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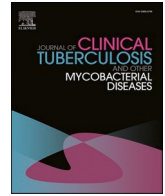
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Barriers and gaps in tuberculosis care and treatment in Iran: A multi-center qualitative study

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ABSTRACT

Introduction: Patients with Tuberculosis (TB) still have barriers in accessing high quality care and treatment services. In this qualitative study, we investigated barriers in accessing TB health services including confirmatory diagnosis, treatment adherence and recurrence of pulmonary TB using patients, physicians, and policy makers point of view.

Materials and methods: In this qualitative research from November to March 2021, 3 policy makers from the Ministry of Health, 12 provincial TB experts and physicians from the TB control program and 33 patients diagnosed with TB from 4 provinces were enrolled for a semi-structured in-depth interview. All interviews were audio recorded and then transcribed. Framework analysis was done by MAXQDA 2018 software to identify key themes.

Results: Several barriers reported for TB care and treatment: Poor knowledge of patents about TB symptoms, failure to screen for TB among at-risk patients by physicians, similar symptoms between TB and other lung diseases, low sensitivity of TB diagnostic tests, incomplete case finding and contact-tracing, stigma related to TB, and patients poor adherence due to long TB treatment. In addition, COVID-19 pandemic disrupted TB services and decreased detection, care and treatment services for TB patients.

Conclusion: Our findings highlight the need for interventions to increase public and healthcare providers awareness about TB symptoms, using more sensitive diagnostic tests, and interventions to reduce stigma, and improve case finding and contact tracing effort. Improving patients' adherence required better monitoring and shorter effective treatment regimes.

1. Introduction

Tuberculosis (TB) is one of the 10 main causes of death worldwide (Harding, 2020). This disease, aggravated by poverty, weak public health systems, and the increasing prevalence of HIV/AIDS, is considered as a permanent challenge for global health and development (Piot et al., 2007). Despite the availability of effective treatment, complications and deaths caused by this disease are high in low- and middle-income countries (Harding, 2020). The reports of the World Health

Organization show that about 10 million people were infected with TB in 2019, and about 1.2 million of them died this. Weakness in disease detection, insufficient and incorrect treatment, drug resistance and epidemic at the same time as HIV have faced the TB control program with a serious problem (World Health Organization, 2021). These factors are considered as important obstacles in the direction of achieving the Millennium Development Goals, that is, the elimination of this disease by 2050 CE.

Considering these issues, the World Health Organization declared

Abbreviations: TB, tuberculosis.

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tuberculosis a global emergency in order to sensitize governments to take effective intervention measures (World Health Organization, 2021; Jong-Wook, 2003). In order to achieve the elimination of TB by 2050, as one of the Millennium Development Goals, the incidence of this disease in Iran should decrease by an average of 13.5% per year. Considering that each smear-positive pulmonary TB patient can infect 10 to 15 other people in a year, if not identified and treated, the timely diagnosis and treatment of patients is considered to be the most important way to control this disease (Yazdani Charati et al., 2010; Rafiee et al., 2009). Obviously, without planning and implementation of active diagnosis and treatment in high-risk groups, along with the development of access to fast and up-to-date diagnostic and treatment tools this will not be possible. Lack of access to health services and non-adherence to treatment (Munro et al., 2007) along with economic problems (Kliner et al., 2015) and the integration of TB services with other health care systems are among the barriers to the diagnosis and treatment of this disease (Sreeramareddy et al., 2014). Delayed diagnosis coupled with poor adherence to treatment has serious health and economic consequences for the individual, family members, and society (Cai et al., 2015). For example, poor access and delay in diagnosis can lead to the severe form of the disease, the spread of the disease among family members and community members (Makwakwa et al., 2014). In addition, poor adherence to treatment can lead to the development of drug-resistant TB, which causes patients to remain as reservoirs of infection in the community (Law et al., 2017). On the other hand, since the emergence of COVID-19, the disease seems to have been significantly neglected. Identifying the Barriers and challenges in the field of diagnosis and treatment of TB and the effects of the COVID-19 epidemic on it in any society can play an important role in helping health policy makers to plan and improve the existing situation. Therefore, the purpose of this qualitative study is to examine the barriers related to different stages of the smear-positive pulmonary TB care cascade, including access to health services, correct diagnosis, completion of treatment, and possible

factors involved in relapse based on the views of patients, health policy makers and personnel in Iran.

2. Methods

2.1. Research team and reflexivity

This qualitative study with content analysis approach was conducted from November to March 2021 in Iran. The report is written according to the consolidated criteria for reporting qualitative research (COREQ) guidelines (Tong et al., 2007). To collect the data, semi-structured interviews with open questions were conducted with TB policy makers at national level and TB control experts and patients suffering from pulmonary TB at provincial level. All the interviews were done by Shoboo Rahmati, female and trained in qualitative methods at PhD level.

2.2. Study design

The sampling was purposeful and an attempt was made to collect data from people who had sufficient experience in the desired field. After explaining the objectives and obtaining informed consent, interviews were conducted with participants at three different levels: 1) three policy makers at the Ministry of Health of Iran (TB control officer, TB control manager and TB control expert), 2) twelve provincial TB experts and physicians who were active in the TB control program for at least 5 years (four laboratory manager, four physicians and four TB expert) from the provinces of Tehran, Kerman, Ilam, Kurdistan, Esfahan, Zahedan, Razavi Khorasan, Chaharmahal and Bakhtiari and Golestan and 3) thirty-three affected patients aged > 18 years who has been living in the interview region at the time of diagnosis from the provinces of Tehran, Kerman, Ilam, Kurdistan (Fig. 1). The interviews with patients were done on-site. However, depending on accessibility, the interviews with experts, physicians and policy makers were done either on-site or

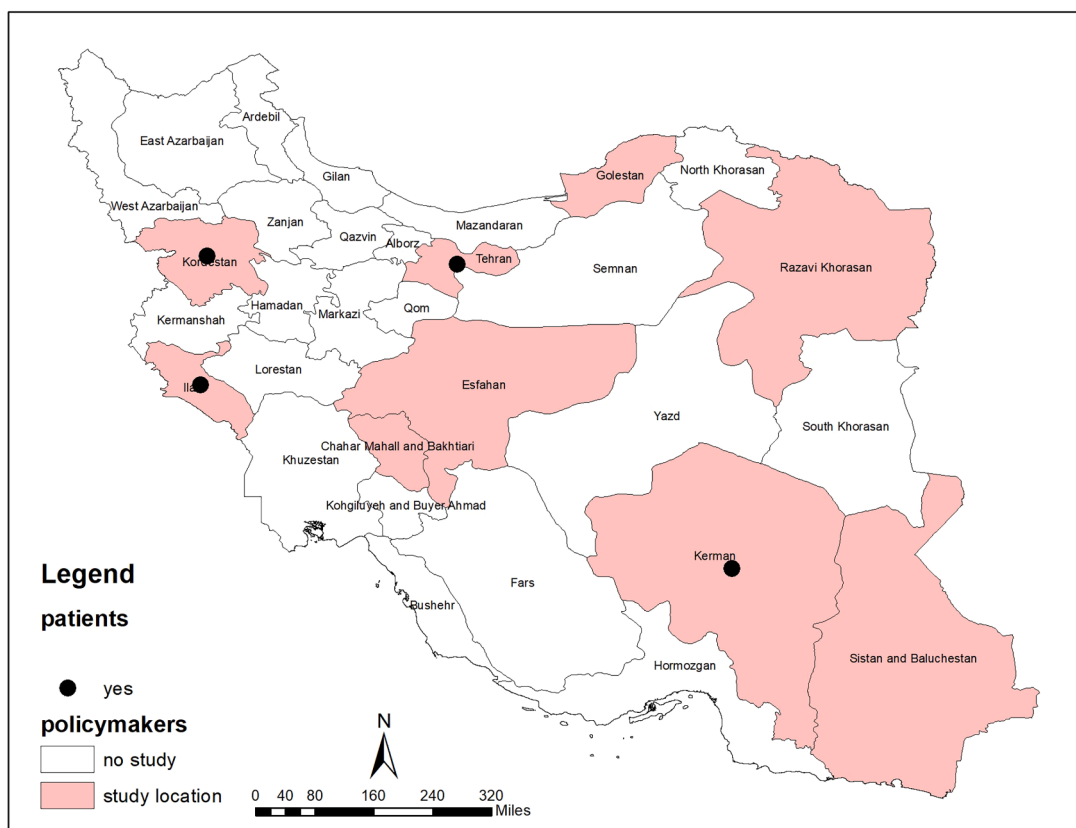


Fig. 1. Policymakers and patients recruitment provinces to study barriers and gaps in tuberculosis care and treatment in Iran.

through video-conference. The recruitment continued until the saturation was reached. The duration of each interview varied from 50 min to 90 min. After obtaining informed consent, all the interviews were audio recorded and transcribed verbatim. Due to lack of accessibility, the transcripts returned only to the health policy makers for comments or correction. All of them provided feedback on the findings.

2.3. Analysis and findings

In this study, the barriers and problems in each stage of the smear positive pulmonary TB care cascade were investigated. TB care cascade includes 6 stages (Fig. 2). The ideal situation is that all patients with smear-positive pulmonary TB being identified, referred to the treatment system, receive appropriate treatment, complete the course of treatment and get a favorable result from the treatment, so that death or relapse from disease approaches to zero. In this case, the height of all the columns of the graph should be the same and equal to the total smear positive pulmonary TB patients in the society. In practice, there is a gap between two consecutive stages, which indicates the existence of barriers to the complete care of the disease. Overall, there are 5 gaps which include as follow: 1st gap: a share of patients with smear-positive pulmonary TB who never refer to care facilities; 2nd gap: a share of patients with smear-positive pulmonary TB who go under diagnostic procedures but the disease will not properly diagnosed among them; 3rd gap: a share of patients with smear-positive pulmonary TB who are being diagnosed but not initiate treatment; 4th gap: a share of patients with smear-positive pulmonary TB who despite of treatment initiation wouldn't complete their treatment; 5th gap: a share of patients with smear-positive pulmonary TB who experience relapse or death from TB within one year after completion of treatment. In the current study we investigated the participants' opinions about the possible causes related to each gap at individual, social, cultural and structural levels and the possible impact of the COVID-19 pandemic in each step.

To analyze the data, the content analysis approach assisted by MAXQDA 2018 software was used. The following steps were down to

analysis the data: Step 1: Familiarization, Step 2: Coding, Step 3: Generating themes, Step 4: Reviewing themes, Step 5: Defining and naming themes and Step 6: Writing up. After coding of all texts and extracting issues and sub-themes, the main themes were created by interpreting the content. Two researchers (Armita Shahesmaeili and shoboo Rahmati) conducted coding to increase the validity. In addition, we asked other co-authors and several faculty members who were familiar with the analysis of qualitative research to review some of the interviews, codes, and extract classes to examine the validity of this coding. For the ease of quoting in the text, we used a unique anonymous code for each participant. So that the PO 1–3 represent policy makers, PE 1–12 represent TB personnel, experts and physicians and PA 1–33 represent the patients.

2.4. Ethics

The study protocol was reviewed and approves by ethics committee of Kerman University of medical sciences. (Ethics code: IR.KMU.REC.1400.649). Informed verbal consent was obtained from participants. To ensure participant's confidentiality only codes were used on the demographic form instead of their names. Furthermore, we used only codes on interview transcripts.

3. Results

Demographic characteristics of participants are shown in Table 1. The mean age ± SD of policy makers, TB personnel and patients were 42 ± 5, 37.41 ± 6.30 and 49.24 ± 12.27 respectively. Majority of participants in policy makers and patients groups were men while most of participants in TB personnel group were female. Tables 2 and 3 show the barriers on different stages of the care cascade from the perspective of policy makers, health personnel (Tuberculosis expert and laboratory manager (and patients, respectively. In the following section, we will comment on the factors affecting each of the examined gaps.

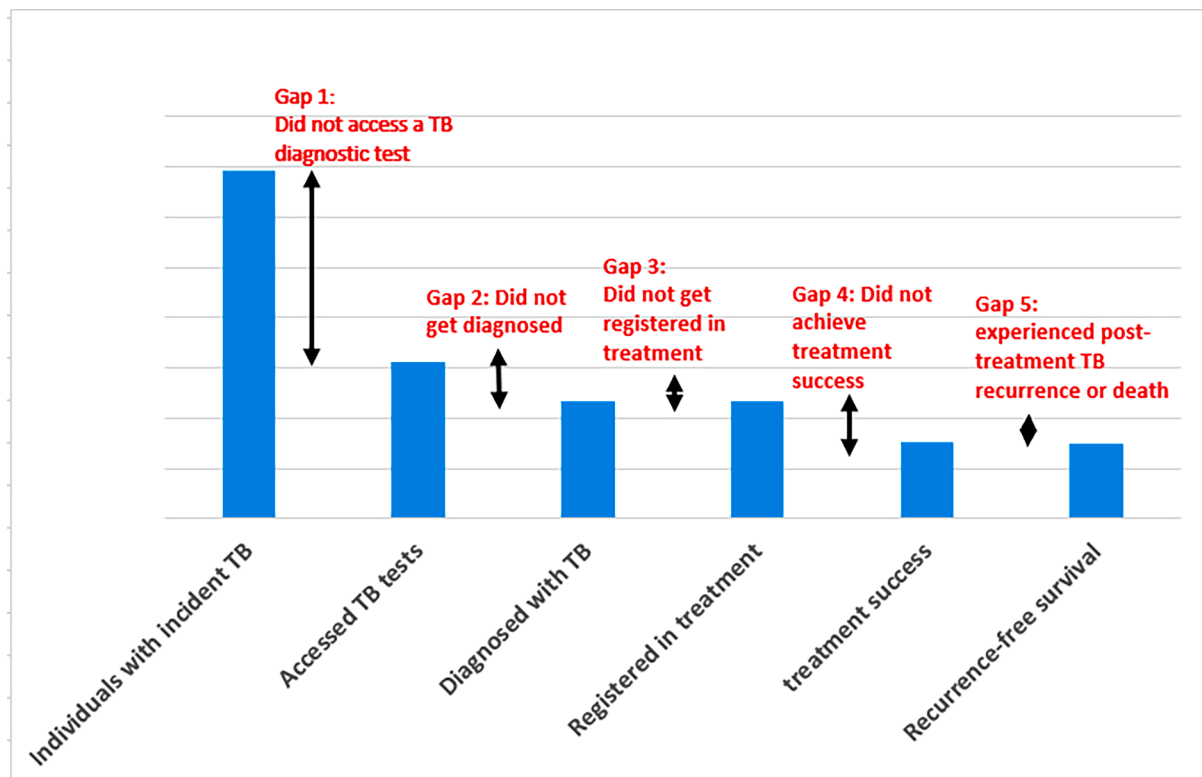


Fig. 2. Generic care cascade model for individuals with active TB in Iran population.

Table 1

Demographic characteristics of participants recruited in qualitative study of Tuberculosis cascade of care barriers in Iran.

Variable	Age(year) (mean ± SD); (Minimize -Maximum)	Sex frequency (%)
Policy makers	42 ± 5; (37–47)	Female: 1 (33.3) Male: 2(66.7)
Tuberculosis control and treatment personnel	37.41 ± 6.30; (28–49)	Female: 7 (58.3) Male: 5(41.7)
Patients	49.24 ± 12.27; (26–72)	Female: 13 (39.4) Male: 20 (60.6)

Table 2

An analysis of the care cascade's barriers from the perspective of Iranian national, regional policymakers and patients.

1st gap: The number of people with smear-positive pulmonary tuberculosis who did not have access or didn't refer to diagnosis and care	
Patient-related factors	<ul style="list-style-type: none"> - Unawareness of patients about the symptoms of TB. - Self-treatment with traditional medicine. - Similarity of TB symptoms with other diseases (asthma and bronchitis). - Resistance in referral among old people. - Referral to private centers.
System-related factors	<ul style="list-style-type: none"> - Unawareness of physicians about TB disease. - Passive nature of diagnosis. - Incomplete contact tracing. - Inadequate education and information.
Factors related to the cultural, social and economic situation	<ul style="list-style-type: none"> - Social stigma. - Unawareness about availability of free services.
2nd gap: failure to correctly diagnose smear-positive pulmonary TB patients referred to TB diagnosis and care centers	
Patient-related factors	<ul style="list-style-type: none"> - Poor quality of sputum samples. - Delay in delivery of culture result in smear negative patients.
System related factors	<ul style="list-style-type: none"> - Lack of proper training of patients to collect sputum samples. - Lack of lab-staff expertise. - Low sensitivity of smear test. - Wear and tear of diagnostic tools.
3rd gap: not initiating TB treatment among patients diagnosed with smear positive pulmonary	
Patient-related factors	<ul style="list-style-type: none"> - Death of the patient before starting treatment. - Relocation of patients. - Homelessness and being marginalized.
System related factors	<ul style="list-style-type: none"> - Lack of adequate counseling and training of patients by the personnel regarding about importance of treatment initiation.
4th gap: failure to complete the treatment in patients who have started anti-TB treatment.	
Patient-related factors	<ul style="list-style-type: none"> - Medication non-compliance. - Death of a patient during treatment - Drug side effects and interaction. - Relocation of patients especially among immigrants mentioned to be a dilemma of treatment by some experts.
System related factors	<ul style="list-style-type: none"> - Factors such as lack of vehicles for home visit especially in remote areas.
5th gap: recurrence or death one year after completing the treatment course.	
Patient-related factors	<ul style="list-style-type: none"> - Having old age, underlying disease, low economic status and lack of proper nutrition and weak immune system.
System related factors	<ul style="list-style-type: none"> - Imperfect sensitivity of confirmatory tests at the end of treatment. - Re-infection and continuous transmission of virus in the community. - Failure to perform the antibiogram test at the beginning of treatment.

Table 3

Impact of COVID-19 on TB cascade of care and treatment in Iran.

Patient-related factors	<ul style="list-style-type: none"> - Not visiting due to the fear of getting infected with Covid-19 - Similarity of symptoms with COVID-19 disease - Turning to traditional medicine - Failure to perform subsequent tests due to the fear of contracting the corona virus
System-related factors	<ul style="list-style-type: none"> - Quarantine policy at the beginning of the pandemic - More focus of the system on Covid-19 - Reducing the space and personnel of the laboratory and replacing them for Covid-19 - Decreasing the quality of samples due to the staff's fear of contracting the Covid-19 - Lack of complete training of patients - premature death due to covid-19 and tuberculosis - Weakening of the DOTS scheme - lack of proper diagnosis of people in contact with infected person during the COVI-19 epidemic

3.1. Factors related to the 1st gap: Patients with smear-positive pulmonary TB who never refer to care centers

National TB health experts and policymakers believed that before the COVID-19 pandemic approximately between 70 and 75% of the infected individuals in the community referred to diagnosis and care centers while this amount reduced to 52% under the influence of the pandemic. But at the environmental level, the health workers and physicians of the TB center believed that this rate before and after the pandemic was 75–97% and 70–90%, respectively. In the following possible factors related to non-referral are mentioned:

3.1.1. Patient related factors

3-1-1-1: Unawareness of patients about the symptoms of TB: Many experts mentioned that most patients believe in eradication of TB at the community level. PO.2: "When we informed them about the existence of TB, they said that "does the TB still exist!""

3-1-1-2: Self-treatment with traditional medicine: The participants believed that patients' self-treatment and turning to traditional medicine can lead them not going to diagnostic centers. PO.1: "The majority of people have now turned to traditional medicine, that is, if they have symptoms such as cough, they treat themselves through traditional medicine, which makes this group of patients stay in the community." Some patients also said that at the beginning, they just took their symptoms easy and instead of referral to doctors, used traditional medicine for relief.

The majority of people have now turned to traditional medicine, that is, if they have symptoms such as cough, they treat themselves through traditional medicine, which makes this group of patients stay in the community.

3-1-1-3: Similarity of TB symptoms with other diseases: Some patients and experts believed that due to the similarity of symptoms of TB with other respiratory diseases, especially asthma and bronchitis, some patients are misdiagnosed with asthma or bronchitis.

3-1-1-4: Resistance in referral among old people: one of the participants stated. PE.3: "Usually, elderly people don't come to us because of too much disability. They ignore and never diagnose TB which leads to death."

3-1-1-5: Referral to private centers: According to some participants, a significant proportion of patients refer to private centers, which brings about the misdiagnosis of disease. PO.3: "consider a person who lives in a very remote village. When he sees the symptoms, he goes to the city and consults with physicians who specialize in other than infectious and lung disease. They never think of TB and this causes such cases of TB to be missed or diagnosed with a delay."

3.1.2. System related factors

3-1-2-1: Unawareness of physicians about TB disease: some experts

and patients believed that physicians other than infectious and lung specialists usually consider TB as their late diagnosis. Even lung and infectious diseases specialists for a patient with TB symptoms make the diagnosis of chronic lung diseases at the early steps. This problem is more evident in low prevalence areas. PA.20: "A physician has diagnosed me with asthma for about 1.5 year and I have been under asthma treatment while I had TB."

3-1-2-2: Passive nature of diagnosis: one of the experts admitted. PE.12: "diagnosing of TB, except among special patients such as people with AIDS is not an active process and there are some which never refer on their own".

3-1-2-3: Incomplete contact tracing: policymakers believed that due to incomplete contact tracing by personnel or incomplete reporting of contacts by patient some infected persons may never be diagnosed.

3-1-2-4: Inadequate education and information: Policymakers and experts believed that poor education about TB makes both people and physicians think of TB late even when they see symptoms.

3-1-3: Factors related to the cultural, social and economic situation

3-1-3-1: Social stigma: Most experts, especially in the western provinces of the country (Ilam and Kurdistan) considered social stigma as one of the barriers of disease diagnosis.

3-1-3-2: Unawareness about availability of free services: According to experts, some people, especially low income and marginalized people (e.g., homeless and people who use drugs), think that diagnosis and treatment is costly and never refer.

3.2. Factors related to the 2nd gap: Failure to correctly diagnose smear-positive pulmonary TB patients referred to TB diagnosis and care centers

National and regional TB control policymakers and regional experts believed that the percentage of cases that had access to diagnostic tests and were successfully diagnosed is approximately 60–70% and 75–90% respectively.

3.2.1. Patient related factors

3-2-1-1: Poor quality of sputum samples: Most experts believed that patients are careless when taking sputum samples. For example, the sputum volume is not enough which may cause under-diagnosis. This is especially problematic in children under 12 years, elderly people and critically ill patients.

3-2-1-2: Delay in delivery of culture result in smear negative patients. PE.2: "when sputum smear in a symptomatic patient is negative, we request for sputum culture. However, the result of the culture comes after a month. This prolonged waiting time avoid some patients to come back to get their result. Some of them don't give us their real address that make us unable to follow them."

3.2.2. System related factors

3-2-2-1: Lack of proper training of patients to collect sputum samples at home reported to be a factor barrier to correct diagnosis of infected individuals.

3-2-2-2: Lack of lab-staff expertise. PE.6: "some personnel do not have sufficient expertise when they perform laboratory test or work with microscopes. They can simply ignore small number of bacilli."

3-2-2-3: Low sensitivity of smear test: Some experts believed that the sensitivity of sputum smear test is not perfect for diagnosing pulmonary TB. PE.5: "Smear test sensitivity is only 75%. In Iran, there are 35 Gene Xpert devices, which has a high sensitivity of 99%. Due to time-consuming nature of process and related costs, Gene Xpert test as well as sputum culture are only being used in special patients".

3-2-2-4: Wear and tear of diagnostic tools: One of the most important barriers mentioned by experts was the wear and tear of devices especially in deprived areas.

3.3. Factors related to 3rd gap: Not initiating TB treatment among patients diagnosed with smear positive pulmonary

National and regional level policy makers and experts believed that the role of this gap in Iran is not significant and in the worst case, up to 2% of diagnosed patients may never receive treatment. Factor related to this gap are referred below:

3.3.1. Patient related factors

3-3-1-1: Death of the patient before starting treatment: According to experts, a very small percentage of patients may die before the start of treatment and therefore never start the treatment.

3-3-1-2: Relocation of patients: Some experts believed that some patients, especially migrated individuals, may move before the start of treatment which makes the staff unable to find them.

3-3-1-3: Homelessness and being marginalized: Expert believed that homeless patients may be missed before the treatment initiation since they usually don't have a fixed living place that enable personnel to follow them up. PA.5: "we don't have anyone and we don't have any motivation for treatment. Personnel hesitate to follow us and as we don't have any means of transportation".

3.3.2. System related factors

Lack of adequate counseling and training of patients by the personnel regarding the importance of treatment initiation were mentioned to be associated with the third gap. Furthermore, a small number of patients, especially in the western regions of Iran, reported that they refuse to take TB medications because of the fear of social stigma against TB. This view was more common among women.

3.4. Factors related to 4th gap: Failure to complete the treatment in patients who have started anti-TB treatment)

3.4.1. Patient related factors

3-4-1-1: Medication non-compliance: Patients' non-compliance especially among homeless and addicted individuals believed to be the main cause of failure to complete the treatment course.

3-4-1-2: Death of a patient during treatment. PE.9: "sometimes it happens that a patient dies during treatment especially when he is old or has an underlying disease."

3-4-1-3: Drug side effects and interaction: Experts believed that due to side effect of medications, treatment process must be discontinued in some patients. Furthermore, some patients, especially those with cancer or multiple sclerosis, said that they stopped taking TB medications while they had interaction with other medication the used. PA.23: "The volume of my medications was too much and they had side effects for me, so I had to stop taking TB drugs or not take them regularly."

3-4-1-4: Relocation of patients especially among immigrants mentioned to be a dilemma of treatment by some experts.

3.4.2. System related factors

Factors such as lack of vehicles for home visit especially in remote areas referred to be a barrier to not completing the treatment course.

3.5. Factors related to 5th gap: Recurrence or death one year after completing the treatment course

Due to the lack of patient follow-up after completing the treatment period in Iran, experts did not have detailed information in this field, but they considered the following possible factors to be related with this gape.

3.5.1. Patient related factors

Having old age, underlying disease, low economic status and lack of proper nutrition and weak immune system were mentioned to be related to death and relapse after completion of treatment period.

3.5.2. System related factors

3-5-2-1: Imperfect sensitivity of confirmatory tests at the end of treatment: According to experts, at the end of treatment, confirmatory tests are being taken to make sure that patient has cured. Because of imperfect sensitivity of these tests, the bacillus may still remain in the person's body but couldn't be detected by the test.

3-5-2-2: re-infection and continuous transmission of virus in the community. PO.2: "Sometimes incomplete contact tracing may lead to undiagnosed infections among people who are in contact with patients. Therefore, the patient may get the infection again after completion of treatment."

3-5-2-3: Failure to perform the antibiogram test at the beginning of treatment was also mentioned to be related to drug resistance and relapse.

3.6. Impact of COVID-19 on TB cascade of care and treatment

Some possible threats of TB care and treatment mentioned by patients, policy makers and experts are presented below:

3.6.1. Patient related factors

Some experts believed that at the beginning of epidemic, the patients' referrals decreased due to the fear of getting infection as well as similarity of the TB symptoms with COVID-19. However, recently with normalization of situation, the referral rate approached to the pre-epidemic time. PA.12: "We thought that we had COVID-19. We used routine medications or traditional medicine. However, after a while when we did not get better, we visited a doctor and he said that we have COVID-19 disease". PE.9: COVID-19 caused some people not to take the second and third smear samples or supplementary tests due to the fear of getting infected."

3.6.2. System related factors

Some experts believed that the implementation of quarantine at the beginning of the epidemic has led to a decrease in people's visits to the care centers. They also believed that as the result of more focus on COVID-19, the number of sputum sampling reduced significantly. PE.4: "in many areas of Iran, for example Kashan, the TB laboratory were become a laboratory for the COVID-19 diagnosis". PA.16: "They (doctors) gave us the diagnosis of COVID-19 only after a long time when we did not get well". Regarding the second gap, some experts believed the emergence of COVID-19 caused many TB diagnostic spaces and lab facilities being used for diagnosis of COVID-19. This double burden has led to the lack of accuracy of the staff when performing TB tests. PO.1: "The fear of some staffs for being infected with COVID-19 made them not to train patients perfectly which in turn resulted in taking low-quality sputum samples." Premature death of patients due to the simultaneous infection with COVID-19 and TB, and therefore never starting the treatment, or not continuing the treatment was referred to be a factor related to the third and fourth gap from policy makers' point of view. In addition, weakening of Directly Observed Therapy Short course (DOTS), especially at the beginning of the COVID-19, said to be a barrier to completion of treatment. In regard to the fifth gap, lack of proper diagnosis of people in contact with infected person during the COVID-19 epidemic was mentioned as a factor related to re-infection of the treated person.

4. Discussion

In this qualitative study barriers to TB care cascade in Iran were addressed from policymakers, local experts and patients' point of view. The most important barriers to access, referral, proper diagnosis and treatment of patients were the unawareness and ignorance of physicians and patients about TB, the similarity of symptoms with chronic lung diseases, incomplete sensitivity of diagnostic tests, inactive process of case finding, incomplete contact-tracing, stigma related to TB as well as

non-compliance of patients during treatment. They also believed that emergence of COVID-19 had a great impact on diagnosis, care and treatment especially at the beginning of epidemic.

In a qualitative study conducted by Mousazadeh and Khanjani in 2012, Iran, the low level of patients' awareness about TB was reported to be a threat to proper diagnosis of disease (Moosazadeh and Khanjani, 2012). The association between low level of awareness in a community and TB incidence has been shown in previous studies (Wandwalo and Mørkve, 2000; Nguyen Phuong Hoa et al., 2003). Patients who are unaware of their infection can spread the disease among the population (Portero Navio et al., 2002; Lescure et al., 2010). In addition to patients, we showed that low level of awareness among physicians about the disease and its ignorance could be another barrier to early diagnosis and treatment of disease. In a study conducted by Sohrabi et al. in 2019, Iran, level of knowledge about TB among general practitioners was poor which consequently result in misdiagnosis or delayed diagnosis of patients (Sohrabi et al., 2019). Delayed diagnosis and misdiagnosis can make patients and their family members not to seek care or take unnecessary and inappropriate doses of antimicrobials (Carmeli et al., 2016; Pokharel et al., 2019). This can further lead to additional delays, distortion of clinical conditions and ultimately antimicrobial resistance (Pokharel et al., 2019). Therefore, increasing the knowledge and awareness of physicians as well as society about disease symptoms, ways of transmission and care and treatment could play an important role in prevention, early detection and control of disease. Designing an educational curriculum based on physician and health care workers needs both during their study and after their graduation should be integrated to education curriculum of these groups.

Incomplete sensitivity of sputum smear as well as poor quality of the sputum samples, lack of trained health personnel and lack of appropriate equipment's were also referred to be related to TB under-diagnosis. In Iran, microscopic examination of three sputum sample obtained in three different days is the main method of diagnosing smear positive pulmonary TB. However, in our recent systematic review and meta-analysis, we estimated the pooled sensitivity of sputum smear to be 75.12% which indicates a 25% under-diagnosis error rate (Rahmati et al., 1936). During the recent years, many efforts have been made to use more sensitive diagnostic methods, including Xpert MTB/RIF assay, a reliable molecular diagnostic tool capable of detecting Mycobacterium TB and identifying genetic determinants of rifampicin (RIF) resistance within a short time in diagnosis centers (Aggarwal et al., 2022). Nevertheless, due to the lack of financial resources, only a limited number of these center are equipped with Xpert MTB/RIF devices. Similarly, as we showed applying low sensitive end-of-treatment confirmation tests can play an important role in disease transmission and relapse after the end of the treatment. Accordingly, equipping more laboratories to sensitive devices as well as informing the personnel about the importance of training the correct methods of taking sputum samples to patients, periodical education of lab personnel especially in places where access to Xpert MTB/RIF assay is limited, should be prioritized in future planning.

As we showed, stigma toward TB is a barrier to referral of patients and initiation or continuation of treatment. Stigma toward TB is considered as "a perceived or internalized attitude of a community or families toward TB patients due to social norms (Datiko et al., 2020)". In previous studies, variety of factors have been associated with TB stigmatization which include perceived associations of TB with malnutrition, poverty, being foreign-born, and low social class. Due to susceptibility of people living with HIV to TB, in areas with high HIV burden, TB is perceived as a marker for HIV positivity (Courtwright and Turner, 2010). The main impact of TB stigma on patients is isolation which negatively affect their employment and job opportunities, family members' marital arrangements, and social opportunities (Marahatta et al., 2018; Baral et al., 2007). TB stigma has been contributed to delay in diagnosis and treatment non-compliance among patients. Also, it has negative effect on screening of disease among at risk individuals as it has been associated with their willingness to be screened for TB and to seek

medical care after the initiation of their symptoms (Courtwright and Turner, 2010). These findings underpin the importance of promoting TB-related stigma as an indicator in national and international TB strategies to reinforce the development and evaluation of stigma-reducing interventions. In this study non-adherence to medications, drug side effects and interactions were mentioned as the main barriers of treatment discontinuation. A review conducted by Kargar et al. showed that patients receiving anti-TB medications are vulnerable to variety of adverse effects. Among them, hepatotoxicity, rash and ototoxicity were the most prevalent ones that resulted in discontinuation of taking drugs by patients or physician (Kargar et al., 2014). In contrast to drug side effects, other reasons of medication discontinuation such as arbitrary non-adherence is pretty well preventable. In a study conducted by Mukherjee et al., it was reported that about 29.8% of patients stop taking drugs after feeling a partial recovery (Mukherjee et al., 2012). Lack of patients' information about the course of disease, anti-TB drugs mechanism of action and their side effects could be related to patients' non-adherence (Driver et al., 2005; Workie et al., 2021). As non-adherence to treatment can followed by prolonged periods of infectiousness, recurrence, drug-resistance, and increased morbidity and mortality, intervention to increase patient's adherence is very important in TB control programs. Although the implementation of the DOTS in Iran, which is based on five elements of political commitment; microscopy services; drug supplies; surveillance and monitoring systems and use of highly efficacious regimens; and direct observation of treatment, has brought great achievement in TB control and treatment adherence (Irajian et al., 2008), more efforts to educate people about the disease and the importance of adherence to treatment in recovery, survival and prevention of disease within their families and community as well as precise monitoring of patients is needed.

From participant's point of view, pandemic of COVID-19 has added an additional burden to diagnosis and care of TB in Iran. Factors such as similarity of COVID-19 and TB symptoms, directing the laboratory and human resources for COVID-19 care and diagnosis, decreased rate of referral due to fear of contracting COVID-19 were mentioned to be the main challenge of TB control during the pandemic. In line with our results, findings of a mixed-method study conducted by Shahnavazi et al. in 2022 showed that COVID-19 epidemic affected the TB control program in Iran through the extending the interval between drug deliveries, overwhelming burden of epidemic on health system, change in priorities, fading out of family-centered DOTS, reduced education time of TB patients at treatment centers due the overload of health workers, avoidance to referral to care centers to get TB medications due to fear of being labeled as infected with COVID and overlap of TB and COVID-19 symptoms (Shahnavazi et al., 2022). Therefore, it is essential that health systems attempt to maintain routine services for TB diagnosis and care to the highest level possible and plan to return to full-service levels as soon as possible.

The main strength of present study was that our findings are not only based on policy makers and experts point of view, but also by recruiting patients we tried to provide a realistic point of view about barriers to TB cascade of care in Iran. However, due to costs and simultaneous COVID-19 epidemic sampling from all parts of country was not possible. In addition, we didn't recruit immigrant patients to our sample which may limit the generalizability of our findings.

5. Conclusion

Our findings highlight the need for interventions to increase public awareness about the TB, improving knowledge of patients, health care workers and physicians about the disease, applying more sensitive diagnostic methods, reducing stigma, precise monitoring of treatment, extending the active case finding, complete contact tracing and increasing patient's adherence to treatment in future planning.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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