions, and increased access to healthcare services could help reduce the incidence of TB and improve overall health outcomes.[10] Poverty is a significant risk factor for TB disease, and it can impact the incidence and transmission of TB in several ways. Crowded and poorly ventilated living and working environments, which are often associated with poverty, constitute direct risk factors for TB transmission.[11] Undernutrition is another important risk factor for developing active TB disease, and it is more prevalent among people living in poverty.[12] Several studies have shown a strong association between poverty and TB and have demonstrated that poor and vulnerable groups are at an increased risk of TB.[13]

Delayed diagnosis of TB is a significant challenge in global TB control and prevention efforts. Delayed diagnosis can lead to prolonged periods of infectivity, more advanced disease at the time of diagnosis, and increased risk of transmission to others.[14] Several factors contribute to these delays, including limited access to healthcare services, low awareness of TB symptoms among the general population, stigma associated with the disease, and the intricacies of TB diagnosis itself.[15] Understanding the factors contributing to delayed diagnosis is crucial for developing targeted interventions and strategies to expedite TB case identification and enhance TB control efforts. Some of the adverse consequences associated with delayed diagnosis of TB include increased mortality, worse clinical outcomes, and increased transmission to contacts. Therefore, early diagnosis and prompt TB treatment are essential for an effective TB control program.[16]

Iran has made progress in controlling TB, but different factors such as immigration from neighboring countries affect TB infection.[17] A study published in 2021 reported that the overall incidence rate of TB in Iran decreased from 13.46 in 2008 to 10.88 per 100,000 people in 2018.[18] However, poverty and low socioeconomic status are still important factors associated with TB in Iran.

Given the significant public health impact of SPPTB in Iran, it is crucial to understand the incidence rates and characteristics of SPPTB patients to develop effective TB control strategies. This study aims to investigate the incidence rates of SPPTB in Iran between 2018 and 2022 and identify the characteristics of SPPTB patients, including age, sex, bacillus density in the initial smear, delayed diagnosis, and geographical distribution. Data from a national TB registry in Iran was used, including SPPTB patients diagnosed during the study period. The study's findings will provide information for developing targeted interventions and improving TB control efforts in Iran. This study aimed to investigate the effect of the Gini coefficient and delayed diagnosis on SPPTB incidence rate using spatial regression. The Gini Index database was obtained from the Statistical Centre of Iran during 2018–2022 for every province. In this study, it is important to clarify the terminology used to describe our data source and analysis.

The incidence and case notification rate (CNR) are crucial measures for tracking the spread and impact of TB in a given population. Although the terms are sometimes used interchangeably, they represent distinct concepts. Incidence refers to the occurrence of new TB cases within a specific population over a certain period, usually 1 year. This measure is an essential determinant of the TB burden in a population and is often used to assess the risk of developing the disease within that community.[19] CNR, on the other hand, refers to the number of new cases of TB that are reported to public health authorities over a specific period, usually 1 year. CNR is a measure of the ability of a health system to detect and report cases of TB. The CNR is typically lower than the incidence rate because not all cases of TB are reported to public health authorities. Various factors can influence the CNR of TB, such as the effectiveness of the healthcare system, the accessibility of diagnostic tools, and the motivation of patients to undergo testing and receive treatment for TB.[20] CNR for TB closely mirrored the incidence rate as observed in other studies.[20,21] Our estimation of the incidence rate is based on the utilization of CNR data.

Methods

Design and study participants

This study involved a national historical cohort analysis in Iran, which was conducted from March 2018 to March 2022, utilizing data from the National Tuberculosis and Leprosy Registration Center of Iran's MOHME. The data collected revealed that in the study period, a total of 30705 cases of TB and 16165 cases of SPPTB were diagnosed in Iran.

The study's eligibility criteria focused on individuals with SPPTB due to its high transmission power in the community and the prioritization of treatment. This resulted in the inclusion of 16165 new SPPTB cases. From the information obtained through the TB registration portal and statistical center of Iran, the incidence rates of SPPTB, delayed diagnosis (the time between TB symptom onset and diagnosis), and Gini index in Iran provinces are included in this study.

Spatial regression analysis

Spatial analysis is a set of methods and techniques used to analyze and interpret spatial data, that is, data that are associated with a specific location or geographic area. Spatial analysis involves the use of specialized tools and techniques to examine patterns, relationships, and trends in spatial data and to develop spatial models that can be used to make predictions and inform decision-making.

Spatial analysis methods are typically implemented using specialized software tools, such as geographic information systems (GISs) and statistical software packages that have spatial analysis capabilities. These tools provide a wide range of functions and analysis techniques that can be used to explore, visualize, and analyze spatial data.

The objective of our research is to examine how the Gini index and delayed diagnosis of SPPTB affect the incidence rate of SPPTB in Iran. We hypothesize that nearby provinces may have more similar observations than provinces that are farther away, and therefore, we will utilize a spatial lag model to account for spatial dependence in our analysis. To clarify, the spatial lag model will allow us to incorporate the influence of neighboring provinces on the incidence rate of SPPTB in a more accurate way than traditional regression models. This is because the spatial lag term in the model represents the weighted average of the dependent variable for nearby provinces, and the weights are determined by the spatial weights matrix. By accounting for spatial dependence in this way, we will be able to obtain more reliable estimates of the relationships between the variables of interest.

The utilization of the spatial lag model will enable us to obtain more accurate and dependable estimates of the associations between the variables of interest by taking into consideration the spatial autocorrelation that is often present in spatial data. The spatial dependence of the dependent variable for a specific observation on the dependent variable for neighboring observations is a common occurrence in spatial data. This happens because nearby observations tend to be more comparable to each other than to observations that are located farther away. Additionally, the spatial lag model aids in addressing spatial autocorrelation, which occurs when the residuals of a regression model are correlated due to the spatial dependence present in the data. By accounting for spatial dependence in the data, the spatial lag model can help to reduce spatial autocorrelation and improve the reliability of the statistical inference. Mathematically, the spatial lag model can be written as

$$y = \rho W_y + X\beta + \varepsilon$$

where y is the dependent variable, ρ is the spatial autoregressive coefficient, W_y is the spatial lag term, X is a matrix of explanatory variables, β is a vector of coefficients, and ε is the error term. W is a spatial weights matrix that reflects the spatial relationships between the observations in the sample. In our study, we utilize a Moran I test and Moran Scatterplot to explore the spatial relationships between province incidence rates and their neighboring provinces. This visualization technique allows us to examine how the values of incidence rates at each province relate to the average incidence rate of their neighboring provinces.

In this research, we specifically analyze the incidence rate, a metric that involves the count of cases reported to the public health system. Given our focus on this particular rate, we rely on the data associated with reporting centers. These reporting centers serve as essential data sources for our study as they capture the cases that are reported to public health authorities. This approach allows us to analyze the geographic patterns of TB incidence, which can provide insights into the effectiveness of the healthcare system in detecting and responding to TB cases.

Statistical software

The data analysis was performed using statistical software programs, including SPSS (version 22, Institute Inc., Chicago, IL, USA), R (version 4.2.2, www.r-project.org), and Excel (version 2019), with a significance level of 0.05 and GIS.

Results

Table 1 presents the characteristics of 16165 patients with SPPTB in Iran and the results of a single risk factor analysis. The mean age of the patients was 52.3 ± 21.2 years, with the highest proportion of patients being in the age group of >64 years (37.1%). There were more male patients (56.4%) than female patients (43.6%). The mean weight of SPPTB patients was 55.1 ± 14.5 kg. Bacilli density in the initial smear was observed in varying proportions, with 3+ (36.2%) being the most common. Delayed diagnosis was found in 23.9% of patients with SPPTB diagnosed within 1 month, 46.1% of patients

Table 1: Baseline characteristics and single risk factor analysis of SPPTB cases in Iran (*n*=16165)

Characteristics		SPPTB patients	*P*
Age (year)	Mean±SD	52.3±21.2	-
Age (year)	<15 (*n* %)	391 (2.4)	
	15-35 (*n* %)	3944 (24.4)	<0.001*
	36-63 (*n* %)	5840 (36.1)	
	>64 (*n* %)	5990 (37.1)	
Sex	Female (*n* %)	7044 (43.6)	<0.001*
	Male (*n* %)	9121 (56.4)	
Weight (kg)	Mean±SD	55.1±14.5	-
Delayed diagnosis (month)	<1 (*n* %)	3865 (23.9)	<0.001 *
	1-3 (*n* %)	7459 (46.1)	
	3> (*n* %)	4841 (29.9)	
Bacilli density in initial smear	1–9 Basil (*n* %)	1501 (9.3)	<0.001*
	1+ (*n* %)	5355 (33.1)	
	2+ (*n* %)	3456 (21.4)	
	3+ (*n* %)	5853 (36.2)	
Nationality	Iranian (*n* %)	13126 (81.2)	<0.001*
	Others (*n* %)	3039 (18.8)	

*Significant at a level of 0.05

were diagnosed after 1–3 months, and 29.9% of patients were diagnosed after 3 months. All variables showed statistically significant differences ($P < 0.05$). The majority of patients were Iranian (82.1%), and most lived in urban areas (67.7%) [Table 1].

The GIS maps presented in this study display the spatial distribution of incidence rates, and Gini index varies across the provinces of Iran. The highest incidence rates are observed in Sistan and Baluchestan (77.62), followed by Golestan (62.05), and the lowest in Kohgiluyeh and Boyer-Ahmad (3.04). The Gini index ranges from 0.27 in Alborz to 0.38 in Golestan, Sistan and Baluchestan, Khorasan Razavi, and Hormozgan, also having a Gini index of more than 0.35. Overall, the data suggest that there are significant differences in the SPPTB incidence rates and the Gini index across the provinces of Iran [Figures 1 and 2].

We investigated the impact of several crucial factors on the incidence rate of SPPTB cases in Iranian provinces over 2018–2022, every month, utilizing a Spatial Lag Model (SLM) regression approach. First, the Gini index had a positive coefficient (33.521, P value = 0.011), implying that regions with higher income inequality, as measured by the Gini index, tend to have higher incidence rates. Second, "Delayed diagnosis" demonstrated a negative coefficient (-0.034, P value = 0.013), highlighting that shorter diagnosis delay times are associated with higher incidence rates. It means that the diagnoses happen in the early months and the proportion of patients who are diagnosed in the later stages is relatively low. As stated in Table 1, 70% of cases are delayed by less than 3 months, that is, within 3 months of the onset of symptoms, about 70% of patients have been diagnosed, and with the increase of time, about 30% of patients have not been diagnosed, and this indicates that most patients are diagnosed in the early months of the disease. That means that the incidence rates are high when delayed diagnosis time is short and shows a negative relationship between incidence rates and delayed diagnosis. These results emphasize income inequality and delayed diagnosis collectively contribute to the observed variations in incidence rates across Iranian provinces [Table 2].

Figures 3 and 4, which display scatter plots illustrating the connections between the Gini index and incidence rates, as well as delayed diagnosis and incidence rates, visually corroborate the statistical results. The Gini index implies that areas with greater income inequality tend

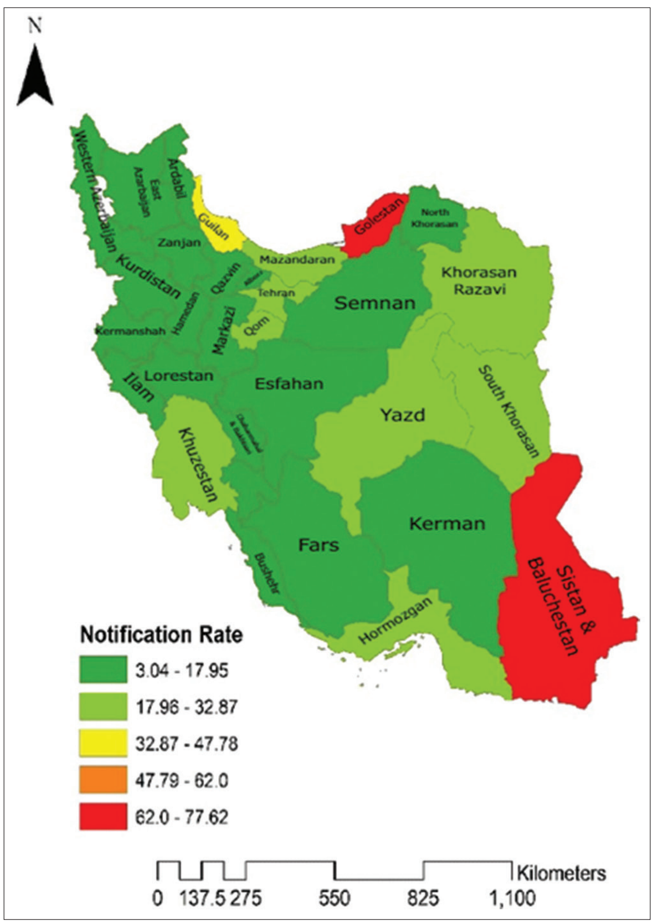

Figure 1: GIS maps of notification rate of incident SPPTB cases per 100,000 populations in Iranian provinces from 2018 to 2022

Table 2: Summary of Spatial Lag Model Output Estimated Using Maximum Likelihood Estimation (MLE)

Variable	Coefficient	Std. Error	*Z*	*P*
(Intercept)	-3.221	5.621	-1.105	0.16
Gini index	33.521	22.237	1.305	0.011
Delayed diagnosis	-0.034	0.007	-2.421	0.013
Moran I Statistic				
Moran I statistic standard deviate	**Moran I statistic**	**Expectation**	**Variance**	***P***
66.828	0.8523	-0.0007	0.0002	<0.0001

*Significant at a level of 0.05

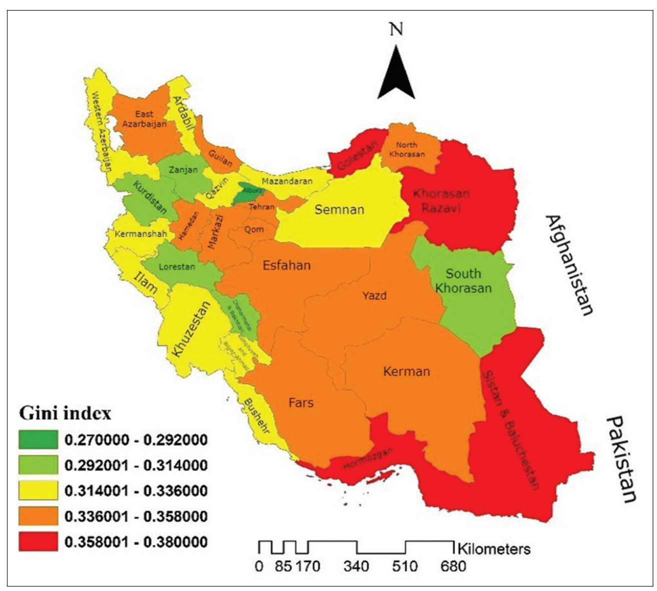

Figure 2: GIS maps of the Gini index in Iranian provinces from 2018 to 2022

to exhibit elevated TB incidence rates. Furthermore, the adverse coefficient associated with the delayed diagnosis indicates that extended delays in TB diagnosis are linked to decreased incidence rates.

The Moran I test was conducted under randomization to assess the spatial autocorrelation in the incidence rate of SPPTB cases across Iranian provinces from 2018 to 2022. The results of this test revealed a Moran I statistic standard deviate of 66.828 (P value < 0.0001) provides strong evidence against the null hypothesis of spatial randomness. The analysis confirms the existence of spatial autocorrelation, highlighting the presence of regional clustering in TB incidence rates across the studied area. This indicates a strong and statistically significant positive spatial autocorrelation in the incidence rate data. In other words, neighboring provinces exhibited similar incidence rates for SPPTB cases, suggesting that TB transmission dynamics were not evenly distributed across the country. These findings emphasize the importance of considering spatial factors when studying TB epidemiology and highlight potential clusters or areas of higher TB transmission risk within Iran [Table 2 and Figure 5].

Discussion

The present study aimed to investigate the spatial distribution and determinants of incidence rate, income inequality, and delayed diagnosis across the provinces of Iran using SLM and maximum likelihood estimation. The SLM output indicated strong spatial dependence in the data, as evidenced by the Moran I statistic standard deviate coefficient of 66.828, suggesting that the incidence rate in one province is influenced by the incidence rate in neighboring provinces. The positive and statistically significant coefficient for the Gini index implied a positive association between income inequality and the dependent variable incidence rate, indicating that provinces with higher income inequality may have higher incidence rates of SPPTB. The findings of this study have important implications for public health policy in Iran. The high incidence rates observed in some provinces highlight the need for targeted interventions to improve early diagnosis and treatment of SPPTB in these areas. Additionally, the positive association between income inequality and incidence rate underscores the importance of addressing socioeconomic disparities in health outcomes as well as the need for targeted interventions in areas with higher income inequality.

Our findings indicate that a significant number of SPPTB cases in Iran are promptly diagnosed, with around 70% of patients receiving diagnoses within 3 months of the onset of the disease. This demonstrates the effectiveness of public health efforts in identifying and diagnosing patients during the early stages of the illness. However, as the diagnosis is delayed beyond this initial period, approximately 30% of patients remain undiagnosed. This highlights the crucial role of early detection, achieved by public health initiatives in the early months of the illness for 70% of patients. Several studies highlight the importance of early detection and timely medical intervention in preventing the spread of

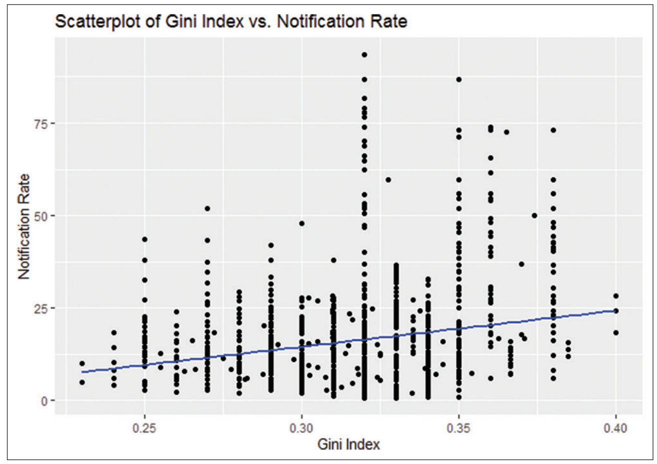

Figure 3: Scatterplot of the relationship between the Gini index and notification rate of incident SPPTB cases in Iranian provinces from 2018 to 2022

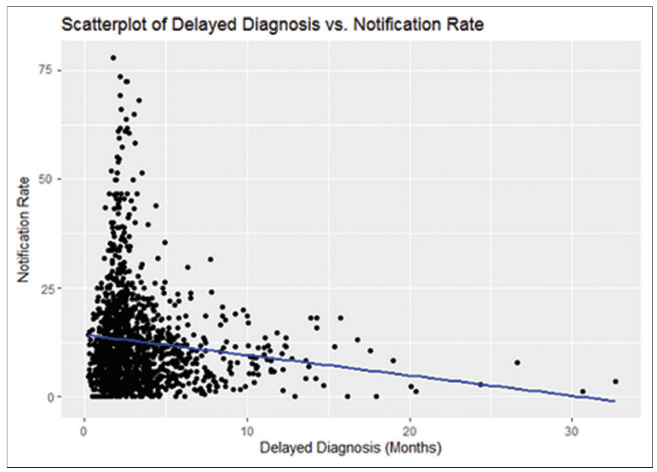

Figure 4: Scatterplot of the relationship between delayed diagnosis and notification rate of incident SPPTB cases in Iranian Provinces from 2018 to 2022

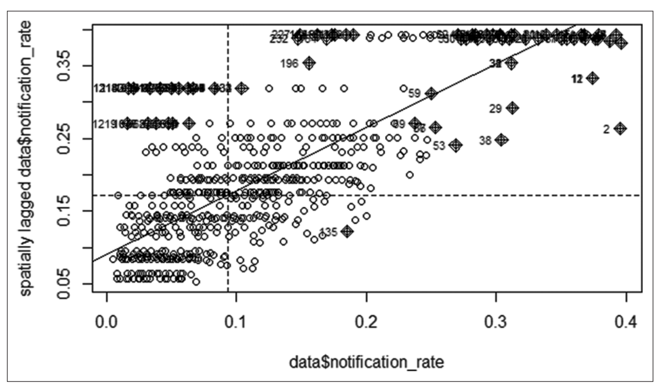

Figure 5: Moran scatterplot of the relationship between a province's notification rate of incident SPPTB cases and the average value of its neighbor's provinces

the disease.[22] Delayed diagnosis of TB increases the risk of transmitting the disease to others. Early detection can help prevent the spread of TB to others. Also, late detection of TB can lead to poor health outcomes. Public health programs focused on providing early diagnosis and treatment can help expedite progress in controlling TB and mitigating its consequences.[23] Also, a study conducted in Portugal by Santos *et al.* (2021)[15] also found a significant association between delayed diagnosis and high TB incidence. These findings support the results of the current study.

The GIS maps provide a visual representation of the variation in SPPTB incidence rates across Iranian provinces, which can be useful for identifying areas with a high burden of TB and targeting interventions to reduce the incidence of the disease. The maps unveiled notable variations in the distribution of incidence rates and Gini indices among the provinces of Iran. Sistan and Baluchestan and Golestan exhibited the highest incidence rates, coupled with elevated Gini indices. The maps reveal significant spatial variation in the distribution of these variables across the provinces. The map highlights the need for improved TB control efforts in provinces with high incidence rates, such as Sistan and Baluchestan, and Golestan, and the need for continued surveillance and monitoring of TB incidence rates across the country. The high prevalence of TB in Sistan and Baluchestan province can be attributed to several factors, including poverty and malnutrition.[24,25] A study conducted in 2020 found that poverty was a significant risk factor for TB in the province, with individuals living in poverty being more likely to develop TB than those living above the poverty line.[26] Several studies have highlighted the high burden of TB in Sistan and Balochistan province.[18,25,26] In conclusion, the high burden of TB in Sistan and Balochistan province is a complex issue that requires a multisectoral approach to address the underlying risk factors and improve access to TB diagnosis and treatment services. Efforts should be made to address poverty, malnutrition, and HIV and to improve the provision of TB diagnosis and treatment services to vulnerable populations, including Afghan refugees and migrants. Overall, the findings of this study highlight the need for continued efforts to control TB in Iran, including early diagnosis, the importance of targeting high-risk groups, and public health education. Furthermore, additional research is required to identify the underlying factors contributing to the high SPPTB incidence rates in certain regions of Iran.

However, the results of this study should be interpreted with caution due to some limitations. The study did not consider other potential determinants of SPPTB, such as environmental factors and individual-level characteristics. SLM can identify spatial associations between variables, but establishing causality requires additional evidence, such as experimental studies or detailed causal inference methods. Also, it is important to note that using reporting center locations may not fully represent the geographic distribution of TB cases at the patient level as cases may reside in different locations than where they are diagnosed and reported. Finally, the study was limited to the analysis of registry-based data, which precludes causal inference.

Conclusions

In summary, the study found that SPPTB is a significant public health concern in Iran, with a high burden among older individuals and males. The study identified significant spatial variation in the distribution of SPPTB incidence rates, income inequality, and delayed diagnosis across the provinces of Iran, which has important implications for public health policy, including the need for targeted interventions in high-risk areas and addressing socioeconomic disparities in health outcomes. However, the study has limitations, including not considering other potential determinants of SPPTB and being limited to cross-sectional data. Another limitation of our study is the reliance on CNR data for calculating the incidence rate, which may introduce the possibility of underestimating the true incidence rate. The study highlights the need for a multisectoral approach to control TB in Iran, including efforts to improve early diagnosis and treatment, address underlying risk factors, and improve access to TB diagnosis and treatment services for vulnerable populations. In conclusion, our findings indicate that a considerable number of patients in Iran receive early-stage diagnoses of TB. Specifically, around 70% of cases are identified within the initial 3 months of the disease, underscoring the effectiveness of public health initiatives in ensuring prompt diagnosis for patients.

List of abbreviations

- TB = Tuberculosis
- CNR = Case notification rate
- SPPTB = Smear-positive pulmonary tuberculosis
- SLM = Spatial lag model.

Ethics approval and consent to participate

The study was approved by the Research Ethics Committee of Mashhad University of Medical Sciences, and all methods were carried out according to relevant guidelines and regulations. Informed consent was waived by (Research Ethics Committee of Mashhad University of Medical Sciences, Code: (IR.MUMS.FHMPM.REC.1401.052).

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Conflicts of interest

There are no conflicts of interest.

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