VIA MEDICA

ORIGINAL RESEARCH

Anushree Chakraborthy, Akshata Jayachamarajapura Shivananjaiah, Swapna Ramaswamy, Nagaraja Chikkavenkatappa

SDS TRC and Rajiv Gandhi Institute of Chest Medicine, Bangalore, India

Chest X ray score (Timika score): an useful adjunct to predict treatment outcome in tuberculosis

The authors declare no financial disclosure

Abstract

Introduction: Chest X-ray (CXR) has been used since long as an aid in the diagnosis of pulmonary tuberculosis (PTB) and also to determine the extent of the disease. The present study was conducted to evaluate the correlation of disease extent on CXR based on the Timika CXR score with clinical and microbiological parameters at baseline, in sputum positive cases of pulmonary tuberculosis.

Material and methods: The study was conducted at a tertiary referral centre for chest diseases in Bangalore, Karnataka from January 2017 to January 2018. This is a prospective study of new sputum smear positive pulmonary tuberculosis cases diagnosed in the Department of Pulmonary Medicine. At baseline, patients' symptoms and signs on chest auscultation were recorded. The clinical scoring was done by the Karnofsky performance score (KPS) and TB score I (Bandim TB score) and II. Baseline CXR postero-anterior (PA) view of each patient was assessed independently by two chest physicians and evaluated by the Timika CXR scoring method. Routine blood investigations and sputum smear for acid fast bacilli were done. The correlation between the CXR score and other disease severity parameters was analysed.

Results: Clinical scores such as the KPS and TB score I and II, did not correlate with the presence of cavitary disease on CXR ($p > 0.05$). 48.6% of patients with cavitary disease had higher baseline AFB density in sputum (i.e. sputum smear microscopy grade 3+) as compared to 40% of patients with non cavitary disease, which was not statistically significant. CXR score > 71 was significantly associated with longer duration of symptoms, higher clinical scores (KPS and TB score I, II) and lower Body Mass Index (BMI) at diagnosis of PTB ($p < 0.05$). 65.2% of the patients with CXR score > 71 had significantly higher baseline AFB density as compared to only 32.4% with CXR score ≤ 71 ($p < 0.04$). CXR score > 71 also had significant association with higher ESR.

Conclusion: Cavitary disease on CXR is associated with a higher mycobacterial load at baseline. The Timika CXR score is a simple, standard scoring system which can be used by a chest physician in a clinical setting. The CXR score significantly correlates with a broad range of clinical and microbiological measures of disease severity in PTB patients. Thus, it has a role in risk stratification, especially in patients not producing sputum or sputum negative PTB at diagnosis.

Key words: tuberculosis, cavitary disease, Ralph s score, chest X-ray score

Adv Respir Med. 2018; 86: 205–210

Introduction

Tuberculosis has a high impact on global health as the ninth leading cause of death worldwide. Among the infectious diseases it is the leading cause of death as per the Global Tuberculosis Report 2017 [1]. Due to the tremendous improvement in the diagnostic modalities like molecular assays, the detection of pulmonary tuberculosis (PTB) in the recent years has been easier [2]. In India, the treatment of tuberculosis is well established and standardised under the national programme [2]. However, many factors influence the treatment response and outcome. The

Address for correspondence: Akshata Jayachamarajapura Shivananjaiah, SDS TRC and Rajiv Gandhi Institute of Chest Medicine, Someshwaranagar 1st Main Road, Dharmaram College Post, Bangalore 560 029, Tel.: +080 26088500, e-mail: drjsakshata@gmail.com

DOI: 10.5603/ARM.2018.0032
Received: 5.06.2018

ISSN 2451–4934

disease extent and severity at diagnosis help to predict the treatment response and outcome [3]. Studies have shown that persistent sputum positivity at the end of 2 months of treatment is one of the predictors of unfavourable treatment outcome [3–7]. Higher smear grades on sputum smear microscopy, extensive lung involvement and the presence of cavities on chest X-ray (CXR) at diagnosis are among the factors associated with persistent sputum positivity [3, 8–10].

CXR has been used since long as an aid in the diagnosis of tuberculosis and also to determine the extent of the disease. Major limitation in determing the disease extent on CXR is the absence of a validated standard scoring system [11]. Ralph *et al.* [12] recently derived a simple CXR disease severity score from adults with smear-positive PTB in Indonesia. They found an association between month 2 sputum smear status and the participant's baseline 'Timika X-ray score' (total percentage of affected lung on CXR + 40 if cavitation is present). They also concluded that availability of a valid and accurate CXR score may help to stratify the patients into high risk groups in terms of treatment outcome [12].

The present study was conducted to evaluate the correlation of the disease extent on CXR based on the Timika CXR score with clinical and microbiological parameters at baseline, in sputum positive cases of pulmonary tuberculosis.

Table 1. Calculation of TB score I and II

Score variables	TB score I	TB score II
Symptoms		
Cough	1	1
Hemoptysis	1	
Dyspnea	1	1
Chest pain	1	1
Night sweats	1	
Signs		
Anaemia	1	1
Pulse > 90 beats/min	1	
Positive finding at lung auscultation	1	
Temperature > 37^{0}C	1	
BMI < 18	1	1
BMI < 16	1	1
MUAC < 220 mm	1	1
MUAC < 200 mm	1	1
Total number of points possible	13	8

BMI — body mass index, MUAC — mid upper arm circumference

Material and methods

The study was conducted at a tertiary referral centre for chest diseases in Bangalore, Karnataka from January 2017 to January 2018. This is a prospective study of new sputum smear positive pulmonary tuberculosis cases diagnosed in the Department of Pulmonary Medicine. The study protocol was approved independently by the institutional ethical committee and the ethical committee of IISc.

Inclusion criteria:

— New sputum smear positive pulmonary tuberculosis patients aged > 18 years; male/female; HIV negative; without any comorbidities.

Exclusion criteria:

— Previously treated tuberculosis cases ; HIV-positive cases; any other viral illness; severe comorbidities; pregnant women; those not willing to give written consent for the participation.

— At baseline, patients' symptoms and signs on chest auscultation were recorded. The clinical assessment was done by the Karnofsky performance score (KPS) and TB score I (Bandim TB score) and II (Table 1).

— Routine blood investigations were done specifically haemoglobin percentage, ESR and serum albumin.

— A standard 6-foot posteroanterior (PA) chest radiograph was obtained for all patients. Cavitary disease was defined as the presence of a gas-containing lucent space at least 1cm in diameter within the lung parenchyma surrounded by an infiltrate or fibrotic wall greater than 1 mm thick. Each X-ray film was examined independently by two experienced chest physicians blinded to each other's readings. The extent of lung involvement was assessed using the radiological score described by Ralph *et al.* [12], which takes into account the proportion of the lung affected and the presence of cavitation.

— The Timika score [12] is calculated as described in Table 2.

— Sputum smear grading was assessed using Ziehl-Neelsen staining method. The results were reported as per the national guidelines [13, 14].

— All the cases were treated with the standard DOTS (Directly Observed Treatment Strategy) Category I regimen under RNTCP (Revised National Tuberculosis Control Programme) [2].

Table 2. Calculation of Timika score

Full-size postero-anterior chest X-ray (CXR-PA view) with proper position and penetration were used for scoring. The CXR was divided into six zones of roughly similar size with two horizontal lines
For each zone, the percentage area that showed active disease (consolidation, nodules) involvement was estimated depending on the visual estimation of the extent of opacification (5 or 10–100% in 10% increments)
The percentage of all six zones were added and divided by 600 to get the total percentage of lung affected
A constant value of 40 was added to the above value if at least one cavity was identified to obtain the final score
CRX score = proportion of total lung affected (%) + 40 if cavitations present

— The statistical software, namely SPSS 18.0 and R environment ver.3.2.2 were used for the analysis of the data and Microsoft Word and Excel have been used to generate graphs, tables etc. The results of continuous measurements are presented as Mean ± SD (Min-Max) and the results of categorical measurements are illustrated in numbers (%).

Student t test (two-tailed, independent) has been used to find the significance of the study parameters on a continuous scale between two groups (intergroup analysis) on metric parameters. Leven's test for homogeneity of variance has been performed to assess the homogeneity of variance. Chi-square/ Fisher exact test has been used to find the significance of the study parameters on a categorical scale between two or more groups, non-parametric setting for qualitative data analysis. Fisher exact test was used when cell samples were very small.

Results

A total of 60 newly detected sputum positive pulmonary tuberculosis (PTB) patients were enrolled in the study. The median age of the study population was 28 years ± SD. There were 40 (66.7%) males and 20 (33.3%) females. Thirty five (58.3%) patients had cavitary disease and 25 (41.7%) had non cavitary disease on CXR. On applying the Timika CXR score, the median score of the study population was 59.5. At a cut-off level of CXR score of 71, 23 (38.3%) had score more or equal to 71 and 37 (61.7%) had scores less than 71.

The relationship between the radiological findings (cavitary versus non cavitary; CXR score ≥ 71 versus CXR score < 71) at the diagnosis of PTB and baseline clinical and bacteriological parameters were analysed. Tables 3 and 4 summarise the demographic and clinical characteristics of the study population.

Clinical scores such as the KPS and TB score I (Bandim TB score), II did not correlate with the presence of cavitary disease on CXR ($p > 0.05$). No significant associations were identified between cavitary disease and the duration of symptoms, body mass index (BMI), blood ESR, haemoglobin and serum albumin level ($p > 0.05$). 48.6% of patients with cavitary disease had higher baseline AFB density in sputum (i.e. sputum smear microscopy grade 3+) as compared to 40% of patients with non cavitary disease, which was not statistically significant.

CXR score > 71 was significantly associated with longer duration of symptoms, higher clinical scores (KPS and TB score I, II) and lower BMI at diagnosis of PTB ($p < 0.05$). 65.2% of the patients with CXR score ≥ 71 had significantly higher baseline AFB density as compared to only 32.4% with CXR score < 71 ($p < 0.04$). CXR score ≥ 71 also had a significant association with higher ESR. However, no significant relationships were identified between high CXR score and haemoglobin or serum albumin levels.

Discussion

Sputum smear microscopy and culture are the standard modalities for monitoring the treatment response in pulmonary tuberculosis. A systematic review and meta-analysis done by Morne *et al.* [15] on sputum monitoring during the treatment of PTB for predicting the outcome concluded that both sputum smear microscopy and culture have low sensitivity and modest specificity for predicting failure and relapse. However, until better predictive markers are available, they will remain the preferred tools for monitoring treatment response and predicting the outcome. The disease severity at diagnosis determines the treatment result. Many surrogate markers are available for estimating the severity of the disease, such as high bacillary load on initial sputum examination, the extent of pulmonary disease and presence of cavitary disease on CXR at diagnosis [3, 8, 16, 17]. Cavitary lesions on CXR among PTB patients are reported to occur in 40–50% [8, 18, 19]. In our study population, 58.3% had

Table 3. Comparison of clinical variables according to cavitary or non-cavitary disease on CXR

Variables	Cavitary n = 35 (58.3%)	Non cavitary n = 25 (41.7%)	p-value
Mean age (yrs) ± SD (median age, yrs)	32.11 ± 14.20 (28)	34.24 ± 11.78 (35)	> 0.05
Gender			
Male	21 (60%)	19 (76%)	> 0.05
Female	14 (40%)	16 (64%)	
Mean duration of symptoms (days) ± SD	65.86 ± 45.72	54.00 ± 38.49	> 0.05
Mean BMI (kg/m^2) ± SD	17.50 ± 3.05	17.74±2.71	> 0.05
Mean KPS ± SD	74.86 ± 11.47	79.20±8.12	> 0.05
Mean TB score I ± SD	6.40 ± 2.44	5.40 ± 2.16	> 0.05
Mean TB score II ± SD	4.03 ± 1.98	3.32 ± 1.91	> 0.05
Mean Timika CXR score ± SD	80.86 ± 18.33	38.24 ± 18.91	< 0.05
Sputum AFB smear grade n (%)			
1+	12 (34.3%)	11 (45.8%)	> 0.05
2+	6 (17.1%)	4 (16.7%)	
3+	17 (48.6%)	10 (40%)	
Mean ESR ± SD	65.91 ± 36.13	61.74 ± 32.86	> 0.05
Mean haemoglobin (g/dl) ± SD	11.37 ± 2.05	11.91 ± 1.62	> 0.05
Mean serum albumin ± SD	3.04 ± 0.83	3.05 ± 0.78	> 0.05

Table 4. Comparison of clinical variables according to Timika score cut-off value of 71 points

Variables	Timika score ≥ 71 n = 23 (38.3%)	Timika score < 71 n = 37 (61.7%)	p-value
Mean age (yrs) ± SD (median age, yrs)	**32.00 ± 13.95 (26)**	**33.62 ± 12.84 (30)**	**> 0.05**
Gender			
Male	14 (60.9%)	26 (70.3%)	> 0.05
Female	9 (39.1%)	11 (29.7%)	
Mean duration of symptoms (days) ± SD	83.04 ± 48.38	47.16 ± 32.88	< 0.05
Mean BMI (kg/m^2) ± SD	16.42 ± 2.86	18.34 ± 2.69	< 0.05
Mean KPS ± SD	70.00 ± 10.87	80.81 ± 7.59	< 0.05
Mean TB score I ± SD	7.04 ± 2.65	5.32 ± 1.92	< 0.05
Mean TB score II ± SD	4.61 ± 2.04	3.19 ± 1.73	< 0.05
Cavitary	21 (91.3%)	16 (42.2%)	
Sputum AFB smear grade n (%)			
1+	5 (21.7%)	18 (48.6%)	< 0.05
2+	3 (13.1%)	7 (18.9%)	
3+	15 (65.2%)	12 (32.4%)	
Mean ESR ± SD	77.14 ± 37.84	56.15 ± 30.19	< 0.05
Mean haemoglobin (g/dl) ± SD	11.02 ± 2.21	11.95 ± 1.59	> 0.05
Mean serum albumin ± SD	2.83 ± 0.73	3.25 ± 0.81	> 0.05

cavitation on CXR. Patients with cavitary disease are shown to have a significantly higher mycobacterial load on sputum smear and culture [12, 20]. Palaci *et al.* [21] in their study found that about 85% of cavitary patients had 3+ sputum smear grade whereas only 38% of non cavitary patients had 3+ smears. In our study, we could also see that 48.6% of patients with cavitary disease had 3+ sputum smear grade as compared to 40% in patients with non cavitary disease though not statistically significant ($p > 0.05$).

KPS is a frequently used clinical tool for indicating disease severity, treatment response and also to predict mortality [22–24]. Similarly, Bandim TB score and TB score II when higher at baseline showed increased mortality risk during treatment [25, 26]. Wejse *et al.* [27] in their study found that a higher TB score of > 8 at baseline increased the mortality to 21% vs. 11% for TB score < 8. Hence KPS, Bandim TB score and TB score II are all good clinical parameters of the disease severity and predictors of poor treatment outcome. In our study, these clinical parameters did not correlate with the presence or absence of cavitary disease on CXR.

Low BMI and lack of weight gain during treatment are found to be independent predictors of poor treatment outcome. Khan *et al.* [28] in their treatment trial showed that the 2 year relapse rate were 4.2%, 11.9% and 20.3% among those not underweight, those underweight but gaining > 5% weight at 2 months of treatment and those underweight and not gaining weight respectively. Palaci *et al.* [21] found that patients with cavitary disease had significantly lower BMI as compared to the patients with non cavitary disease. However we did not find significant association between BMI and cavitary disease on CXR in our study.

Studies have shown that the bacterial burden increases with the radiographic severity of the disease irrespective of the presence or absence of cavitation [21]. Ralph *et al.* [12], in their study involving sputum smear positive PTB patients in Indonesia developed and validated the Timika CXR score. The score is a simple numerical score to grade the radiographic severity of disease extent and is found to be a predictor of 2-month sputum conversion status. At a cut-off level of 71, the score could predict a positive sputum smear at 2 months with a sensitivity of 80% and a specificity of 67.7% [12]. A recent study done in South Africa further validated the Timika CXR score and found a high inter-reader agreement or reliability [29]. The median Timika CXR score of our study population was 59.5%. Higher CXR scores are significantly associated with higher sputum smear grade at diagnosis [12]. However Olaru *et al.* [30] in their study failed to demonstrate correlation between CXR score with baseline smear grade. In our study we found that higher CXR score (≥ 71) was significantly associated with the baseline sputum smear grade as compared to lower CXR score (< 71). 62.2% of patients with CXR ≥ 71 had 3+ sputum smear grade as compared to 32.4% patients with lower CXR score ($p < 0.04$).

Ralph *et al.* [12]showed that the CXR scores were inversely related to BMI, FEV_1, Hb% and 6 min walk distance and directly related to SGRQ total score indicating the quality of life. Kriel *et al.* [29] also found that the mean CXR score for participants with baseline BMI < 18.5 kg/m^2 was significantly higher than those with higher BMI values [29]. We in our study also found that a higher CXR score was significantly associated with higher duration of symptoms, lower BMI and higher clinical scores (KPS, Bandim TB score and TB score II) at baseline ($p < 0.001$).

The ESR is shown to be positively correlated with the radiological extent of disease on CXR [31]. We also found a significant association between CXR score and baseline ESR in our study population ($p < 0.04$). Ralph *et al.* [12] concluded that the CXR score was significantly associated with a broader range of baseline severity measures than the presence of cavitation alone. Our study also shows that the Timika CXR score shows significant correlation with various baseline clinical and microbiological parameters as compared to the presence of cavity alone. The Timika score is a recently developed and validated chest x-ray score. We further tried to evaluate the score and its correlation with multiple clinical outcomes and sputum bacterial load in assessing the severity of disease extent. And our study could show that the score correlates with a broader spectrum of disease severity parameters as compared to cavitation alone.

Limitations

Our study is limited by the relatively small sample size, exclusion of HIV/AIDS patients in whom the CXR manifestations may be subtle and varied. Small cavitary lesions may be missed while interpreting the disease extent on CXR rather than CT. However CT is not feasible in all clinical settings.

Conclusion

Cavitary disease on CXR is associated with a higher mycobacterial load at baseline. Timika CXR score is a simple, standard scoring system

which can be used by a chest physician in a clinical setting. The CXR score significantly correlates with a broad range of clinical and microbiological measures of disease severity in PTB patients. Thus, it has a role in risk stratification especially in patients not producing sputum or sputum negative PTB at diagnosis. Its role in comparing the extent of disease severity between two patients or time points and in predicting treatment response needs further validation.

Conflict of interest

The authors declare no conflict of interest.

References:

1. www.who. int/tb/publications/global_report/en/ (16.05.2018).
2. https://www.tbcindia.gov.in/view.php?lid=3219&type=1 (16.05.2018).
3. Aber VR, Nunn AJ. Short term chemotherapy of tuberculosis. Factors affecting relapse following short term chemotherapy. Bull Int Union Tuberc. 1978; 53(4): 276–280, indexed in Pubmed: 387141.
4. Feng-Zeng Z, Levy MH, Sumin W. Sputum microscopy results at two and three months predict outcome of tuberculosis treatment. Int J Tuberc Lung Dis. 1997; 1: 570–572.
5. Lienhardt C, Manneh K, Bouchier V, et al. Factors determining the outcome of treatment of adult smear-positive tuberculosis cases in The Gambia. Int J Tuberc Lung Dis. 1998; 2(9): 712–718, indexed in Pubmed: 9755924.
6. Salaniponi FM, Christensen JJ, Gausi F, et al. Sputum smear status at two months and subsequent treatment outcome in new patients with smear-positive pulmonary tuberculosis. Int J Tuberc Lung Dis. 1999; 3(11): 1047–1048, indexed in Pubmed: 10587328.
7. Wallis RS, Doherty TM, Onyebujoh P, et al. Biomarkers for tuberculosis disease activity, cure, and relapse. Lancet Infect Dis. 2009; 9(3): 162–172, doi: 10.1016/S1473-3099(09)70042-8, indexed in Pubmed: 19246020.
8. Singla R, Osman MM, Khan N, et al. Factors predicting persistent sputum smear positivity among pulmonary tuberculosis patients 2 months after treatment. Int J Tuberc Lung Dis. 2003; 7(1): 58–64, indexed in Pubmed: 12701836.
9. Rathman G, Sillah J, Hill PC, et al. Clinical and radiological presentation of 340 adults with smear-positive tuberculosis in The Gambia. Int J Tuberc Lung Dis. 2003; 7(10): 942–947, indexed in Pubmed: 14552563.
10. Telzak EE, Fazal BA, Turett GS, et al. Factors influencing time to sputum conversion among patients with smear-positive pulmonary tuberculosis. Clin Infect Dis. 1997; 25(3): 666–670, indexed in Pubmed: 9314458.
11. Pinto LM, Pai M, Dheda K, et al. Scoring systems using chest radiographic features for the diagnosis of pulmonary tuberculosis in adults: a systematic review. Eur Respir J. 2013; 42(2): 480–494, doi: 10.1183/09031936.00107412, indexed in Pubmed: 23222871.
12. Ralph AP, Ardian M, Wiguna A, et al. A simple, valid, numerical score for grading chest x-ray severity in adult smear-positive pulmonary tuberculosis. Thorax. 2010; 65(10): 863–869, doi: 10.1136/thx.2010.136242, indexed in Pubmed: 20861290.
13. https://tbcindia.gov.in/index1.php?lang=1&level=2&sublinkid=4573&lid (16.05.2018).
14. www.tbcare1.org/publications/toolbox/tools/eqa/...microscopy/AFB_Microscopy.ppt (16.05.2018).
15. Horne D, Royce S, Gooze L, et al. Sputum monitoring during tuberculosis treatment for predicting outcome: systematic review and meta-analysis. The Lancet Infectious Diseases. 2010; 10(6): 387–394, doi: 10.1016/s1473-3099(10)70071-2.
16. Singla R, Singla N, Sarin R, et al. Influence of pre-treatment bacillary load on treatment outcome of pulmonary tuberculosis patients receiving DOTS under revised national tuberculosis control programme. Indian J Chest Dis Allied Sci. 2005; 47(1): 19–23, indexed in Pubmed: 15704711.
17. Gopi PG, Chandrasekaran V, Subramani R, et al. Association of conversion & cure with initial smear grading among new smear positive pulmonary tuberculosis patients treated with Category I regimen. Indian J Med Res. 2006: 807–814.
18. Hamilton CD, Stout JE, Goodman PC, et al. The value of end-of-treatment chest radiograph in predicting pulmonary tuberculosis relapse. Int J Tuberc Lung dis. 2008; 12(9): 1059–1064.
19. Heo EY, Chun EJ, Lee CH, et al. Radiographic improvement and its predictors in patients with pulmonary tuberculosis. Int J Of Infectious Diseases. 2009; 13(6): 371–376.
20. Perrin F, Woodward N, Phillips P, et al. Radiological cavitation, sputum mycobacterial load and treatment response in pulmonary tuberculosis. Int J Tuberc Lung Dis. 2010; 14(12): 1596–1602.
21. Palaci M, Dietze R, Hadad DJ, et al. Cavitary disease and quantitative sputum bacillary load in cases of pulmonary tuberculosis. J Clin Microbiol. 2007; 45(12): 4064–4066, doi: 10.1128/JCM.01780-07, indexed in Pubmed: 17928422.
22. Mugusi FM, Mehta S, Villamor E, et al. Factors associated with mortality in HIV-infected and uninfected patients with pulmonary tuberculosis. BMC Public Health. 2009; 9: 409, doi: 10.1186/1471-2458-9-409, indexed in Pubmed: 19909501.
23. Wilson D, Nachega J, Morroni C, et al. Diagnosing smear-negative tuberculosis using case definitions and treatment response in HIV-infected adults. Int J Tuberc Lung Dis. 2006; 10: 31–38.
24. Rudolf F. The Bandim TBscore — reliability, further development, and evaluation of potential uses. Glob Health Action. 2014; 7: 24303, indexed in Pubmed: 24857613.
25. Rudolf F, Lemvik G, Abate E, et al. TBscore II: refining and validating a simple clinical score for treatment monitoring of patients with pulmonary tuberculosis. Scand J Infect Dis. 2013; 45(11): 825–836, doi: 10.3109/00365548.2013.826876, indexed in Pubmed: 24041274.
26. Janols H, Abate E, Idh J, et al. Early treatment response evaluated by a clinical scoring system correlates with the prognosis of pulmonary tuberculosis patients in Ethiopia: a prospective follow-up study. Scand J Infect Dis. 2012; 44(11): 828–834, doi: 10.3109/00365548.2012.694468, indexed in Pubmed: 22812387.
27. Wejse C, Gustafson P, Nielsen J, et al. TBscore: Signs and symptoms from tuberculosis patients in a low-resource setting have predictive value and may be used to assess clinical course. Scand J Infect Dis. 2008; 40(2): 111–120, doi: 10.1080/00365540701558698, indexed in Pubmed: 17852907.
28. Khan A, Sterling TR, Reves R, et al. Lack of weight gain and relapse risk in a large tuberculosis treatment trial. Am J Respir Crit Care Med. 2006; 174(3): 344–348, doi: 10.1164/rccm.200511-1834OC, indexed in Pubmed: 16709935.
29. Kriel M, Lotz JW, Kidd M, et al. Evaluation of a radiological severity score to predict treatment outcome in adults with pulmonary tuberculosis. Int J Tuberc Lung Dis. 2015; 19(11): 1354–1360, doi: 10.5588/ijtld.15.0098, indexed in Pubmed: 26467588.
30. Olaru ID, Heyckendorf J, Grossmann S, et al. Time to culture positivity and sputum smear microscopy during tuberculosis therapy. PLoS One. 2014; 9(8), doi: 10.1371/journal.pone.0106075, indexed in Pubmed: 25171337.
31. Ozsahin SL, Arslan S, Epozturk K, et al. Chest X-ray and bacteriology in the initial phase of treatment of 800 male patients with pulmonary tuberculosis. J Bras Pneumol. 2011; 37(3): 294–301, indexed in Pubmed: 21755183.