Research Article

Diagnostic Errors in Tuberculous Patients: A Multicenter Study from a Developing Country

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Although there is still much to learn about the types of errors committed in health care and why they occur, enough is known today to recognize that a serious concern exists for patients. Tuberculosis (TB) is an infectious disease that is frequently subject to diagnostic errors. Missed or delayed diagnosis of TB can affect patients and community adversely. Our aim in the present study was at evaluating the type of diagnostic errors in TB patients from symptom onset to diagnosis. This was a multicenter cross-sectional study conducted in three university hospitals in Mashhad, Iran. We showed a long delay in diagnosing TB that is mostly related to the time from first medical visit to diagnosis. Errors in the diagnostic process were identified in 97.5% of patients. The most common type of error in diagnosing TB was failure in hypothesis generation (72%), followed by history taking and physical examination. In conclusion, it seems likely that efforts to improve public awareness of and health literacy for TB, to coordinate the referral and follow-up systems of patients, and to improve physicians' skills in history taking and physical examination and clinical reasoning will result in reduced delay in diagnosis of TB and, perhaps, improved patient safety and community health.

1. Introduction

Medical error is one of the leading causes of death throughout the world [1]. Although most of the information available on the damage caused by medical care has been reported by developed countries, sufficient evidence suggests that unsafe medical care is of the major concerns in developing countries and countries with economies in transition [2, 3].

Diagnostic errors, defined as missed or delayed diagnosis, account for an important part of medical errors. They are usually multifactorial in origin, caused by a combination of system errors and cognitive biases. These errors are common in everyday clinical practice and are of great importance in all specialties [4–6]. Despite the rapid advancement in medical technology, the frequency of diagnostic errors has not been diminished significantly [7]. Although a systematic review on more than fifty autopsy series between 1966 and 2002 reported a relative decline in the rate of major diagnostic errors, the error rates estimated are still likely to be a significant issue [8]. Delayed or misdiagnosis rates of 10–50% have been identified in studies of patients with tuberculosis (TB), HIV-associated complications, coronary artery diseases, and a wide range of malignancies [9].

No physician is immune to diagnostic errors, no matter how experienced or knowledgeable he or she is [6]. Although the study of physicians' diagnostic thinking process is complicated issue, it is estimated that 75% of diagnostic errors can be attributed to failure in physician thinking [4].

TB is an infectious disease with significant mortality and morbidity. According to the World Health Organization (WHO), the TB epidemic is worse than previously thought [10]. The main objectives of TB control programs currently include early diagnosis and immediate treatment of contagious cases to reduce the transmission of disease [11]. However, numerous studies published in recent years demonstrated TB diagnosis is in many cases subject to significant errors. A diagnostic error occurs if TB is over- or underdiagnosed. However, the important issue concerning public health is about underdiagnoses [11]. Missed or delayed diagnosis of TB can be catastrophic because it affects patients and community through delayed treatment, increased the period of infectivity, consequently increased transmission of disease, and increased medical costs and mortality [12]. Several autopsy-based studies from around the world indicate that the diagnosis of TB is missed in a significant percentage of cases in the lifetime of the individual and only diagnosed after death [13, 14]. Efforts to reduce the errors leading to failure or delay in the diagnosis of TB require awareness of the type of these errors and corrective policies to reduce them. Even though diagnostic errors occur commonly among patients with TB, limited information about the type of these errors is available. The aim of the present study is to investigate the type of diagnostic errors in TB patients from symptom onset to diagnosis in Iran, as a developing country. We also evaluate the possible relationship between patient- or disease-related characteristics and occurrence of different types of diagnostic errors.

2. Methods

The present study was conducted in three university hospitals, including Imam Reza, Ghaem, and Doctor Shariati hospitals affiliated with Mashhad University of Medical Sciences, Mashhad, Iran, from July 1, 2016, to Dec 31, 2017. It was a cross-sectional observational study. All hospitalized adult (≥15 years old) patients with microbiologically and/or histopathologically documented diagnosis of TB were included if their diagnoses were made for the first time during hospitalization or immediately before admission.

Exclusion criteria were patient dissatisfaction for participating in the study.

2.1. Outcome Measures

(1) Primary outcome measure: to estimate the frequency of different types of diagnostic error in the study patients.

(2) Secondary outcome measure: to evaluate the relationship between the occurrence of different types of diagnostic errors and several patient- or disease-related

characteristics, including age, gender, educational level, geographical strata, site of involvement, chronic medical illnesses, history of close contact with TB, history of recent imprisonment, and typical findings on chest radiography.

2.2. Definitions

2.2.1. Tuberculosis (TB). Tuberculosis (TB) diagnosis was based on consistent clinical findings along with positive smear, culture, or PCR from the appropriate clinical specimen, compatible histopathological study results or combination of them.

2.2.2. Diagnostic Error. Diagnostic error was defined as a missed or delayed diagnosis. The type of diagnostic errors was defined based on DEER Taxonomy Chart Audit Tool [5].

This tool provides a useful framework of classifying the causes of diagnostic errors based on where in the process the error occurred. Each diagnostic error may have more than one failure point. Failure may arise during different diagnostic processes including access/presentation (failure/delay in presentation and/or failure/denied care access), history taking, physical examination, ordering diagnostic tests (failure/delay in ordering needed test(s) and/or suboptimal test sequencing), performance of diagnostic tests (failure/delay in performing ordered test(s)), hypothesis generation, referral/consultation, and follow-up.

2.2.3. Acute or Subacute Life-Threatening Complications of TB from Admission to Discharge. Several acute and subacute complications of TB may occur which may impact patient care and TB disease management [15]. In addition, several longer-term sequela and anti-TB-related adverse effects may result in morbidity and even mortality. We only recorded the life-threatening acute and subacute complications that had occurred on admission or during hospitalization, including massive hemoptysis, major thromboembolic events, ICU admission, respiratory failure requiring mechanical ventilation, pneumothorax/pyopneumothorax, progressive hydrocephalus requiring surgical shunting, and others. Death was regarded as a separate variable.

2.3. Data Collection. The process of gathering and processing information was performed in a stepwise approach.

2.3.1. First Step: Extracting Information from Patient (and/or Knowledgeable Relatives) Interview and Accompanying Medical Record Documents. This included several phases:

(1) Open questions regarding the clinical course of symptoms, medical visits, referrals, and diagnostic and therapeutic measures; for example, "*What happened at your first medical visit and after that*?"

(2) Purposive questions regarding the clinical course of symptoms, medical visits, referrals, and diagnostic and therapeutic measures; for example, "*Did the*

doctor listen to your chest?" or "Did the doctor request for you a sputum exam?"

(3) Completing and matching patients' reports with accompanying documents and completing the checklist designed for this step.

2.3.2. Second Step: Recording Other Information Related to Patient and Disease. In this phase, other data including demographic characteristics, clinical findings, final diagnosis, clinical outcome in the hospital, and complications occurring during hospitalization were collected from medical record abstractions and information provided by inpatient physician in charge of patient care. Collected data were recorded in a separate checklist.

2.3.3. Third Step: Reviewing and Processing Raw Data. After collecting and recording the data from the first and second steps, the information were reviewed and cases were discussed by two physicians who were well-experienced in the diagnosis and management of TB patients and discussed whether an error occurred before the diagnosis or not. In cases where there was an agreement on the occurrence of error, the appropriate approach to be taken, the type of error (s), and the factors contributing to the error(s) were discussed.

In cases where there was no agreement on the occurrence or nonoccurrence of an error or type of error, the opinion(s) of the third physician, who was a highly qualified infectious diseases specialist, was considered. Finally, based on the results of this step, the third checklist that was the Diagnostic Error Evaluation and Research (DEER) Taxonomy Chart Tool [5] was completed to categorize the type of diagnostic errors.

2.4. Statistical Analysis. All observations were described based on descriptive statistical methods including frequency and agreement tables, frequency distribution and rectangular charts, and calculation of central tendency and dispersion indices. The research objectives and questions were investigated using inferential statistical methods including the mean comparison test in the parametric and nonparametric states (Student t-test or Mann–Whitney test), as well as Fisher's exact or chi-squared tests. Descriptive methods and Lilliefors and Shapiro–Wilk tests were used to examine the frequency distribution of quantitative variables. Information could not be identified for demographic and disease-related variables for all patients; therefore, denominators sometimes varied for the variables.

2.5. Research Ethics. The ethics committee of Mashhad University of Medical Sciences approved this study with code of IR.mums.fm.rec.1394.266.

3. Results

A total of 158 patients were enrolled in the study. Characteristics of patients and their tubercular diseases are summarized in Table 1.

Finally, 144 (89.4%) patients survived to discharge, whereas 17 (10.6%) died. The median (25th percentile, 75th percentile) duration of hospitalization was 12 (9, 19) days.

Sufficient information was accessible through interviews and document review to investigate the possibility of occurrence of diagnostic errors in 157 patients. Errors in the diagnostic process were identified in 154 (97.5%) of them. 101 (62.7%) of these 157 patients were admitted to Imam Reza Hospital, 17 (10.5%) to Ghaem Hospital, and 43 (26.7%) to Doctor Shariati Hospital. Ten (6.2%) patients chose a primary-care physician in the health/TB center for the first medical visit, 109 (67.7%) visited a primary-care physician out of the health/TB center, and 38 (23.6%) cases visited the specialist physicians. The median lag time (25th percentile, 75th percentile) from onset of symptoms to first medical visit was 20 (10, 30) days, and from onset of symptoms to diagnosis was 50 (22, 99) days. Furthermore, 20 (12.8%) patients from onset of symptoms to diagnosis had referred to only one physician, 30 (19.2%) to two physicians, 40 (25.6%) to three physicians, and 66 (42.3%) to four physicians or more. Comparison of mean lag time from onset of symptoms to first visit and from onset of symptoms to definitive diagnosis for different groups of patients is shown in Table 2.

The frequency distribution of different types of errors in patients was as follows: failure in access/presentation in 80 (51%) cases, history taking in 109 (69.4%) cases, physical examination in 101 (64.3%), ordering test in 94 (59.9%), hypothesis generation in 113 (72%), performance of diagnostic tests in 21 (13.4%), recognizing urgency/complications in 11 (7%), referral/consultation in 26 (16.6%), and follow-up in 27 (17.2%) (Figure 1). Diagnostic errors were not found in only 4 (2.5%) cases. There was a lack of patient adherence to follow-up or diagnostic procedures in 16 (10.2%) cases. The rare or atypical manifestations of the disease were observed in 19 (12.1%) patients.

The relationship between the occurrence of different types of diagnostic errors and patient- or disease-related characteristics is shown in Table 3.

4. Discussion

According to the present study on the TB patients who ultimately needed to be admitted to the hospital to confirm diagnosis or immediately after diagnostic confirmation, the median lag time from onset of symptoms to first medical visit was 20 days and from onset of symptoms to confirmed diagnosis (total diagnostic time) was 50 days. About half of the patients saw four or more physicians before diagnosis of TB. The most common errors in diagnosing TB were failure in hypothesis generation (72%), followed by history taking, physical examination, ordering tests, and other types of error with less frequency [16, 17].

TB is a major health concern in developing countries and remains a serious challenge in developed countries. The disease is referred to as a great imitator in that it can be challenging to diagnose, and previous studies reported a high number of errors in diagnosing TB [18, 19]. These errors have allowed the organism to infect a large number of other people. By missing and delaying the diagnosis of TB,

Table 1: Characteristics of patients and their tubercular diseases.

Number of TB patients	158
Age (mean ± SD)	52.4 ± 21.1 (15–59)
Male to female ratio	1.26
Site of involvement	
Pulmonary TB	
Smear positive	96 (59.6%)
Smear negative	4 (2.5%)
Extrapulmonary TB	
Pleural	15 (9.3%)
CNS	13 (8.1%)
Disseminated	16 (9.9%)
Bone and joint	6 (3.7%)
Lymph nodes	4 (2.5%)
Peritoneal cavity	3 (1.9%)
Other sites	4 (2.5%)
Nationality	
Iranian	151 (94.9%)
Afghan	7 (4.4%)
Educational level	
Illiterate	61 (39.1%)
Secondary school or lower	59 (37.8%)
High school diploma or associate degree	31 (19.9%)
Academic	5 (3.2%)
Geographical strata	
Urban	133 (84.2%)
Rural	25 (15.8%)
History of close contact with TB	38 (24%)
Previous history of TB	16 (10.2%)
Drug addiction	33 (20.8%)
History of recent imprisonment	11 (6.9%)
Underlying conditions	
Diabetes mellitus	40 (25.3%)
Hypertension and heart disease	26 (16.4%)
Chronic pulmonary disease	13 (13.2%)
Taking corticosteroids or other immunosuppressive drugs	11 (6.9%)
HIV/AIDS	9 (5.6%)
Overall rate of diagnostic errors	154 (97.5%)
One type of error	26 (16.8%)
Two types of error	21 (13.6%)
Three or more types of error	107 (69.4%)
Life-threatening complications from admission to discharge	
TB-associated sepsis or acute respiratory failure	29 (18.5%)
Massive hemoptysis	13 (8.3%)
Major thromboembolic events	11 (7.6%)
Pneumothorax/pyopneumothorax	2 (1.2%)
Progressive pneumothorax requiring surgical shunting	2 (1.2%)
Others	13 (7.6%)

the chances of controlling the spread of this disease will be lost once more ("missed opportunities") [20]. The reported rate of diagnostic errors in TB patients varied according to the populations studied as well as the accuracy of the methods using for detection of diagnostic errors. For example, about 9.8% of hospitalized TB patients in Bolivia were estimated to be misdiagnosed [16], whereas the estimated rate of diagnostic errors in 6489 Iranian TB patients were reported 1.5% [21]. These rates might be grossly underestimated because significantly higher rates have been reported by autopsy-based studies [13, 14], as well as those evaluated errors by structured tools such as TB Process-Based Performance Review (TB-PBPR) Tool [12].

Studies regarding the factors associated with the delay in diagnosing TB have not reported the consistent results [21, 22]. Since TB is a potentially lethal highly infectious disease, and by the time most patients are treated, they have already infected many others, even one day longer delay in diagnosis could be harmful for both patient and public health. Time delays in diagnosis of TB are often reported as total delay, patient delay, and health system delay [23, 24]. While a recent systematic review about time delays in diagnosis of pulmonary TB demonstrated that the reported average patient delay was similar to health system delay (28.7 versus 25 days) [25], Nasehi et al. showed that a large part of the delay from onset of symptoms to diagnosing TB in Iran was related to the health care system (and not the patient), which was the same as our result. However, the average delay in diagnosis among Iranian smear-positive TB patients has been reported to be 59 days [22].

Here, we describe the possible underlying causes of errors in diagnosing TB based on the three categories of diagnostic errors including system-related (technical failure or organizational flaws), "no fault" (unusual manifestation of a disease or patient-related error such as deception or poor cooperation), and cognitive errors [4].

4.1. "No Fault" Errors. It has been pointed out that because TB has changed its face today, the doctors are fooled again by TB, and this has led to several-month delay in diagnosing the disease [20]. There is some evidence in favor of this statement. For example, a large autopsy-based study in Poland showed that the errors in diagnosing TB in most cases were associated with atypical localization of lesion on chest radiography, as well as spreading the disease out of the lungs [26]. However, this is not always the case. While diagnostic errors may sometimes reflect encounters with extremely rare diseases or very unusual presentations of common diseases; in many cases, it is a relatively common disease that is mislabeled or missed entirely [9]. In our study, only about 12% of patients were presented with atypical or rare manifestations of TB.

In addition, the "no fault" error rate associated with poor cooperation of the patient after medical visit was found in only about 10% of our patients. Poor adherence to follow-up recommendations, such as changing their doctors based on their own decision, was also reported by some of our patients; some others had lost a bunch of time because of dissatisfaction with a particular diagnostic intervention (e.g., diagnostic bronchoscopy).

It is also important to note that most of TB patients in our study were illiterate or semiliterate (74.5%). As previously demonstrated, educational level affects health literacy and may determine the type of health-seeking behavior necessary to achieve favorable treatment outcomes and subsequent follow-up [27]. Several studies reported low levels of health literacy among people regarding infectious

TABLE 2: Comparison of mean lag time from onset of symptoms to first visit and from onset of symptoms to definitive diagnosis for different groups of patients.

		Mean lag time from symptom onset to first medical visit (days)	P value	Mean lag time from symptom onset to diagnosis (days)	P value
Gender	Male	74.58	<0.001	75.26	0.29
	Female	49.19		67.98	
Age	15–39 years	64.86	0.83	64.18	0.23
	40–64 years	60.28		78.46	
	Years ≥ 65	63.72		71.57	
Geographical strata	Urban	63.45	0.44	71.36	0.80
	Rural	56.09		68.95	
Educational level	Secondary school or lower	63.02	0.58	72.14	0.38
	High school diploma or higher degree	58.97		65.18	
Chronic medical illness	Positive	58.37	0.11	74.04	0.57
	Negative	68.47		70.20	
Close contact with TB patients	Positive	66.19	0.54	72.31	0.89
	Negative	61.81		71.23	
Drug addiction	Positive	68.11	0.44	78.27	0.32
	Negative	62.18		70.19	
Site of involvement	Pulmonary	68.68	0.002	72.73	0.36
	Extrapulmonary	47.60		66.23	
First medical visit	Primary-care physician	62.22	0.90	71.38	0.65
	Specialist/Subspecialist	61.34		67.94	
Acute or subacute life-threatening complications	Positive	56.39	0.45	65.18	0.58
	Negative	61.51		69.19	
Clinical outcome	Survived	63.55	0.99	73.50	0.89
	Died	63.50		71.85	

*Statistical analyses are descriptive methods; Lilliefors and Shapiro–Wilk tests to determine the frequency distribution of quantitative variables and Mann–Whitney test to compare two groups; TB: tuberculosis.
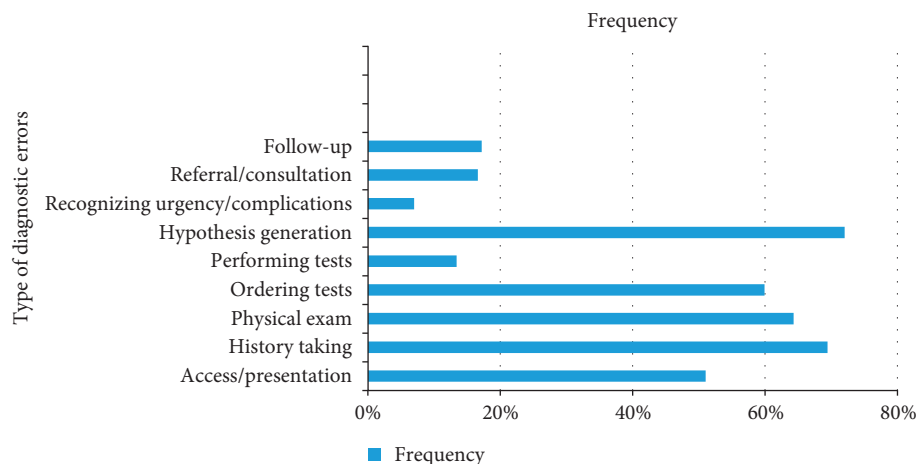

FIGURE 1: Frequency distribution of different types of diagnostic errors in tuberculous patients.

diseases, and in particular TB in endemic countries [21, 28–30]. A number of patients in our study visited herbalists instead of doctors. Such behaviors have also been reported in studies from other countries [28]. However, the analysis in this study showed no significant difference in the mean lag time from symptoms onset to presentation to doctor between illiterate or semiliterate subjects and other patients with higher level of education. People living in rural areas experienced significantly more diagnostic errors in recognizing urgency/complications, ordering tests, and referral/consultation.

In our study, the delay between symptoms onset and first medical visit was significantly higher in patients with pulmonary TB than in patients with extrapulmonary TB, as well as in male patients compared with female patients. Further studies are needed to find out the root causes of greater delay to medical visit in these groups of patients.

TABLE 3: The relationship between the occurrence of different types of diagnostic errors and patient- or disease-related characteristics.

Variables		History		Physical exam		Tests				Hypothesis generation		Assessment		Referral/ consultation		Follow-up	
						Ordering		Performance				Recognizing urgency/ complications					
		n (%)	P*	n (%)	P	n (%)	P	n (%)	P	n (%)	P	n (%)	P	n (%)	P	n (%)	P
Gender	Female	48 (44)	0.36	46 (45.5)	0.21	42 (44.7)	0.38	5 (23.8)	0.04	52 (46)	0.11	4 (36.4)	0.66	9 (34.6)	0.36	14 (51.9)	0.28
	Male	61 (56)		55 (54.5)		52 (55.3)		16 (76.2)		61 (54)		7 (63.6)		17 (65.4)		13 (48.1)	
Age, years	15–39	39 (35.8)	0.59	34 (34)	0.96	32 (34.4)	0.20	5 (23.8)	0.71	38 (33.9)	0.91	4 (40)	0.64	7 (28)	0.30	8 (30.8)	0.90
	40–64	37 (33.9)		34 (34)		32 (34.4)		10 (47.6)		38 (33.9)		1 (10)		12 (48)		10 (38.5)	
	≥65	33 (30.3)		32 (32)		29 (31.2)		6 (28.6)		36 (32.1)		5 (50)		6 (24)		8 (30.8)	
Educational level	Illiterate	48 (44.9)	0.18	44 (44.4)	0.05	37 (39.8)	0.47	11 (52.4)	0.08	46 (41.4)	0.14	4 (36.4)	0.85	11 (44)	0.08	13 (48.1)	0.94
	Secondary school or lower	35 (32.7)		37 (37.4)		38 (40.9)		8 (38.1)		43 (38.7)		5 (45.5)		13 (52)		7 (25.9)	
	High school diploma or associate degree	21 (19.6)		15 (15.2)		16 (17.2)		2 (9.5)		20 (18)		2 (18.2)		1 (4)		5 (18.5)	
	Academic	3 (2.8)		3 (3)		2 (2.2)		0 (0)		2 (1.8)		0 (0)		0 (0)		2 (7.4)	
Geographic strata, rural	Urban	91 (85)	0.51	82 (82.8)	0.67	77 (82.8)	0.85	14 (66.7)	0.02	94 (84.7)	0.61	6 (54.5)	0.006	17 (68)	0.02	19 (70.4)	0.03
	Rural	16 (15)		17 (17.2)		16 (17.2)		7 (33.3)		17 (15.3)		5 (45.5)		8 (32)		8 (29.6)	
Close contact with TB patients		28 (25.7)	0.35	26 (26)	0.52	23 (24.7)	0.84	5 (23.8)	0.59	26 (23.2)	0.59	0	0.64	7 (28)	0.64	6 (23.1)	0.86
Chronic medical illness		50 (45.9)	0.99	48 (47.5)	0.57	43 (45.7)	0.39	10 (47.6)	0.86	57 (50.4)	0.04	2 (18.2)	0.05	13 (50)	0.64	11 (40.7)	0.55
Site of involvement, pulmonary %	Pulmonary	68 (62.3)	0.98	65 (64.3)	0.31	58 (61.7)	0.43	10 (47.6)	0.13	71 (62.8)	0.87	1 (9)	<0.001	11 (42.3)	0.01	13 (48.1)	0.07
	Extrapulmonary	41 (37.6)		36 (35.6)		36 (38.2)		11 (52.3)		42 (37.1)		10 (90.9)		15 (57.6)		14 (51.8)	
History of recent imprisonment		10 (9.2)	0.09	10 (9.9)	0.04	10 (10.6)	0.38	1 (4.8)	0.55	9 (8)	0.35	0 (0)	0.43	2 (7.7)	0.57	1 (3.7)	0.40
History of previous TB		6 (5.5)	0.003	6 (5.9)	0.01	5 (5.3)	0.69	2 (9.5)	0.63	7 (6.2)	0.01	0 (0)	0.60	1 (3.8)	0.47	2 (7.4)	0.50
Typical chest radiography		46 (42.2)	0.75	44 (43.6)	0.46	43 (45.7)	0.47	10 (47.6)	0.53	47 (41.6)	0.93	4 (36.4)	0.72	11 (42.3)	0.91	9 (33.3)	0.35

*The comparisons were performed within variables. Chi-squared and Fisher's exact tests were used to compare groups; TB: tuberculosis.

4.2. Cognitive Errors. The most common type of diagnostic error observed in our study was failure in *hypothesis generation* by the physician. It is not clear what causes the patient to visit a doctor by complaining of subacute or chronic respiratory symptoms or other TB suggestive clinical syndromes [31] in an endemic country, but the diagnosis of TB is not considered by the physician. A basic knowledge of common cognitive biases is essential to try on preventing these errors [6]. Cognitive errors are divided into four areas of faulty knowledge, faulty data gathering, faulty data synthesis, and failure in verification of data [4]. Although this type of classification is useful, it cannot be indicative of why there are errors in the proper ordering test, or the correct interpreting physical signs or diagnostic tests [4].

Based on available studies, the most common cognitive cause of diagnostic errors is premature closure of diagnosis or search satisfying, meaning the desire to stop after an initial working diagnosis instead of considering other possibilities on the differential diagnosis [4]. For decades, methods of TB diagnosis have not changed significantly; resting primarily on clinical history, physical examination, chest radiography, and sputum smear and culture [11]. Although it is expected that the physician should advise patients with clinical scenario suggestive of TB to perform relevant diagnostic tests or refer them to the TB/Health center or relevant specialist, none of these recommendations was made in most of our patients; a great majority of them were only prescribed antibiotics or advised symptomatic therapy. The underlying reason for such clinical practice is not clear, and several hypotheses can be raised that are discussed in the following section:

(1) *Failure to Pay Attention to the Importance of History Taking and Physical Examination.* Although the detailed and comprehensive history taking and physical examination are the first and most important components of diagnostic assessment in a patient, this issue is often overlooked and done incompletely. The incomplete history taking, disregarding the physical examination, and the inability to correctly interpret laboratory data have been associated with delay in the correct diagnosis of disease [32]. According to Graber's study and reinforced by our study results, the errors occurred in the early stages of diagnosis (such as incomplete history taking or physical examination) probably can lead to errors at later stages [4]. It has been demonstrated that the main cause of diagnostic errors in TB patients is ignoring simple but basic diagnostic measures, such as lung auscultation, chest radiograph, and sputum smear and culture [11].

(2) *Insufficient Knowledge regarding the Clinical and Paraclinical Findings in TB.* Substantial number of patients in our study pointed out that they repeatedly complained to the doctor about prolonged respiratory symptoms along with constitutional symptoms and even were hospitalized in some cases, but TB was diagnosed only following massive or nonmassive hemoptysis. It seems that the physician's perception of a TB patient was a cachectic person who coughed blood as pictured in old-time movies. However, TB can cause diseases of different severity and a wide range of symptoms. More than 40% of patients in our study had typical chest radiographs for TB; however, the presence or absence of this clue indicated no significant correlation with frequency of errors in hypothesis generation or other types of errors.

(3) *Failure to Pay Attention to the Disease Timeline (Acute vs. Chronic).* Proper and accurate understanding of the nature and timeline of symptoms is essential for conceptualizing the underlying disease process, correctly identifying the problem presentation, and guiding an effective approach. Initially, broadly categorizing disease presentation as acute, subacute, and chronic can help narrow the initial differential diagnosis [33]. In TB endemic areas, TB is strongly associated with the presence of chronic respiratory disease in adults; however, the contribution of pulmonary TB to the etiology of chronic respiratory disease is rarely considered [17]. In dealing with most patients with chronic respiratory disease/chronic pneumonia, a methodical and thorough diagnostic evaluation is the initial priority and choosing the appropriate treatment to start is made based on the etiologic diagnosis [34]. Despite this fact, the results of our study showed that most TB patients in our study were treated for alternative diagnoses such as common cold, bronchitis, pharyngitis, etc., while upper respiratory tract infections are commonly known to be acute-type diseases; if symptoms last longer than usual the diagnosis should be questioned, or a complication should be expected.

(4) *Tendency to Treat the Symptom instead of the Disease.* In our study, the majority of patients had been treated symptomatically, and the root cause of the problem was not searched at all. For example, a patient with the complaints of prolonged coughing, sputum production, weight loss, and anorexia had been only prescribed a cough medicine. Thus, the disease essentially had not been diagnosed in many patients; instead, the efforts had been directed to relief a symptom using various medications. Since the proper cause is not investigated, the patient is running around in circles until he/she develops complications of the disease. Although it is difficult to estimate the number or cost of these unnecessary interventions and treatments, these might be extremely high.

(5) *Inability to Generate Hypothesis and Raise the Structured Clinical Syndrome.* The structured syndromes build a bridge between the symptoms and diseases and form the foundation for differential diagnosis. Syndromes are linked to the affected morphological structures on the one hand and

diseases on the other. Raising the appropriate clinical syndrome is expected to be followed by correct hypothesis generation and making the correct diagnosis [35].

(6) *Underestimation of the Prevalence of TB.* One type of cognitive error, known as "base-rate neglect," refers to a diagnostic error in which the physician tends to ignore the true prevalence of a disease, resulting in over- or underestimation [5]. This type of error can occur due to either the unawareness or ignorance of the prevalence of a certain disease by a physician or the lack of documented information and statistics about the prevalence of a disease in a community.

(7) *Lack of Paying Attention to the Patient's Underlying Conditions and Risk Factors.* In the large autopsy-based study of Poland, a previous history of TB was recognized as a factor facilitating the diagnosis of TB, which is similar to the results of our study [26]. Many cases in our study mentioned that doctors did not ask questions about the history of close contact with TB, history of recent imprisonment, drug addiction, and so on, while it is expected that each or a combination of these clues will help the physician in the intuitive consideration of TB in the list of differential diagnoses.

(8) *Lack of Appropriate Follow-Up after the First Visit.* This could be due to a lack of adherence of a patient to the follow-up or lack of a physician's recommendation to visit again. In addition, setting follow-up visits or arranging referrals are very difficult in the communities such as our country with too many independent providers who cannot easily access patients' records from other independent providers.

The issue of cognitive bias is more challenging in the patients with extrapulmonary TB. In our study, more than one-third of the patients were suffering from extrapulmonary TB that was disseminated in 40% of them. A Supplementary Table (available here) is provided in the appendix of this article to present several examples of errors in diagnosing the extrapulmonary TB. Diagnosing the complex cases such as those mentioned in the Supplementary Table could be difficult and challenging. Generally, the physicians begin the diagnosis generation process very quickly in dealing with the patient. The dual-process theory describes two systems used by physicians to make diagnostic decisions: intuitive (mental perception) and analytical approaches. The experienced physicians are aware of how to maneuver between these two approaches and when it is appropriate to "slow down" and devote more time to analyze existing data [36]. They invoke the analytical approach to diagnose a complex patient presentation that does not readily fit into a common illness script [36]. In fact, in dealing with such patients with unusual or complex presentation, there is a need for "problem representation." The problem representation is an abstract one-sentence summary that elaborates the key features of the case. This representation triggers probable diagnostic hypotheses [37].

For example, in facing the first case of Supplementary Table, the relevant problem representation can be as follows: *an aged patient with fever and subacute, progressive encephalopathy*; then, differential diagnoses in different categories including infectious, neoplastic/paraneoplastic, autoimmune, cardiovascular, or drug-induced disorders should be raised and weighed. In this case, given that the central nervous system infection is considered as one of the most important candidates in the list of differential diagnosis, the doctor not only does not ignore the neck stiffness and focal neurologic deficits in physical examination but also especially attempts to connect these clinical findings with laboratory and imaging studies, rather than suggesting some unmatched diagnoses (e.g., new onset dementia, underlying pulmonary fibrosis, and urinary tract infection).

4.3. System-Related Factors.

According to the available data, 95% of TB cases are occurring in developing countries [38]. Although anti-TB medicines have prevented dozens of millions of deaths, important diagnostic and treatment gap remains in place. This gap is due to underreporting of TB cases, especially in countries with large unregulated private sectors and underdiagnoses in countries with major barriers to accessing care [10].

None of the patients in our study had pointed to the difficulty or lack of access to primary-care physicians or TB/health centers. Although many studies in different countries noted that their problem of the referral system lies in the poor specialist referral process and communication between primary-care physicians and consultants [39, 40], in our country, a major issue is that primary-care doctors are not patients' first point of contact in many cases. Nearly a quarter of patients in our study choose specialist physicians instead of primary-care physicians for the first medical visit. They change their doctors frequently based on their own decision. More than 90% of the patients had visited more than one doctor, which in many cases did not go through the referral process. These health-seeking behaviors and utilizing health facilities lead to poor continuity of care, unnecessary testing, and delayed diagnoses and can therefore decrease the quality of care. Similarly, a systematic review of 58 studies addressing delay in diagnosis and treatment of TB concluded that the essential problem in delay of diagnosis and treatment seemed to be a cycle of repeated visits at the same healthcare level, resulting in nonspecific antibiotic treatment and failure to access specialized TB services [38].

Some other system-related errors noted in our study that could contribute to the delayed or missed diagnosis included no admission of patients for a few reasons, such as hospital or emergency department overcrowding and bed shortages, symptomatic treatment of patients, especially in emergency departments, without any diagnostic measures, and early discharge from the hospital (with the patient's consent or the doctor's decision) before the definite diagnosis was made. Such shortcomings lead the patients through a "maze of healthcare corridors before reaching the correct diagnosis and treatment" or death in some cases (Figure 2). If the system (latent) errors that are associated
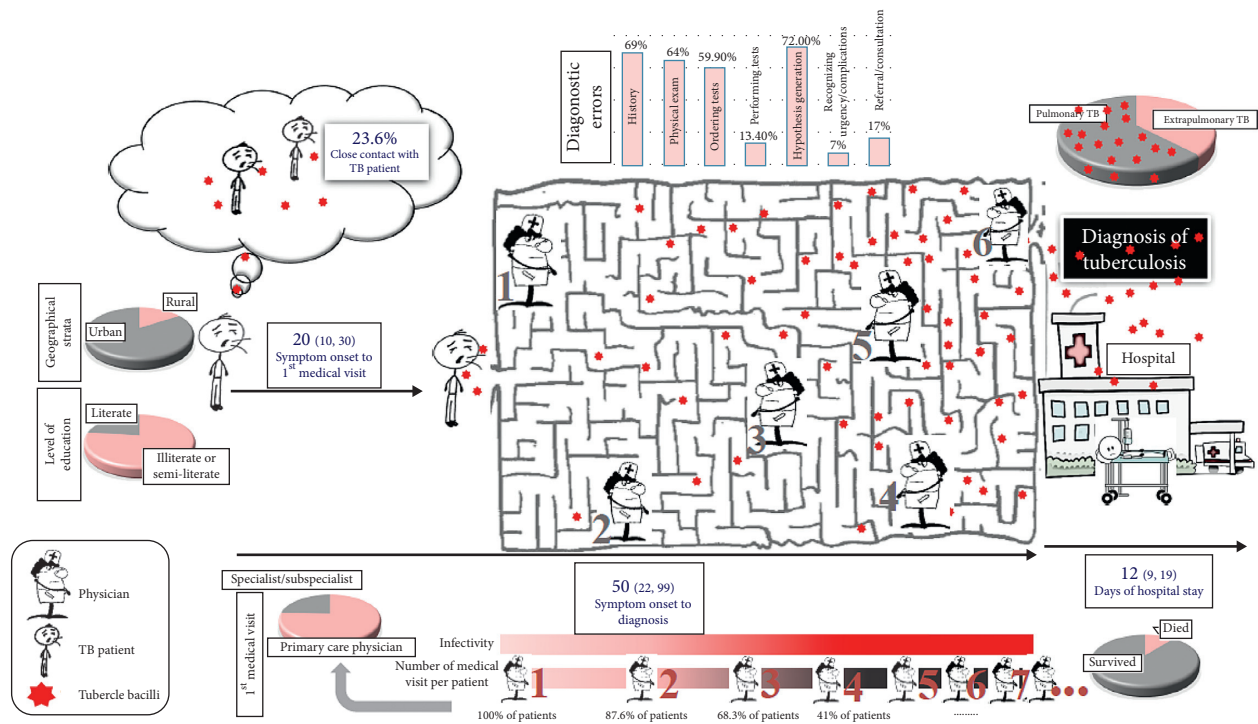
FIGURE 2: "Maze of healthcare corridors before reaching the correct diagnosis and treatment" or death in TB patients (adopted from the present study results).

with such a dis-coordinated care are not addressed, their aggregation will make the healthcare system more prone to shortcomings in the future [39]. In fact, care among multiple providers must be coordinated to avoid wasteful duplication of diagnostic testing, perilous polypharmacy, and conflicting care plans [40].

Our study has several limitations. First, there is the possibility of hindsight bias, in which "people who know what's going on almost always overestimate the knowledge of others who had insufficient information." In fact, it is very difficult to detect retrospectively the cause of a diagnostic error in the actual clinical situation [41]. Second, the difficulty in discerning exactly how a given diagnosis was reached. Third, given that TB is commonly a chronic disease that lasts for months from its beginning to diagnosis in some cases, the chance of patients forgetting the clinical course, medical visits and referral process, and the events occurred existed. The fourth limitation was the unawareness of patients from standard history taking and physical examination. Therefore, their responses to the study questions were influenced by various factors such as patient's experience with other doctors, level of literacy and culture, patient's perception of standard physical examination, and personal bias in response. To reduce the impact of these issues, we used the stepwise systematic approach described in "Materials and Methods". Fifth, we are likely to overestimate the error rate occurred in TB patients from symptom onset until diagnosis because those patients enrolled in our study ultimately needed to be admitted to hospital, which in turn could be one of the signals of potential errors associated with TB patients, especially in pulmonary TB. On the contrary,

because our study was not autopsy-based, the possibility of underestimation of error rate exist because some patients might have died before the diagnosis.

Based on our study findings, we suggest several signals of potential diagnostic error (*trigger tools*) as potential criteria for screening diagnostic errors in TB, including the need for hospitalization at the time of verifying the diagnosis of sputum smear-positive pulmonary TB, the high degree of sputum smear-positivity in pulmonary TB at the time of verifying the diagnosis, multiple exacerbations of underlying chronic respiratory disease until verifying the diagnosis of pulmonary TB, the occurrence of pyopneumothorax in pulmonary TB cases, multiple visiting or referral through the healthcare system before the diagnosis is reached, receiving multiple courses of antibiotics before the diagnosis is reached, long delay from symptom onset to diagnosis, and manifestation of the patient with a severely depressed level of consciousness or the occurrence of focal neurological deficits in CNS TB.

5. Conclusion

This study showed that although an important part of the delay in diagnosis of TB is related to the delay from onset of symptoms until the first medical visit by patient, the more significant part is associated with delayed time from first medical visit to diagnosis, which is associated with diagnostic errors. Similar to other diagnostic errors, in the TB patients, the combination of cognitive and system errors leads to a delayed or missed diagnosis that leads to significant damage to the patient and the community. Based on

the results of this study, the atypical or unusual presentation of TB had not an important role in diagnostic errors, but the most common errors occur in the hypothesis generation, followed by failure in history taking and physical examination.

In conclusion, we emphasized on the necessity of efforts to organize and improve the health referral system in our country. It seems that efforts to improve the following goals can reduce the delay in diagnosing TB and it's possible damages and infectivity and thus can be effective in improving disease control in the community: trying (1) to improve the awareness and health literacy of people in the community regarding TB, (2) to raise the awareness of physicians about the endemic diseases of the region, such as TB, (3) to promote physicians diagnostic reasoning, (4) to give physicians feedback on their patient's outcome and the errors caused by them in the diagnosis and treatment process, (5) to promote syndrome-based diagnosis among physicians and emphasizing treatment based on disease rather than symptoms, and (6) continuous notification of statistics on the incidence and prevalence rates of diseases at regular intervals.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

Supplementary Materials

The supplementary table is provided to present several examples of errors in diagnosing the extrapulmonary TB and their consequences. Although diagnosing the complex cases such as those mentioned in this table could be difficult and challenging, hypothesis generation by using analytical diagnostic approach could prevent some of these misdiagnoses. (*Supplementary Materials*)

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