Original Article

Delayed inpatient diagnosis and isolation of active pulmonary tuberculosis patients, a large tertiary care academic hospital experience in Riyadh, Saudi Arabia

What are we missing?

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ABSTRACT

الأهداف: معرفة مدة تأخر تشخيص مرض السل الرئوي (PTB) لدى المرضى المنومين: المدة والعوامل المساهمة في أحد المراكز الأكاديمية في المملكة العربية السعودية (SA).

المنهجية: أجريت مراجعة بأثر رجعي لجميع الحالات المؤكدة PTB خلال الفترة من مايو 2015م وأبريل2019م. وكانت النتائج الزمن اللازم حتى الاشتباه أو العزل، المجموعة المبكرة: التي يتم الاشتباه والعزل خلال ٢٤ ساعة من الوصول للمستشفى. المجموعة المتأخرة: التي يتم الاشتباه والعزل بعد ٢٤ ساعة من الوصول من المستشفى.

النتائج: أُدرجت 49 حالة بمتوسط عمر 49 سنة ؛ الثلث كان فوق 65 عام من العمر. وكان معظم المرضى من الجنسية السعودية وذكور. المجموعة المتأخرة شكلت 38% من الحالات بمتوسط تأخر التشخيص إلى 5.5 أيام بعد التنويم في المستشفى. المجموعة المتأخرة كانت مرتبطة بالعمر أكبر من 65 سنة (odds ratio [OR]=8.93، 95% confidence interval [CI]=2.22–35.95)، وجود السرطان (OR=13.38، 95% CI= 1.46–122.71)، وجود أمراض مزمنة (OR=4.90، 95% CI= 1.31–18.32)، وجود أعراض مصاحبة غير تنفسية (OR=5.6، 95% CI= 1.56–19.98)، عدم تحليل الأشعة السينية للرئة (OR=48، 95% CI= 8.63–266.88)، ارتفاع مستوى هرمون البروكالسيتونين (OR=12، 95% CI= 1.58–91.08).

الخلاصة: يوصى الأطباء في المستشفيات المماثلة في السعودية بالحرص على وضع تشخيص مرض الدرن الرئوي في الاعتبار لدى المرضى كبار السن والمرضى ذوي الأمراض السرطانية بشكل دائم وذلك بمراجعة الأشعة السينية للرئة بدقة وعدم الانخداع بوجود أعراض مصاحبة أو بارتفاع هرمون البروكالسيتونين.

Objectives: To identify pulmonary tuberculosis (PTB) delayed inpatient diagnosis duration and contributing factors in an academic center in Saudi Arabia (SA).

Methods: Retrospective review of all culture-confirmed PTB cases between May 2015 and April 2019. The outcomes were the timing between admission and suspicion of PTB or isolation to either: early group (within 24 hours of admission) and late group (24 hours after admission).

Results: Forty-nine cases were included with a median age of 49 years; a third of them were above 65 years of age. Most patients were of Saudi nationality and male. Approximately 38% of the cases were in the delayed group, half of them were smear-positive, with an average delay of 5.5 days. This was significant with: age above 65 years (odds ratio [OR]=8.93, 95% confidence interval [CI]=2.22-35.95) presence of non-respiratory symptoms (OR=5.6, 95% CI=1.56-19.98), malignancy (OR=13.38, 95% CI=1.46-122.71), chronic medical problems (OR=4.90, 95% CI=1.31-18.32), missed chest x-ray findings (OR=48, 95% CI=8.63-266.88) or procalcitonin level above 0.5 ng/mL (OR=12, 95% CI=1.58-91.08).

Conclusion: Physicians in SA need to have a low threshold for PTB consideration in elderly patients or those with a history of malignancy. A careful review of the initial chest x-ray might help to overcome missing cases of PTB.

Keywords: pulmonary tuberculosis, early diagnosis, infection control

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Tuberculosis (TB) is among the 10 reasons for death worldwide. Approximately 13% of 10 million *human immunodeficiency virus*-negative people who were diagnosed with TB in 2017 eventually died.[1] In the Kingdom of Saudi Arabia (KSA), In all age groups, 3.2 per 100,000 population were estimated to die from TB in 2017.[1] Although recent studies have found TB is becoming a disease of young people; older age is still associated with a 20% fatality rate.[2-4]

Early detection and treatment are the main pathways to eliminate TB. These help to implement the appropriate infection control measures promptly and initiate appropriate treatment. Therefore, the World Health Organization goal is to reach TB diagnosis within 2 to 3 weeks of symptom onset.[1] Once pulmonary TB is suspected, a prompt isolation to an airborne-infection isolation (AII) room is recommended by the Centers for Disease Contol.[5] Failure to achieve these goals could facilitate the transmission of the disease, lead to more severe illness, and result in worse outcomes.[6] Tuberculosis was diagnosed late in many previous reports, including studies from Arab countries, with a median delay of 2 months.[7-10] In addition to the delay in patient presentation, the diagnosis of pulmonary TB (PTB) was delayed in two-thirds of the cases until more than 3 days after admission in one report.[11] Moreover, a longer delay (5 days) was reported among patients in the intensive care unit (ICU) from a study in KSA.

However, there is lack of studies in the region that have previously investigated stable, non-ICU patients, who are expected to be misdiagnosed or missed.

This study aimed to identify the interval time between the initial patient assessment in the emergency room and inpatient diagnosis of PTB and to explore the risk factors that might be linked to this delay in the diagnosis.

Methods. This study was performed at King Saud University Medical City, Riyadh, KSA. As per the hospital policy, cases of typically presenting respiratory infections have to be admitted under the general medicine team. Once a special diagnosis (example, PTB) is made, the transfer of care to the appropriate specialty is made. All clinical specimens were processed in the mycobacteriology level III laboratory of King Khalid University Hospital, Riyadh, KSA. In this laboratory, a positive culture was reported approximately 111 times annually. The study was approved in December 2018 from the University's Institutional Review Board (IRB) [18/0843/IRB].

This study is a retrospective review of all cases of culture-confirmed PTB between May 2015 and April 2019. All patients who were diagnosed with non-tuberculous *Mycobacterium*, who were not admitted through the emergency department, or patients known to have PTB who were already on anti-tuberculous treatment (ATT) were not included. Patient data were collected from the Hospital Information System (HIS). All data were collected from the progress notes of the initial medical assessment. The time interval was calculated from the date of hospital admission until a physician had documented suspicion of PTB, or if not clearly documented, the date of collection of respiratory samples or the date of initiation of ATT. Cases were categorized based on the timing of isolation in an airborne-infection negative pressure isolation room, into early isolation (within 24 hours of presentation) and late isolation (after 24 hours of presentation). All recruited patients have signed consent and agreed to be part of any study undertaken in the hospital.

All demographic and clinical data were collected, including past medical history, clinical presentation including duration of symptoms (3 weeks or more), diagnosis of physician on admission, interval until diagnosis, interval until ATT initiation, length of hospital stay, and outcome. Physicians who first suspected of PTB were classified, based on their qualifications and according to their job level in the hospital, (resident doctor, fellow/registrar, or consultant).

Laboratory investigations (including procalcitonin, [PCT]) and radiological findings were recorded. Microbiological data, including the type of sample and result of acid-fast bacilli (AFB) smear classified into negative, +1 (1-9/100 fields), and +2 or more, in addition to culture identification, were also included. PubMed search and Mesh databases were performed with the terms "delayed diagnosis" and "pulmonary tuberculosis" to review previous studies in the literature.

Statistical analysis. Data are presented as frequency, mean, median, and standard deviation. Data analysis was performed by the Statistical Package for Social Sciences for Mac, version 23 (IBM Corp, Armonk, NY, USA) using the Chi-square test with p-value of <0.05 of statistical significance. The odds ratio (OR) for the study outcome was also calculated.

All sputum samples were collected, transferred, and processed on the same day by the microbiology

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department. Samples were stained by the Ziehl-Neelsen and auramine-rhodamine stains in which smear results were reported based on the Centers for Disease Control and Prevention classification. Then it was cultured in mycobacterial growth indicator tube (MGIT) Bactec 960 liquid medium, Lowenstein-Jensen solid pyruvate, and glycerol media. Xpert MTB/RIF molecular testing (Cepheid Inc, Sunnyvale, California, USA) was directly performed on all samples. Incubation at 37°C in the aerobic atmosphere was carried out for the solid media until mycobacterial growth. Identification was based on colony morphology, pigmentation, rate of growth, and biochemical tests, including niacin test, nitrate reductase test, and heat-stable catalase and pyrazinamidase tests.

Results. During the 4-year study period, 444 positive TB cultures were identified. Of them, 49 cases of culture-proven PTB were included. The median age was 49 years (range 16-91), a third of them (30.6%) were above 65 years of age. The majority of cases were male (65.3%), of Saudi nationality (83.7%), and were treated in non-ICU settings (81.6%), further details on patients' characteristics, presentation, investigations and hospital course is presented in Tables 1 & 2. Processed respiratory samples were obtained from expectorated sputum in 38 cases (77.6%), induced sputum in 9 cases (18.4%), or deep sample (bronchioalveolar lavage or tracheal aspirate) in 2 cases (4%). Two-thirds of the cases' respiratory samples were positive for acid-fast bacilli smear (35 cases, 71.4%), 26 cases were considered +2 or more. Xpert MTB/RIF was performed in 95.9% of cases; only 5 cases were negative. In addition to pulmonary TB, disseminated TB was also diagnosed in 9 cases (18.4%); TB meningitis in 4 cases (8.2%); vertebral TB in 2 cases (4.1%), and lymphadenitis in 2 cases (4.1%). Overall time interval from admission to suspicion was 2.6 days (±5.3), to isolation was 3.4 days (±6.1), to respiratory sample collection was 4.5 days (±5.9), to anti-TB initiation was 7.6 days (±10.8), to discharge was 40.8 days (±29.7), and to death was 43.4 days (±28.3).

Pulmonary TB was not suspected upon admission in 38.8% of the cases (delayed group); therefore, they were not transferred to an AII room within 24 hours of admission, while the rest (30 patients, 61.2%) were in the early group. Compared to the early group, the delayed isolation group had a longer average interval until transfer to AII room (0 versus [vs.] 5.5 days), interval until the physician order to collect the respiratory specimen (2 vs. 6.4 days).

As shown in Table 3, late decision for admission to an AII room (delayed group) was significantly associated with age above 65 years (p=0.001), presence of non-respiratory system symptoms (p=0.006), malignancy (p=0.006), chronic medical problems (p=0.014), missed chest x-ray findings (p=0.001), or PCT level above 0.5 ng/mL (p=0.01). In contrast, factors that prevented late diagnosis were the presence of cough, presence of cough in addition to at least one symptom of weight loss, night sweats or loss of appetite (p=0.018), differential diagnosis of pneumonia (p=0.001), previous hospital

Table 1 - Overall characteristics of patients with pulmonary tuberculosis included in the study.

Variable	n (%)
Age	
Above 65 years	15 (30.6)
Below 65 years	34 (69.4)
Gender	
Male	32 (65.3)
Female	17 (34.7)
Nationality	
Saudi	41 (83.7)
Other nationality	8 (16.3)
Prior medical history	
No known history (medically free)	21 (42.9)
Malignancy	7 (14.3)
Diabetes	17 (34.7)
Tuberculosis history	
Previous TB disease	2 (4.1)
Previous TB exposure	7 (14.3)
Body mass index, kg/m²	
Below 18	21 (42.9)
18-25	18 (36.7)
Above 25	10 (20.4)
Smoker	
Yes	18 (36.7)
No	31 (63.3)
Previous hospital visit	
At least 1 previous hospital visit	29 (59.2)
2 or more visits	6 (12.2)
Symptoms	
Cough	40 (81.6)
Cough + any B symptoms*	33 (67.3)
Fever	31 (63.4)
Appetite loss	28 (57.1)
Sputum	24 (49.0)
Night sweats	24 (49.0)
Weight loss	23 (46.0)
Dyspnea	23 (46.0)
Fatigue	20 (40.8)
Pleuritic chest pain	15 (30.6)
Hemoptysis	8 (16.3)
Duration of suffering (since first symptom)	
More than 3 weeks	14 (28.6)
Less than 3 weeks	34 (69.4)

Values are presented as numbers and percentages (%).
TB: tuberculosis, *B symptoms (excluding fever): weight loss, loss of appetite, or night sweats

Table 2 - Hospital course and laboratory and radiological investigations of cases with pulmonary tuberculosis included in the study.

Variable	n (%)
Interval until suspicion	
After first 24 hours (delayed group)	19 (38.8)
Smear positive	11
Within first 24 hours (early group)	30 (61.2)
Doctor who first suspected PTB	
Resident	30 (61.2)
Fellow/registrar	13 (26.5)
Consultant	6 (12.2)
Hospital course and outcome	
Required ICU (average= 4.22 days)	9 (18.4)
Discharged home	38 (77.6)
Died	11 (22.4)
White-blood-cell counts (x 10^9/L)	
Above 11	30 (61.2)
Below 11	19 (38.8)
Procalcitonin (ng/mL)	
Above 0.5	12 (24.5)
Below 0.5	10 (20.4)
Not done	27 (55.1)
C-reactive protein (mg/L)	
Above 10	33 (67.3)
Not done	16 (32.7)
Erythrocyte sedimentation rate (mm/hr)	
Above 25	33 (67.3)
Below 25	7 (14.3)
Not done	9 (18.4)
ATT initiation	
Within 7 days of admission	34 (69.4)
After 7 days of admission	12 (24.5)
Chest x-ray first impression	
Normal	3 (6.1)
Did not comment on CXR	12 (24.5)
Abnormal	34 (69.4)
Location upper	15
Infiltration	13
Cavity	13
Miliary	3
Effusion	3
Pneumothorax	1
Physician impression on CXR compared to CT (total 19)	
Missed infiltration	7
Missed cavity	6
Missed miliary	3

PTB: pulmonary tuberculosis, LRT: lower respiratory tract, TB: tuberculosis, CXR: chest x-ray, CT: computed tomography, ICU: intensive care unit, ATT: anti-tuberculous therapy

visit (p=0.011), and active smoking status (p=0.012). Non-significant variables are presented in Table 4.

Discussion. Leading to potential infection transmission in hospital settings, more than a third (38%) of the PTB cases were missed upon admission. In particular, elderly patients and those with a history of malignancy, which could be due to co-existing confounding or misleading symptoms or atypical presentation in these patient groups. Previous studies have shown a higher proportion of failed cases upon admission, ranging from 45-67% of PTB cases.[7,12] Smear-positive cases constitute approximately half of these failed cases, which is in accordance with the proportion of smear positivity in our cases (57%).[13] In the late isolation group, the median interval from date of admission until isolation date was shorter in our study compared to the study by Greenaway et al[13] (5.5 vs. 12.5 days); and, similar to ICU patients in KSA previously reported by Mahmoud et al[14] (5.5 vs. 5 days). Older age was significantly related to delay in diagnosis or isolation of PTB (OR=8.93, 95%CI= 2.22-35.95), in agreement with previous reports. [7,11] This might be explained by the unusual presentation that is usually encountered in those patients.[15]

A delay in PTB diagnosis was previously linked to the absence of cough (30-day delay) or to the presence of non-respiratory symptoms (15-day delay) on presentation.[16,17] Similarly, in our data, the OR of late PTB diagnosis was 8.16 (95% CI= 1.47-45.18) for the absence of cough (OR=5.60; 95%CI=1.56-19.98) for the presence of non-respiratory symptoms. The majority of these symptoms were gastrointestinal in origin (41.61%).

A previous hospital visit was reported in the literature to be associated with outpatient late diagnosis of PTB in Egypt, Somalia, and Pakistan.[10] We found that those patients reported with at least one previous hospital visit were more likely to have an earlier inpatient diagnosis of PTB.

The presence of comorbid medical condition is known to influence later diagnosis of PTB. For example, Han et al[11] reported the late diagnosis of PTB in patients with malignancy.[11] Although patients with malignancy represent a small proportion in our study population, they were more likely to have a late diagnosis of PTB (OR=13.38, 95%CI=1.46-122.71).

Normal chest x-ray upon admission was one of the causes that might lead to delay in diagnosis of PTB, according to a meta-analysis.[7] However, in our study, having normal (n=3) or abnormal (n=34) chest x-ray did not influence the time of diagnosis (p=0.86). However, we identified 19 cases in which the initial assessment did not include chest x-ray interpretation. Despite being ordered and conducted, missing (or lack of documented interpretation of) chest x-ray findings were associated with late PTB diagnosis (OR=48, 95% CI: 8.63-266.88). Out of the 19 cases, we were able to assess 16 cases' chest x-rays, and compared them to CT scans if available. Infiltration (n=7), cavity (n=6), and

Table 3 - Significant variables in relation to timing of suspicion and isolation of patients with pulmonary tuberculosis included in the study.

Variables	Late isolation[†]	Early isolation	*P*-value	OR for late isolation	(95% CI)
Age above 65 years	11	4	0.001	8.93	(2.22-35.95)*
Previous hospital visit	7	22	0.011	0.21	(0.06-0.72)
Smoker	3	15	0.012	0.17	(0.04-0.73)
Had at least 1 comorbid condition	15	13	0.014	4.90	(1.31-18.32)
Medically free	4	17	0.014	0.20	(0.05-0.76)
Malignancy	6	1	0.006	13.38	(1.46-122.71)*
Absence of cough	7	2	0.012	8.16	(1.47-45.18)
Cough + any B symptoms[‡]	9	24	0.018	0.22	(0.06-0.80)
Co-existing other symptoms[§]	14	10	0.006	5.6	(1.56-19.98)*
Initial diagnosis of LRT infection	5	29	<0.001	0.012	(0.001-0.116)
Missed CXR finding	16	3	<0.001	48	(8.63-266.88)*
Procalcitonin above 0.5 (ng/mL)	9	3	0.01	12	(1.58-91.08)*

*Positive significant result. [†]After 24 hours of presentation. [‡]B symptoms (excluding fever): Weight loss, loss of appetite, or night sweats. [§]Including any symptom that does not belong to respiratory or constitutional symptoms. CI: confidence interval, LRT: lower respiratory tract, CXR: chest- x-ray, ATT: anti-tuberculous therapy, OR: odds ratio

Table 4 - Non-significant variables in relation to timing of suspicion and isolation of patients with pulmonary tuberculosis included in the study.

Variables	Late isolation (after 24hrs)	Early isolation	*P*-value
Female gender	7	10	0.801
Fever	11	20	0.535
Sputum	6	18	0.309
Dyspnea	7	16	0.260
Pleuritic chest pain	3	12	0.073
Hemoptysis	2	6	0.324
Weight loss	6	17	0.086
Night sweats	7	17	0.176
Appetite loss	9	19	0.271
Fatigue	10	10	0.181
Duration of suffering >3 weeks	13	21	0.766
Any finding in respiratory examination	10	17	0.782
Admitted under other than general medicine	6	18	0.052
Level of physician who first suspected PTB			
Resident	11	19	
Fellow/Registrar	7	6	0.281
Consultant	1	5	
Smear negative	8	16	0.09
WBC above 11 (x 10^9/L)	6	13	0.411
Discharged home	12	26	0.059
Death at 30 days	7	4	0.059

WBC: white blood cells, CXR: chest x-ray.

miliary (n=3) findings were missed by the first medical assessment. Leung et al[18] found that smoking history is more likely to be associated with TB (OR >12.09). Therefore, previous meta-analysis has shown that history of smoking might influence physicians early PTB suspicion.[7] Similarly, our data reproduced this finding with early suspicion and isolation (OR=5.71, 95% CI: 1.36-23.93).

Procalcitonin level is a good deferential tool between lower respiratory tract infections due to TB versus common bacterial pathogens. A meta-analysis reviewed the use of PCT to distinguish TB from non-TB causes of pulmonary infections and found that negative likelihood ratio (LR [-] 0.67, 95%CI 0.50-0.90) for PCT above 0.25 ng/ml.[12] Although we used higher cut-off for PCT, patients who were eventually diagnosed with PTB and had PCT above 0.5 were more likely to have delayed isolation (OR=12, 95%CI: 1.58-91.08), increasing the possibility of bacterial superinfection.[12]

The specialty of the admitting team might lead to a short time between admission to isolation. Han et al[11] reported delayed diagnosis among patients who were admitted under other than infectious diseases or pulmonology teams. No significant association was found in our study in relation to admitting team specialty (p=0.052).[11]

Study limitations. The study was retrospective and included a relatively small number of patients. Also, it was based on a single center experience, which may limit the strength of the study and subsequently the ability to generalize the conclusion. However, addressing this issue in this study should draw researchers' attention to preform larger studies to explore more predictors compared to control cases and to build a scoring tool for early detection of PTB in low-incidence countries.

In conclusion, despite being in a country with a low prevalence of TB, physicians should have a low threshold to consider early isolation in patients who

are elderly or those who present with a history of malignancy. A careful review of the initial chest x-ray might help to overcome missing cases of PTB. Lastly, a physician should not be deterred from suspecting PTB by the presence of non-respiratory symptoms or high PCT levels.

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