ORIGINAL ARTICLE

Factors Associated with High-grade Smear Positivity Levels in Pulmonary Tuberculosis

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ABSTRACT

Objective: *The high-grade level of smear acid-resistant bacilli (ARB) positivity has been linked to increased infectiousness in pulmonary tuberculosis (TB). The ability to predict infectiousness is important in the management of the disease. The present study aimed to investigate the relationship between smear results, the clinical features, and the levels of radiological involvement of TB.*

Methods: *A total of 245 cases diagnosed with pulmonary TB were admitted to the study. Data including age, sex, case definition, numbers and characteristics of symptoms, smear results, smear positivity grades, and levels of radiological involvement were recorded. Relations between smear results and other data were determined via cluster tree and regression analysis.*

Results: *The group with only coughing had higher rates of both positive smear and high smear positivity levels (*$p = 0.014$ *and* $p = 0.02$*, respectively) compared to the group without coughing. Similarly, the groups with moderate or high radiological involvement showed significantly higher rates of both positive smear and high smear positivity level when compared to the group exhibiting low radiological involvement (*$p < 0.001$*).*

Conclusion: *Patients with coughing and a moderate to high level of radiological involvement should be closely monitored due to their high-level risk of transmission.*

Keywords: Cough, pulmonary tuberculosis, radiological involvement, smear positivity grade, symptom.

INTRODUCTION

Tuberculosis (TB) remains an important problem, specifically in developing countries (1). Pulmonary tuberculosis (PTB) is the most common and infectious form of the disease. Therefore, the diagnosis of PTB in the population is very important. Notable respiratory symptoms in patients with PTB include coughing, production of sputum and haemoptysis. Systemic symptoms including weakness, weight loss and fever (2) are not specific to PTB, and may be observed in other diseases.

The definitive diagnosis of PTB is made by observation of acid-resistant bacilli (ARB) in the sputum smear (3). An increased level of smear positivity is associated with increased infectiousness (4–10). Mostly sputum examination is not usually performed by primary health care centres. Therefore, the suspicion of PTB is predominantly based on symptomatology and radiology (9, 10). Referrals of suspicious infectious forms of PTB cases with TB-compatible symptoms to tuberculosis dispensaries or secondary health care centres (hospitals) are more crucial.

The aim of the present study is to investigate the relationship between the grade of ARB positivity in sputum smear and other clinical and radiological features in PTB in order to predict more contagious cases. Not only primary health care, but also secondary and tertiary clinicians, will benefit from such information in patient management and in the reduction of infectiousness.

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SUBJECTS AND METHODS

A total of 245 patients who were hospitalized at the chest diseases clinic between December 2008 and June 2012 and who were diagnosed with PTB were included in this study. After approval from the Research Ethics Committee, we retrospectively reviewed patient data that were recorded in the hospital registration system. Patient data including age, sex, nature and number of symptoms, case definitions, sputum smears, smear positivity levels, and standard pulmonary radiography were recorded for each patient.

Case definitions

Case definitions and bacteriological characteristics of the cases were identified in accordance with the 2013 revision of the WHO definitions and reporting framework for TB (11). Accordingly:

A bacteriologically confirmed TB case is one in which a biological specimen is positive by smear microscopy or culture.

A clinically diagnosed TB case is one that has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment; these patients do not fulfil the criteria for bacteriological confirmation. This definition includes cases diagnosed on the basis of X-ray abnormalities, suggestive histology and extrapulmonary cases without laboratory confirmation. Clinically diagnosed cases that are subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

Case of TB: A patient in whom TB has been confirmed by bacteriology or diagnosed by a clinician.

Pulmonary tuberculosis refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the trachea-bronchial tree. Patients with miliary TB have lesions in the lungs and, therefore, it is classified as PTB. Cases of extrapulmonary TB include tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion without radiographic abnormalities in the lungs. A patient with both pulmonary and extrapulmonary TB should be classified as a case of PTB.

New patients have never been treated for TB or have taken anti-TB drugs for less than 1 month.

Previously treated patients have received one or more months of anti-TB drugs in the past. They are further classified by the outcome of their most recent course of treatment as follows:

Relapsed patients were previously treated for TB, declared cured or had completed their treatment at the end of their most recent course of treatment, and have been diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).

Treatment after failure patients were previously treated for TB, but their treatment failed at the end of their most recent course of treatment;

Treatment after loss to follow-up patients was previously treated for TB and was declared lost to follow-up at the end of their most recent course of treatment. (These were previously known as treatment after default patients);

Other previously treated patients include those who were previously treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.

Smear results are reported as follows:
0 = no ARB
(1–9) = exact number if 1-9 ARB/100 high-power microscopic fields (HPF) (scanty)
+ = 10–99 ARB/100 HPF
++ = 1–10 ARB/HPF
+++ = >10 ARB/HPF

Radiographic classification

A radiological specialist and a pulmonary specialist were assigned to evaluate the chest X-ray graphs of patients with PTB. The graphs were then classified in line with the extent of the disease that was evident on chest radiography (12, 13) as follows: stage 1 was classified as minimal to mild disease, stage 2 as moderate disease and stage 3 as advanced disease. In those with mild disease conditions, lesions were classified as minimal if there was no evidence of cavitation, while lesions were classified as having slight to moderate density if they were located above the second chondro-sternal joint. In addition, the lesions in mild disease patients were only required to involve a segment of one or both lungs, and the combined extent of the lesions had to be smaller than the volume of a single lung. Patients with moderate disease had dispersed lesions of slight to moderate density in one or both lungs, and the collective lesion volume could not be in excess of that of a single lung. In moderate disease conditions, the lesions could be densely packed so as to appear confluent, although these areas of high-density lesions cannot represent more than one-third of

the volume of one lung. Furthermore, patients with a moderate disease cannot have a total diameter of cavitation greater than 4 cm. The patient was classified as having advanced disease if the lesions were more extensive than they were in moderate disease conditions.

Study groups

The patients were divided into subgroups according to their gender, age groups, case definitions, radiological characteristics, and symptoms as follows: those with respiratory symptoms (coughing, sputum, dyspnoea, haemoptysis and dysphonia); those with systemic symptoms (weakness, weight loss, loss of appetite, fever, and abdominal pain); and those with both respiratory and systemic symptoms. The patients were initially divided into two groups in line with their sputum smear characteristics (*ie*, ARB-positive and negative groups). Smear-positive patients were grouped according to their positivity levels.

Statistical analysis

We examined the correlation between the smear characteristics and smear positivity levels with variables such as age, sex, case definitions, and number and nature of symptoms and radiological score (via the Spearman test). A cluster tree analysis chi-square test was used to find the relation between both the smear result and smear positivity levels and other variables. Finally, a logistic regression test was utilized to identify factors in predicting smear results. SPSS 21.0 (IBM. Corp, Armonk, NY, USA) was used for statistical analyses. Values of $p < 0.05$ at 95% confidence interval were considered statistically significant.

RESULTS

Of the 245 cases diagnosed with PTB, 140 (57.1%) were males, and their average age was 36.4 ± 18.4 years. Only three patients had no symptoms (1.2%). These three patients were diagnosed with TB via microbiological and radiological terms. In addition, 27% of the patients only exhibited pulmonary symptoms, 24% only systemic symptoms, and 36% both pulmonary and systemic symptoms (Table 1). The most frequently observed symptoms were coughing, weight loss, fever, and expectoration (Table 1). Thirty-eight percent of the patients had three or more symptoms. Data from the current study revealed that the rates of low, moderate and high radiological involvement were 41.4%, 28.8% and 28.9%, respectively (Table 1).

Table 1: Descriptive characteristics of the tuberculosis cases

Properties		n	(%)
Gender	Male	140	57.1
	Female	105	42.9
Symptom group	No symptom	3	1.2
	Pulmonary symtoms	67	27.3
	Systemic symptoms	85	34.7
	Pulmonary+systemic symptoms	90	36.7
Number of symptoms	0.00	3	1.2
	1.00	79	32.2
	2.00	69	28.2
	3.00	78	31.8
	≥ 4.00	16	6.5
Case definition	New case	212	86.5
	Recurrence	27	11.0
	Others	6	2.4
ARB positivity level	ARB negative (–)	53	21.6
	1 positive (+)	62	25.3
	2 positive (++)	59	24.1
	3 positive (+++)	43	17.6
	4 positive (++++)	28	11.4
Radiological involvement score	Mild	89	41.4
	Moderate	62	28.8
	Severe	64	29.8
Symptoms	Cough	111	45.3
	Sputum	49	20.0
	Night sweat	55	22.4
	Dyspnoea	37	15.1
	Weight loss	100	40.8
	Haemoptysis	27	11.0
	Fever	58	23.7
	Chest pain	11	4.5
	Weakness	21	8.6

ARB = acid-resistant bacilli.

The percentage of patients having a positive sputum smear test was 78.4%. When considering the level of smear positivity, the highest percentage belonged to 1-positive (+) cases (25.3%) and the lowest percentage to 4-positive (++++) cases (11.4%). The rates of positive smear result were similar between men (80%) and women (76.2%) ($p = 0.474$). New cases (76.9%) and relapsed cases (92.6%) also had similar smear positivity percentages ($p = 0.068$).

The percentage of positive smear rate among patients exhibiting coughing (88.3%) was significantly higher than those without coughing (70.1%). There was no significant difference in terms of positive smear results, when the patients were grouped according to the presence and absence of the other symptoms studied.

The positive smear result rate in cases with moderate radiological involvement (88.7%) and in those with high radiological involvement (90.6%) were significantly higher than that in patients with low radiological involvement (60.7%) ($p < 0.001$)

The binary logistic regression analysis that was conducted within the scope of the study revealed that the presence of coughing increased the possibility of a positive smear result by a factor of 2.7 (confidence interval [CI]: 1.3, 6.3). When compared to those with low radiological involvement, the possibility of a positive smear result was 4.4 times higher in those with moderate radiological involvement (CI: 1.8, 11.2) and 6.1 times higher in those with high radiological involvement (CI: 2.3, 16.0) (Table 2).

Table 2: Factors determining positive smear ARB results in pulmonary tuberculosis—binary logistic regression analysis (backward method)

Factors	*p*	OR	95% CI
Rad score (moderate/mild), score (severe/mild), score (severe/mild), score (moderate/mild)	0.001	4.4	1.8–11.2
Rad score (severe/mild)	0.000	6.1	2.3–16.0
Cough (+/–)	0.015	2.7	1.3–6.30

ARB = acid-resistant bacilli.

The Spearman correlation test revealed that the following data positively correlated with the smear positivity level: female sex ($p = 0.048$, $R = –0.126$), coughing ($p < 0.001$, $R = 0.276$), sputum ($p = 0.002$, $R = 0.200$), weakness ($p = 0.048$, $R = –0.126$), number of symptoms ($p < 0.001$, $R = 0.232$), and grade of radiological involvement ($p < 0.001$, $R = 0.427$). However, when linear regression analysis was applied, only coughing (CI: 0.10, 0.84) and level of radiological involvement (CI: 0.42, 0.80) were found to be predicting factors determining higher level ARB positivity (Table 3).

In cluster tree chi-square analysis, both smear-positive cases and cases with high positive smear grade were clustered at a higher rate in the coughing group than in the group without coughing ($p = 0.014$; $p = 0.02$, respectively) (Fig. 1). Likewise, the groups with moderate and high radiological involvement had significantly higher rates of both the number of smear-positive cases and cases with high smear positivity levels compared with the mild radiological involvement group ($p < 0.001$) (Fig. 2). Different smear ARB result clusters could not be created significantly with any other symptoms and properties.

Table 3: Factors determining smear ARB positivity level (linear regression model)

Factors	Unstd. B	SE	Std.B	T	Sig.	95% CI (LB)
(Constant)	0.47	0.36		1.3	0.19	–0.23, 1.1
Gender (female/male)	–0.24	0.16	–0.09	–1.4	0.13	–0.56, 0.07
Cough (+/–)	0.47	0.18	0.17	2.5	0.01	0.10, 0.84
Number of symptoms	0.11	0.09	0.08	1.2	0.22	–0.07, 30
Radiological score (2-3/1)	0.61	0.09	0.38	6.3	0.00	0.42, 0.80
Sputum (+/–)	–0.01	0.24	0.01	–0.01	0.99	–0.47, 0.47
Weakness (+/–)	–0.34	0.30	–0.07	–1.1	0.25	–0.94, 0.25

ARB = acid-resistant bacilli.

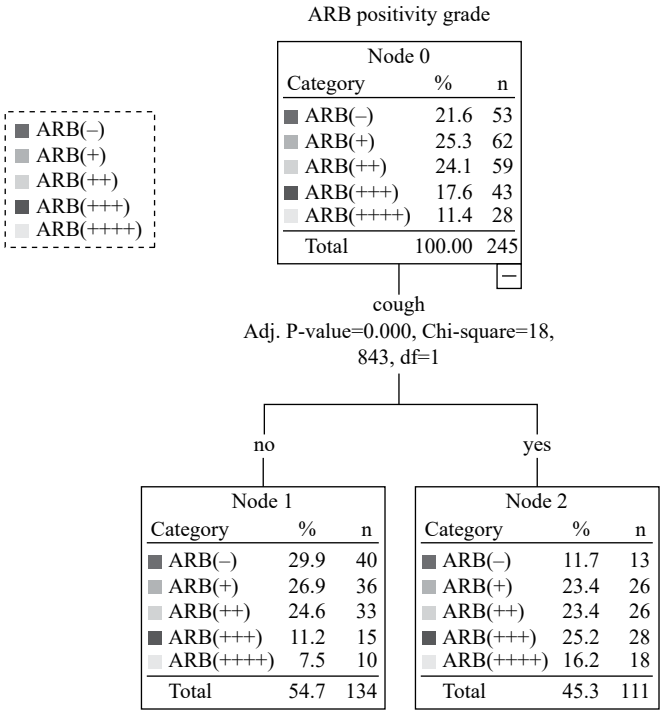

Fig. 1: Cluster tree between cough symptom and ARB positivity level.

DISCUSSION

Data from the present study indicate that the presence of coughing (as a symptom) and moderate-to-high radiological involvement are independent predictors of positive smear result and also high-grade smear positivity. Age, gender, any case definition group, all other symptoms rather than cough and number of symptoms, were not found to be related to smear results.

The symptomatology of PTB is variable. Cases may individually or concurrently exhibit one or more pulmonary symptoms, including coughing, sputum and

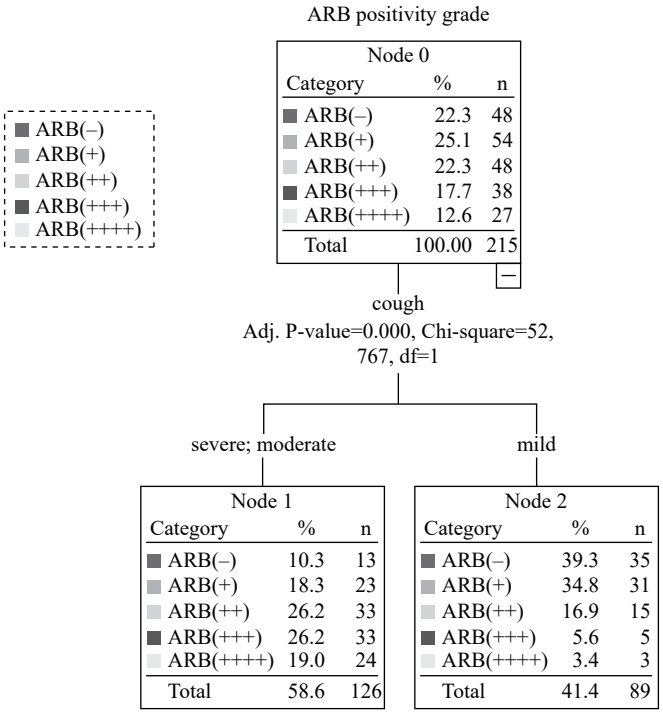

Fig. 2: Cluster tree between radiological involvement severity and ARB positivity level.
ARB (≥ 2+) cases clustered especially in those with moderate or severe radiological involvement groups.

haemoptysis, and one or more systemic symptoms, including weakness, night sweats, weight loss, fever, and loss of appetite (14). A surveillance study evaluating 16 432 patients in Japan revealed that 25.8% of patients had only pulmonary symptoms, 16.7% had only systemic symptoms, and 31.7% had both pulmonary and systemic symptoms. In the present study, 27% of the patients had only pulmonary symptoms, 34% had only systemic symptoms, and 36% had both pulmonary and systemic symptoms (15). Pulmonary TB cases are rarely asymptomatic, and their diagnosis is only possible through suspicion arising from radiological findings (3). In the present study, only three patients had no symptoms (1.2%), and their diagnoses were established through radiological monitoring and sputum smear.

Literature indicates that the most frequent symptom of TB is coughing, while other notable symptoms include weakness, weight loss and fever (16–19). Specifically, patients with a complaint of coughing for at least 3 weeks should be considered as TB in the differential diagnosis. A study that addressed cases with normal radiographic findings and positivity in sputum smear ARB culture revealed that the following were significant in suspicion of a TB diagnosis: the presence of coughing for at least 1 month, fever persisting longer than 1 week and a positive result in tuberculin *purified protein derivative* test (20). Cohen *et al* reported that the presence of coughing for less than 2 weeks, sputum, weight loss, and the absence of typical findings via chest radiography were strong negative predictors for PTB (21). In agreement with the literature, data from the present study revealed that the most common symptoms were coughing, weight loss, fever, and expectoration.

Pulmonary tuberculosis is an extremely infectious disease. The involvement of organs other than the lungs rarely leads to infectiousness (22, 23). Infectiousness may increase up to 28 times in smear-positive patients (24), and increases in more symptomatic cases with a higher grade of smear positivity. Lohmann *et al* reported that patients with a ≥ 4+ ARB smear were eight times more infectious when compared to smear-negative patients (7). Therefore, identifying smear-positive cases with higher grades of positivity is of great importance for disease management.

Previous studies established an association between smear positivity and age and sex. Reider *et al* found that men between the ages of 15 and 24 years had the lowest ARB positivity; women older than 65 years of age had the highest (8). Tadesse *et al* determined that smear positivity among women was twice as high as that among men (25). In the present study, we found no significant relationship between the level of smear positivity and age and sex.

However, we did find a significant relationship between coughing and smear positivity. The (binary) logistic regression analysis conducted within the scope of the study revealed that the presence of coughing increased the possibility of smear positivity 2.7-fold when compared to the absence of coughing. The number of symptoms and increased grade of radiological involvement were significantly and positively correlated with the level of smear positivity.

Chest radiography is the essential radiological finding in suspected cases of TB. Radiological findings that are frequently observed among TB cases are cavitary lesions, parenchymal infiltrations in apical and posterior segments of the upper lobe, or superior segments of the lower lobe (26, 27). One study suggested that smear-positive PTB patients exhibited higher radiological involvement when compared to smear-negative patients (28). Wang *et al*. reported an association between normal chest radiography and smear-negative PTB; in addition, they showed that the involvement of the upper lobe and the presence of cavitary lesions and consolidation were strong independent risk factors for ARB positivity (29).

In the present study, we identified that the possibility of positive smear ARB result was 4.4 times higher in patients with moderate radiological involvement and 6.1 times higher in patients with high involvement compared to those with low radiological involvement.

Prevalent lung involvement is not only related with positive smear ARB result. A previous study established an association between higher radiological involvement and high-grade smear positivity (30). In agreement with the literature, data from the present study revealed a significant relationship between the level of ARB positivity in sputum smear and the grade of radiological involvement. Accordingly, ARB-negative and 1+ cases were mostly associated with low radiological involvement, while 2+, 3+ and 4+ cases were principally associated with moderate and prevalent radiological involvement.

In conclusion, in TB management, it should be considered that the symptom of coughing, and prevalent lung involvement may indicate a positive result in sputum smear and a high level of smear positivity. Specifically in areas with limited laboratory facilities, clinicians and persons in close contact with patients should be mindful of infectiousness in the management of patients with these symptoms and findings.

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