Factors associated with tuberculosis cases in Semarang District, Indonesia: case–control study performed in the area where case detection rate was extremely low

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Abstract

Objectives Indonesia is ranked as the 4th highest contributor to tuberculosis (TB) in the world. Semarang District in Central Java displays extremely low case detection rate (CDR), possibly contributing to the local prevalence of TB.

Methods A case–control study was performed to explore the factors that cause such low CDR. We recruited 129 TB cases and 83 controls that visited the same centers and were not diagnosed with TB.

Results The cases had 7.5 ± 2.3 symptoms/person on average, indicating the delay in diagnosis because the controls only displayed 1.0 ± 1.7. The multiple logistic regression analysis comparing the cases/controls extracted following factors as a risk to have TB: farmer, close contact with TB patients, ignorance of whether Bacillus Calmette-Guérin (BCG) was accepted or no, smoking, low income, a lot of people living in the same room, irregular hand wash before meals, not wash hands after blow, soil floor, and no sunlight and no ventilation in the house.

Conclusions Neither the cases nor the controls knew the symptoms and how to avoid TB infection, which probably caused the delay in diagnosis. It is difficult to change the current living conditions. Thus, the amendment of the community-based education program of TB seems to be required.

Keywords Tuberculosis · Case detection rate · Risk factors · Indonesia · DOTS

Abbreviations

BCG Bacillus Calmette-Guérin
CDR Case detection rate
CI Confidence interval
DOTS Directly observed treatment short course
HIV Human immunodeficiency virus
MA Monovariate analysis
MDR Multidrug resistant
MLR Multiple logistic regression analysis
TB Tuberculosis

Introduction

Tuberculosis (TB) is one of the biggest problems throughout the world and a leading cause of death and major public health problem [1]. Many people with TB remain poorly diagnosed or are diagnosed only after long delays. The high burden of undiagnosed TB causes much suffering such as economic hardship and sustained transmission [2–4].

According to Global Tuberculosis Report 2012 [5], Indonesia is ranked as the 4th (0.4–0.5 million) highest contributor to the TB world after India (2.0–2.5 million), China (0.9–1.1 million), and South Africa (0.4–0.6...
Since 2000, 22 high burden countries account for 82% of all estimated incident cases [5].

The diagnosis of TB in Indonesia in 2011 is 807 per 100,000 population and that in Central Java 637 per 100,000 population [6]. The TB case detection rate (CDR) of Central Java Province is estimated to be 56.93% [7], but among its local districts Semarang displays an extremely low CDR, 19.21% [8]. National target for TB control strategy in Indonesia, according to the strategic plan of the Ministry of Health from 2010 to 2014, is to reduce the TB prevalence to 224 per 100,000 population. Output targets are to (1) increase the CDR of new cases of smear-positive pulmonary TB from 73 to 90%, (2) reach successful treatment of new cases of smear-positive pulmonary TB to 88%, (3) increase “the percentage of province with CDR above 70%” to 50%, and (4) increase “the percentage of the province with treatment success rate above 85%” from 80 to 88% [9].

To achieve the national targets for controlling TB, some strategies seem to be very important: empowerment in the community; early detection and registration of TB patients; improvement of the quality of directly observed treatment short course (DOTS) services; facing the challenges of TB/HIV, multidrug-resistant (MDR-TB) and childhood TB; meet the demands of poor and other vulnerable groups in the society [9]. Domain knowledge is very important in the formation of action. In several developing countries, TB patients are perceived to seek late care or avoid care, due to misunderstanding of popular TB etiologies such as sharing utensils, heavy labor, smoking, bewitchment, and hereditary transmission [10–12]. Thus, it seems very important to know the basic knowledge, attitude, and behavior of the people in such a low CDR region to implement TB programs.

In the present study, differences in the basic knowledge, attitude, and behavior were compared among the TB cases registered in 2012 at the health centers in Semarang District and the controls that visited the same health centers and were diagnosed differently.

Methods

This study was designed to be a case–control study [13] from 2012 January to 2013 October. TB cases (129) were recruited from the cases registered as TB diagnosis at the health centers in Semarang District and 50% were female. The controls (83) were recruited among those who visited the same health centers and were diagnosed differently, and 52% were female. The average age of the cases and controls (Mean ± SD) was 41.2 ± 15.3 and 35.7 ± 11.7, respectively. This research was approved by the ethical committees of Kanazawa University School of Medicine, Japan, and Diponegoro University School of Medicine, Dr Kariadi Hospital Semarang, Indonesia, and Semarang State University, Indonesia. All participants approved this research and gave written informed consent.

TB information of the cases

TB cases were sent to the health center from clinics and diagnosed to have TB using physical examination, microscopic examination by Ziehl Neelsen staining, X-ray, etc.

The method of diagnosis, symptoms, and treatment methods were examined. All of them were treated with DOTS properly regardless of having side effects.

Characteristics of the cases and controls

Demographic characteristics such as gender, age, occupation, origin, BCG experience, close contact with TB patients, smoking habit, having pets, and income were examined. The source of TB information (multiple answers) was also examined. Thereafter, differences in living condition and attitudes in daily life were examined.

Knowledge and opinion about TB

The participants were questioned about the symptoms of TB (multiple answers) and the ways to avoid it (multiple answers). Differences in the opinion and attitude against TB between the cases and controls were examined.

Statistical analysis

The difference in the age and numbers of complaint of the cases and controls was estimated using Student’s t test. The differences in the frequency of answers between the cases and the controls were estimated by Chi square (χ²) test (monovariate analysis, MA). Multiple logistic regression analysis (MLR) with the cases/controls as the dependent variable was utilized with the independent variables using groups classified by characteristics of the cases and controls. All analyses were performed with SPSS ver. 19 (SAS Institute Inc., Cary, NY). In all analyses, p < 0.05 was taken to indicate statistical significance.

Results

The 129 cases included 65 males and 64 females, respectively, and the average age was 41.2 ± 15.3 (Table 1). Although all the cases were registered at the health centers, around 20% were diagnosed at the different medical facilities (Table 2). Sputum smear was the first choice for diagnosis [1, 14], but 20 cases were diagnosed without any clinical examination. Chest X-ray was utilized for the
diagnosis of more than half of the cases. Long-lasting cough with sputum was the most common symptom that was followed by chest pain, malaise, anorexia, and weight loss. Around two-thirds displayed hemoptysis, dyspnea, sweat at night, and long-lasting subfever at night. The cases had many symptoms, 7.5 ± 2.3 complaints/person on average. These cases were registered; hence, all of them underwent treatment, whether they knew it was under DOTS or not (Table 3). Nine had no supervisors and at least one-fourth had to pay treatment fee, suggesting that they were not under DOTS. More than 85% of the cases quit taking medicine at 6 months, regardless of the frequency of medication in the first 2 months. Treatment with 4 drugs was most common, but that with 2 drugs was also observed in around 15% of the cases. Sputum smear was the most common examination during treatment followed by chest X-ray.

The controls were selected from people who visited the same health center and diagnosed as not having TB. We tried to obtain age- and gender-matched controls. We could achieve gender-matched controls, but their age was slightly lower than the cases (Table 1). Around 80% of the cases were farmers and around 30% of them had graduated from elementary school alone. More than half of the controls had received BCG, whereas more than half of the cases did not

### Table 1 Demographic characteristics of the cases and control

|          | Cases | Controls |          | Cases | Controls |
|----------|-------|----------|----------|-------|----------|
| N        | %     | N        | %        | N     | %        |
| Total    | 129   | 83       |          | 41    | 32       |
| Gender   |       |          |          |       |          |
| Male     | 65    | 50       | 40       | 48    |           |
| Female   | 64    | 50       | 43       | 52    |           |
| Occupationa |   |          |          |       |          |
| Farmer   | 101   | 78       | 31       | 37    |           |
| Others   | 28    | 22       | 52       | 63    |           |
| Educationa |   |          |          |       |          |
| Elementary school | 38 | 29       | 8        | 10    | <100      |
| Jr high school | 59 | 46       | 32       | 39    | 100–150   |
| High school or higher | 32 | 25       | 43       | 52    | >150      |
| Origin   |       |          |          |       |          |
| Rural    | 106   | 82       | 70       | 84    |           |
| Urban    | 23    | 18       | 13       | 16    |           |
| Have you ever had BCG?a |     |          |          |       |          |
| Yes      | 33    | 26       | 46       | 55    |           |
| No       | 30    | 23       | 21       | 25    |           |
| Do not know | 66  | 51       | 16       | 19    |           |
| Close contact with TB patientsa |   |          |          |       |          |
| Yes      | 18    | 9        | 0        | 0     |           |
| No       | 111   | 86       | 83       | 100   |           |

a Significant difference in the rate of answers between the case and the control (p < 0.05, χ² test)

b For multiple answer questions, the difference in the rate of each source was examined using χ² test. The case and control displayed significant differences in all sources (p < 0.05)

### Table 2 The diagnosis method and symptoms

|          | N     | %     |
|----------|-------|-------|
| Location of diagnosis |       |       |
| Health center | 101   | 78    |
| Private clinic | 16    | 13    |
| Others | 12    | 9     |
| Way of diagnosis |       |       |
| No clinical examination | 20    | 16    |
| Smear alone | 39    | 30    |
| Smear, X-ray | 70    | 54    |
| Symptoms (multiple answers) |       |       |
| Cough with sputum | 125   | 97    |
| Cough >2w | 123   | 95    |
| Hemoptysis | 78    | 60    |
| Dyspnea | 86    | 67    |
| Chest pain | 102   | 79    |
| Malaise | 108   | 84    |
| Anorexia | 108   | 84    |
| Weight loss | 101   | 78    |
| Sweat at night | 77    | 60    |
| Subfever >1 Mo | 72    | 56    |

Mantoux test was utilized only in 2 cases. The mean ± SD of complaints/person was 7.5 ± 2.3, whereas that of the controls only 1.0 ± 1.7 (p < 0.05, Students’ t test)
know whether they received BCG or not. Nine percent of the cases experienced close contact with TB patients, but none of the controls did. The income of the cases was significantly lower than that of the controls, and three-fourths of them got less than 100 $/month. The cases had already been diagnosed, and hence they obtained more TB information from the medical staff than the controls, but they usually did not use other sources (Table 1). When the living conditions were compared, all conditions were significantly different between the cases and the controls (Table 4). “Ceramic floor”, “outside kitchen”, “gas for cooking”, “open windows every day”, “sunlight into the house”, and “ventilation in every room” were more common in the controls, whereas “window in each room” and high “humidity in the house” were common in the cases. The cases less frequently “washed their hands before eating”, but more frequently “shared their dishes with others” and “drunk from the same glasses/bottles” than the controls, whereas no difference was observed in the frequency of whether “they worked when they felt unwell” between these two groups.

To clarify what kinds of physical factors were the most affected differences in the cases and the controls, the MLR was applied (Table 6). The cases/controls were the dependent variables and the groups divided by the above-
mentioned information were used as determinants. The method of obtaining TB information was removed from the determinant, because that from the cases was modified as described above. The obtained risks were “farmers”, “close contact with TB patients”, “whether or not they did not know they received BCG”, “smoking”, and “low income “100 $/month”. “High income ”150 $/month” was also extracted as a risk compared with “middle income 100–150 $/month”. To “wash hands before eating”, “wash hands after nose blowing” and “not work when unwell” were protective. Among living conditions, “live with more than 3 person in the same room”, “soil floor”; no “sunlight in the house” and no “ventilation in the house” were extracted as risk.

Regardless of many symptoms, the cases did not always display significant differences with the controls regarding what they thought were TB symptoms (Fig. 1). “Long-lasting subfever” alone was significantly greater in the controls.

More than 70 % of both the cases and the controls thought that it was important to “cover mouth/nose when someone sneezed” (Fig. 2). More than half of the controls thought that “avoiding sharing dishes”, “avoiding drinking from the same glass/bottle”, “washing hands after touching items in the public” and “maintaining good nutrition” were the ways to avoid getting TB and the rates were significantly higher than the cases. In fact, 76 % of the controls washed hands before eating and only 35 % of the cases did so (Table 5). Moreover, 76 % (9 + 67) of the cases at least sometimes “shared their dishes” and “drank from the same glass”, which was significantly higher than the controls. On the other hand, 87 % (39 + 48) of the controls at least sometimes “washed hands after blowing nose”. “Vaccination” was also higher in the controls than in the cases. In fact, 76 % of the controls washed hands before eating and only 35 % of the cases did so (Table 5). More than half of the controls thought that it was important to “cover mouth/nose when someone sneezed” (Fig. 2). More than half of the controls thought that “avoiding sharing dishes”, “avoiding drinking from the same glass/bottle”, “washing hands after touching items in the public” and “maintaining good nutrition” were the ways to avoid getting TB and the rates were significantly higher than the cases. In fact, 76 % of the controls washed hands before eating and only 35 % of the cases did so (Table 5). Moreover, 76 % (9 + 67) of the cases at least sometimes “shared their dishes” and “drank from the same glass”, which was significantly higher than the controls. On the other hand, 87 % (39 + 48) of the controls at least sometimes “washed hands after blowing nose”. “Vaccination” was also higher in the controls than in the cases (Fig. 2).

Opinions related to the seriousness and shame did not display any significant difference between the cases and the controls (Table 7). Although many of the cases and controls thought TB to be “serious”, they did not always think that TB was “serious at workplaces” and “affected work performance”. Significant difference was not observed in

| Table 5 The differences in attitudes between the participants |
|-------------------------------------------------------------|
| Cases | Control |
|-------|---------|
| Do you wash your hands before eating? | |
| Yes | 45 | 35 | 63 | 76 |
| Sometimes | 72 | 56 | 18 | 22 |
| No | 12 | 9 | 2 | 2 |
| Do you eat from the same dish with others? | |
| Yes | 11 | 9 | 8 | 10 |
| Sometimes | 86 | 67 | 28 | 33 |
| No | 32 | 25 | 47 | 57 |
| Do you drink from the same glasses/bottles with others? | |
| Yes | 7 | 5 | 9 | 11 |
| Sometimes | 92 | 71 | 35 | 42 |
| No | 30 | 23 | 39 | 47 |
| Do you wash your hands after blowing nose? | |
| Yes | 25 | 19 | 40 | 48 |
| Sometimes | 69 | 53 | 32 | 39 |
| No | 35 | 27 | 11 | 13 |
| Do you work when you are unwell? | |
| Yes | 23 | 18 | 25 | 30 |
| Sometimes | 78 | 60 | 40 | 48 |
| No | 28 | 22 | 18 | 22 |

* Significant difference between the cases and the controls (p < 0.05, χ² test)

| Table 6 Multiple logistic regression analysis using case/control as the dependent valuable and living status as determinants |
|-------------------------------------------------------------|
| Occupation | Workers | Farmers | 0.05 | <0.01 | 0.00 | 0.20 |
| Others | Farmers | 0.05 | 0.01 | 0.00 | 0.54 |
| Close contact with TB patients | No | Yes | 0.00 | 0.02 | 0.00 | 0.49 |
| BCG | Yes | Do not know | 0.04 | <0.01 | 0.00 | 0.32 |
| Smoking | No | Yes | 0.14 | 0.04 | 0.01 | 0.92 |
| Income ($/Mo) | 100–150 | <100 | 0.05 | <0.01 | 0.00 | 0.33 |
| 100–150 | >150 | 0.08 | 0.04 | 0.01 | 0.89 |
| Person/room | 1 | ≥3 | 0.00 | <0.01 | 0.00 | 0.35 |
| 2 | ≥3 | 0.00 | <0.01 | 0.00 | 0.27 |
| Wash hands before eating | Yes | Sometimes | 0.06 | <0.01 | 0.01 | 0.32 |
| Wash hands after blowing nose | Sometimes | No | 0.06 | 0.01 | 0.01 | 0.46 |
| Work when unwell | No | Yes | 0.09 | 0.02 | 0.00 | 0.66 |
| Floor | Ceramics | Soil | 0.06 | 0.04 | 0.00 | 0.90 |
| Sunlight in the house | Yes | No | 0.06 | 0.02 | 0.00 | 0.67 |
| Ventilation in the house | Yes | No | 0.02 | <0.01 | 0.00 | 0.24 |
“being ashamed of having TB”, but the cases tended to want to “hide having TB”. Significantly more controls thought “TB affected relationship with others” and “wanted to be isolated”, whereas there was no significant difference in “TB affecting family responsibility” against the controls. Both of the cases and controls usually tried to be good to TB patients. Around 50% of the controls believed that “TB treatment was very costly”, but around one-fourth of the cases did not think so. “HIV-positive people’s concern about TB” was significantly higher in the controls than in the cases. Around one-fourth to one-third of the cases and controls believed that TB was hereditary.
Table 7 Differences in the opinion against TB between the cases and controls

| Opinion                                      | Cases N | %  | Controls N | %  |
|----------------------------------------------|---------|----|------------|----|
| Do you think that TB is serious?             |         |    |            |    |
| Yes                                          | 91      | 71 | 67         | 81 |
| No                                           | 2       | 2  | 3          | 4  |
| Do not know                                   | 36      | 28 | 15         | 18 |
| Do you think that TB is serious at workplaces?|         |    |            |    |
| Yes                                          | 46      | 36 | 34         | 41 |
| No                                           | 14      | 11 | 10         | 12 |
| Do not know                                   | 69      | 53 | 39         | 47 |
| Does TB affect your work performance?         |         |    |            |    |
| Yes                                          | 51      | 40 | 43         | 52 |
| Not always                                   | 60      | 47 | 29         | 35 |
| No                                           | 18      | 14 | 11         | 13 |
| Do you feel ashamed of having TB?             |         |    |            |    |
| Yes                                          | 49      | 38 | 22         | 27 |
| No                                           | 53      | 41 | 35         | 42 |
| Do not know                                   | 27      | 21 | 26         | 31 |
| Do you want to hide having TB?               |         |    |            |    |
| Yes                                          | 14      | 11 | 10         | 12 |
| Not always                                   | 74      | 57 | 30         | 36 |
| No                                           | 41      | 32 | 43         | 52 |
| Does TB affect your relationship with others?|         |    |            |    |
| Yes                                          | 20      | 16 | 36         | 44 |
| Not always                                   | 72      | 56 | 35         | 42 |
| No                                           | 37      | 29 | 12         | 14 |
| Does TB affect family responsibilities?      |         |    |            |    |
| Yes                                          | 58      | 45 | 41         | 49 |
| Not always                                   | 53      | 41 | 35         | 42 |
| No                                           | 18      | 14 | 7          | 8  |
| Do you want to live isolated due to having TB?|         |    |            |    |
| Yes                                          | 5       | 4  | 12         | 14 |
| Not always                                   | 43      | 33 | 25         | 30 |
| No                                           | 81      | 63 | 46         | 55 |
| How do you feel about a person with TB?      |         |    |            |    |
| Desire to help                                | 94      | 73 | 59         | 71 |
| Want to stay away                             | 28      | 22 | 20         | 24 |
| No particular feeling                         | 7       | 5  | 4          | 5  |
| Is TB treatment very costly?                  |         |    |            |    |
| Yes                                          | 32      | 25 | 42         | 51 |
| Not always                                   | 44      | 34 | 21         | 25 |
| No                                           | 53      | 41 | 20         | 24 |
| Do you think that HIV-positive people should be concerned about TB? |      |    |            |    |
| Yes                                          | 23      | 18 | 39         | 47 |
| Not always                                   | 79      | 61 | 30         | 36 |
| No                                           | 27      | 21 | 14         | 17 |
| Do you think that TB is hereditary            |         |    |            |    |
| Yes                                          | 30      | 23 | 24         | 29 |
| No                                           | 79      | 61 | 47         | 57 |
| Do not know                                   | 20      | 16 | 12         | 14 |

*a Significant difference between the cases and the controls (p < 0.05, \( \chi^2 \) test)
Discussion

In Indonesia, regular health examination is not mandatory [6]. Therefore, after symptoms became apparent, the person visited the clinic where sputum smear was not always available. The cases in the present study displayed 7.5 ± 2.3 complaints/person on average, indicating the delay of diagnosis [15]. Although early diagnosis and initiation of treatment of infectious cases are the best measures to reduce transmission [3, 16, 17], in some countries 20% of patients were not diagnosed for over 6 months from the onset of symptoms [18]. Even after the symptoms became obvious, it took at least 2 more days for diagnosis, because positive TB was defined as more than 2 positive sputum smears in the smear performed three times within 2 days [14]. Household contacts continued meantime, when patients were with potentially infectious forms proceeding to high prevalence of TB [19, 20]. On the other hand, culture was not common, whereas patients with smear-negative, culture-positive TB were reportedly responsible for TB transmission [21, 22]. Immediate introduction of culture examination is required because, in addition to high sensitivity, it allows determining whether the patient is sensitive to anti-TB drugs and useful for finding extrapulmonary TB [14].

The cases did not always know whether they were under DOTS treatment or not, but all the cases could luckily quit taking medicine regardless of the obvious delay of diagnosis. Around 80% of the cases were farmers and around 30% had graduated from elementary school alone; hence, their income was lower than the controls. Low income and low education are reportedly associated with TB infection [4, 23–25]. They also had lost the chance of BCG injection. This occupation was also extracted as a risk by the MLR. However, the MLR extracted high income as a risk as well. Such a result is not always in accordance with several studies [4, 23–25], whereas it is conceivable that people with high income, regardless of their occupation, have more chances to live and/or work at places with a lot of people where a risk of TB transmission is supposed to be high. The number was small, but only cases had a chance of close contact with TB patients. TB contact was absolutely a risk factor for TB transmission [18, 26]. No significant difference was found in the rate of “smoking” by the MA, but the MLR extracted “smoking” as a risk. This is in good accordance with a previous report [23]. It is natural that the “source of TB information” of cases was medical staff, but the cases were not always eager to collect information from other sources compared with the controls. All the items related to living condition were significantly different between the cases and the controls according to the MA. Among them, the MRL extracted “small number of persons in a room”, “ceramic floor”, “sunlight in the house”, and “ventilation in the house” as protective. The importance of good ventilation has been emphasized elsewhere [3, 23]. Excluding “work when unwell”, their attitudes displayed significant differences between the cases and the controls by the MA. “Share the dish” and “drink from the same glasses/bottles” were not extracted by the MLR. Instead, “work when unwell” was extracted as well as “wash hands before eating” and “wash hands after nose blowing”. These findings may be a reflection that TB is airborne. In general, the cases were not aware of the danger in their attitudes, which was in good accordance with previous reports [10–12].

Both the cases and the controls did not recognize “dyspnea” and “chest pain” as TB symptoms. Significant differences existed, but “long-lasting subfever” was also not considered as TB symptoms. “dyspnea”, “chest pain,” and “long-lasting subfever” were less frequent than “cough with sputum”, “malaise”, and so on, but a number of cases complained of these. Thus, it seems necessary make people aware of TB symptoms [10–12].

TB itself was recognized to be dangerous both by the cases and the controls, but they did not recognize its dangerousness at work places. Many of the cases were farmers; hence, it seems less possible to spread TB than workers. However, TB-positive workers can work and be able to transmit TB to their colleagues. On comparing the rate of both the cases and controls who thought “having TB was a shame”, the rate of “wanted to hide having TB” was less. It seems natural that more controls who did not receive TB treatment believed that TB “affected relationship with others” and wanted to “live isolated in case of TB” than the cases. DOTS performed under the governmental hospitals and health centers were free [9], but some cases visiting private hospitals/clinics had to pay the treatment fee. A higher rate of “HIV-positive people should be concerned about TB” in the control was reflection that they were more eager to collect information than the cases. HIV infection reportedly affected TB infection [27]. However, the number who believed “TB was hereditary” was not different between the two groups.

Some aspects underlying the low coverage CDR are socioeconomic, education/knowledge, and stigma problems [4]. Economic conditions will affect the public in obtaining not only good environmental home conditions, but also an excellent level of education. The level of education in this study was relatively low because many people only finished elementary school where sufficient TB education was impossible. Poor education will cause shortage of knowledge about TB, leading the public into embarrassment and sometimes attitude to hide their disease if they are exposed to TB. Such conditions in some people may cause delay in going to health service [18]. As a result, TB has spread among farmers even when their contact has
not always been intense like workers. It is very difficult to change occupation, income, and housing conditions immediately. Thus, community-based TB education is very important. It may be useful to educate and expose not only public, but also private practitioners to community-based TB programs [9, 28].

Some cases were not dependent on the free DOTS program. To inform about the existence of this program is also good education. Utilization of this program not only reduces multidrug-resistant TB, but also helps reduce out-of-pocket expenses to patients [27]. The number of symptoms of the cases absolutely indicates the delay in diagnosis.

The classic symptoms of TB are fever, cough, and weight loss, but they are non-specific and can be mimicked by other conditions, including malignancy and other pulmonary infections. That is, in an early stage, such symptoms are not always specific to TB. However, importance of these classic lung related with syndromes should be aware of that they are possible signs of initiation of TB expansion [29].

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