Editorial Manager(tm) for Journal of Thoracic Imaging
Manuscript Draft

Manuscript Number: JTI-06-64R2

Title: HIGH-RESOLUTION CT FINDINGS IN PATIENTS WITH PULMONARY TUBERCULOSIS: CORRELATION WITH THE DEGREE OF SMEAR POSITIVITY

Article Type: Original Study

Section/Category:

Keywords: hrct, tuberculosis, smear

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Manuscript Region of Origin: TURKEY

Abstract: Background: There are data about the relationship between morphologic findings on HRCT and the number of acid-fast bacilli (AFB) on sputum smears in patients with pulmonary tuberculosis (PTB). It was also shown that existence of cavities and airspace consolidation might be related to smear positivity in PTB patients. However there is no study suggesting a relationship between AFB on sputum smears and radiological extent of disease based on HRCT findings.
Aim: In this study, we investigated a relationship between the degree of smear positivity and radiological extent of disease based on HRCT findings and, the degree of smear positivity and different pulmonary parenchymal changes on HRCTs of the PTB patients.

Methods: Sixty-one male patients with PTB (mean age: 22+/-3.2) were included into the study. HRCT images were assessed for patterns, distribution, and profusion of pulmonary abnormalities. Dividing the lungs into three zones, profusion of abnormalities was assessed. A profusion score was given. Patients were divided as smear positive and smear negative and compared for the scores of HRCT findings. Smear positive patients were divided into four groups as per grading of the sputum AFB smear: Group I (sputum1+), Group II (sputum 2+), Group III (sputum 3+) and Group IV (sputum 4+). Correlations were investigated between the degree of smear positivity and the scores of HRCT findings.

Results: A significant correlation between radiological extent of the disease based on HRCT and the degree of smear positivity was found (r=0.63, p=0.0001). There were also significant correlations between the degree of smear positivity and the scores of different HRCT findings. Nodule, cavity, and bronchial lesions are the most important contributors of the predictive properties of the total score. There was significant differences for the scores of HRCT findings between smear positive and smear negative patients.

Conclusion: Our study suggests that radiological extent of disease based on HRCT findings in patients with PTB correlated with the degree of smear positivity. Different HRCT findings such as nodule, cavitation, ground-glass opacity, consolidation and bronchial lesion are significantly associated with smear-positive PTB. Particularly, nodules, cavities and bronchial lesions might be predictors of smear positivity in patients with PTB. This study also suggests that the thickness of cavity wall and the distance of cavity from central airways might be related to the degree of smear positivity.

*** Response to Editor**

Dear Editor,

We revised the manuscript according to your kind and vitally contributive recommendations.

Comment 1

Change the Title to "HIGH-RESOLUTION CT FINDINGS IN PATIENTS WITH PULMONARY TUBERCULOSIS: CORRELATION WITH THE DEGREE OF SMEAR POSITIVITY"

Amendment 1

We changed the title to "HIGH-RESOLUTION CT FINDINGS IN PATIENTS WITH PULMONARY TUBERCULOSIS: CORRELATION WITH THE DEGREE OF SMEAR POSITIVITY" as you recommended.

Comment 2

A statement regarding the IRB is necessary in the Patients section. You can simply state that IRB approval was not required for this retrospective study at the end of the section.

Amendment 2

We added the sentence "Institutional review board (IRB) approval was not required for this retrospective study" at the end of the patients section.

Comment 3

In figure 2, and Table 1 the word "bant" should be changed to "band".

Amendment 3

We changed the word "bant" to "band" in figure 2 and table 1.

Comment 4

The figure 4 findings of micronodules and bronchial lesions are shown in other figures and can be deleted unless there is some other reason for retaining it, particularly since other figures have been added.

Amendment: 4

We deleted the figure 4,since there is no other reason for retaining it.

Comment 5

Figure 6 is very confusing. What do nodules <3, cavities <3, etc mean? How would one use this tree. Please provide a clear desciption in the figure legend.

Amendment 5

We changed the legend of this figure as follows "Classification tree to predict grade of smear positivity. At each termination point of the tree branches, the most likely grade is shown, together with the probability for each grade in the second line [(P) signifies the probabilities for smear positivity grades: 0, 1, 2, 3 and 4 respectively, in the parantheses]. For example, if a patient's nodule score is less than three , the likely grade for sputum positivity is 0, with a probability of 84%. However, if a patient's nodule score is three or more , cavity score is three or more, and bronchial lesion score is 4 or more, then the most likely grade for sputum positivity is 4, with a probability of 75%."

* Title Page (Title and Author Listing)

Type of manuscript :
Original Article
The title of the article:
HIGH-RESOLUTION CT FINDINGS IN PATIENTS WITH PULMONARY TUBERCULOSIS: CORRELATION WITH THE DEGREE OF SMEAR POSITIVITY
Key Words:
HRCT, tuberculosis, smear
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HIGH-RESOLUTION CT FINDINGS IN PATIENTS WITH PULMONARY TUBERCULOSIS: CORRELATION WITH THE DEGREE OF SMEAR POSITIVITY

ABSTRACT

Background: There are data about the relationship between morphologic findings on HRCT and the number of acid-fast bacilli (AFB) on sputum smears in patients with pulmonary tuberculosis (PTB). It was also shown that existence of cavities and airspace consolidation might be related to smear positivity in PTB patients. However there is no study suggesting a relationship between AFB on sputum smears and radiological extent of disease based on HRCT findings.

Aim: In this study, we investigated a relationship between the degree of smear positivity and radiological extent of disease based on HRCT findings and, the degree of smear positivity and different pulmonary parenchymal changes on HRCTs of the PTB patients.

Methods: Sixty-one male patients with PTB (mean age: 22+/-3.2) were included into the study. HRCT images were assessed for patterns, distribution, and profusion of pulmonary abnormalities. Dividing the lungs into three zones, profusion of abnormalities was assessed. A profusion score was given. Patients were divided as smear positive and smear negative and compared for the scores of HRCT findings. Smear positive patients were divided into four groups as per grading of the sputum AFB smear: Group I (sputum1+), Group II (sputum 2+), Group III (sputum 3+) and Group IV (sputum 4+). Correlations were investigated between the degree of smear positivity and the scores of HRCT findings.

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Conclusion: Our study suggests that radiological extent of disease based on HRCT findings in patients with PTB correlated with the degree of smear positivity. Different HRCT findings such as nodule, cavitation, ground-glass opacity, consolidation and bronchial lesion are significantly associated with smear-positive PTB. Particularly, nodules, cavities and bronchial lesions might be predictors of smear positivity in patients with PTB. This study also suggests that the thickness of cavity wall and the distance of cavity from central airways might be related to the degree of smear positivity.

HIGH-RESOLUTION CT FINDINGS IN PATIENTS WITH PULMONARY TUBERCULOSIS: CORRELATION WITH THE DEGREE OF SMEAR POSITIVITY

Introduction

Pulmonary tuberculosis (PTB) is a worldwide medical and social problem causing important mortality and morbidity especially in developing countries. Early diagnosis and treatment of PTB patients is important, since determining the degree of infectiousness among such patients is needed for clinical and public health management. Microscopic examination of sputum smears is a common and easy to perform technique for diagnosing PTB. If acid-fast bacilli (AFB) are detected in the stained sputum (AFB smear-positive), a diagnosis of pulmonary tuberculosis can be almost made [1,2]. The bacterial count in the stained sputum might indicate the degree of infectiousness. Chest-X ray is usually the first diagnostic tool when there is a suspicion of PTB. In primary PTB a hilar adenopathy and/or a consolidation might be usually seen on chest X ray [2-4]. Post-primary form of the disease develops years after exposure to *Mycobacterium Tuberculosis*. This form is the most common form seen in adult patients [1-4]. Upper zones of one or both lungs are usually involved and cavity or cavities might exist on chest-x ray. Even though, chest-x ray remains the first choice of initial evaluation of patients with PTB, CT scans provide more accurate information about the extent and distribution of PTB, the presence of cavities and satellite lesions that cannot be visualized on chest-x ray [3,4]. Moreover, CT can contribute to distinguish active from inactive disease [5,6]. There are data about the relationship between morphologic findings on HRCT and the number of AFB on sputum smears in patients with PTB. It was also shown that existence of cavities and airspace consolidation might be related to the degree of smear positivity in PTB patients [7,8]. However there is no study suggesting a relationship between AFB on sputum smears and radiological extent of disease based on HRCT findings.

We hypothesized that PTB patients having extensive disease on HRCT might have higher bacillary load and higher rate of the degree of smear positivity when compared to moderately or minimally extensive disease. We also investigated existence of a relationship between different individual parenchymal findings on HRCT and the degree of smear positivity.

MATERIAL AND METHOD

PATIENTS

This study was conducted at the Departments of Pulmonary Medicine and Radiology in Gulhane Military Medical Academy (GMMA) in Ankara. GMMA is a teaching hospital that serves as the biggest referral center for Turkish Armed Forces and a primary care facility in Ankara. We retrospectively analyzed the HRCT and sputum smear results of 92 patients who were diagnosed as having active pulmonary tuberculosis from the patient files between 2003 and 2005. Patients with a coexistence of other pulmonary or extra pulmonary diseases, a history of antitubercular treatment and having less than three sputum samples were excluded from the study. As a result sixty-one male patients with active PTB aged 22+/-3.2 years (mean ± SD and range, 20-47 years) were included into the study. All the patients were male since the study was conducted in a Military Hospital and all of the PTB patients were soldiers. Twenty-eight of the patients were sputum positive, whereas remaining 33 patients were smear negative.Institutional review board (IRB) approval was not required for this retrospective study.

DIAGNOSTIC CRITERIA

Diagnosis of PTB was based on positive sputum cultures. Lowenstein Jensen (LJ) medium and Bactec 460 TB system were used for culture. At least three sequential sputum samples were collected from each patient before starting anti-tuberculous chemotherapy and acid fast bacilli were identified by Ziehl-Neelsen staining. Patients under study were divided into four groups as per grading of the sputum AFB smear: Group I (sputum1+), Group II (sputum 2+), Group III (sputum 3+) and Group IV (sputum 4+). Sputum samples were classified according to the highest number of AFB per specimen.

HRCT EXAMINATION AND SCORING

HRCTs were performed at 10 mm section interval (120 kV, 175 mA), [1mm slice thickness, 1.5s scanning time] with a window level between -650 to –800 Hounsfield Units(HU) and window width between 1400 to 1600 HU using the GE Medical System HiSpeed CT/i (Milwaukee, USA). HRCT scans were evaluated for the presence, distribution, and extent of the following signs: (1)micronodule (MN) (nodules; 1 to 3-mm); (2) nodule (nodules; 4 to 10-mm); (3) consolidation (panlobular and polylobular opacities bigger than 10 mm); (4) ground glass opacity (GGO); (5) cavity; (6) bronchial lesion (bronchial wall thickening, bronchiectasis); (7) parenchymal bands. Also if the patient had cavitiy or cavities on HRCT, some parameters of cavity such as total diameter of cavities, the thickest wall of cavity and distance of cavity from nearest central airway were measured.

On the HRCT scans, the lungs were divided into six zones (upper, middle, and lower zones of the right and left lung). These areas of the lung were defined as the "upper zones" above the level of the carina; the "middle zones" between the level of the carina and the level of the inferior pulmonary veins; and the "lower zones" below the level of the inferior pulmonary veins. The HRCT score was determined by visually estimating the extent of disease in each zone [9]. The score was based on the percentage of lung parenchyma that showed evidence of each recorded abnormality: (1) involvement of less than 25% of the image; (2) 25 to 50%; (3) 50 to 75%; (4) more than 75%. A profusion score (1–4) was given and the scores of each zone were then summed to obtain a global profusion score for HRCT ranging from 0 to 12 for each lung. A total score for each area was generated adding the partial scores of 7 parameters considered, in particular those defined with the numbers 1-7 (theoretically ranging between 0 and 24). Altogether, the total score for two lungs ranged between 0 and 168.

STATISTICAL ANALYSIS

The statistical difference between the means was calculated by Student's t test if the population was Gaussian. Otherwise, the Mann–Whitney U test for testing statistical difference between the medians was assessed. Correlations were calculated by means of the Pearson correlation test if data were Gaussian distributed otherwise they were calculated by means of the Spearman rank correlation test. A p value lower than 0.05 was considered as significant. To determine the components of the total score that contribute to its ability to predict the smear positivity, we used classification trees using binary recursive partitioning (10). This method has been described in detail elsewhere (11). In brief, the method uses the input data that consists of the predictor (independent) variables such as cavity, nodule, micronodule, consolidation, bronchial lesion, ground glass opacity, profusion score and total score (range 0 to 168). The output or dependent variable was smear positivity which was coded as 0, 1, 2, 3, or 4. First, the root of the tree is determined by the probability of each smear grade based on the prevalence in each grade in the data set. Then, each predictor variable is selected in turn to determine which one produces the most accurate classification. This process of binary recursive partitioning is continued until there is no further improvement in classification. The resulting tree is then tested to determine if the tree is overfitting the data. A tenfold cross-validation is used to determine this minimum. The data is divided randomly into ten mutually exclusive subsets. Nine subsets are used to grow a new tree; the remaining subset is used to test the accuracy of the tree in predicting the correct grade of the smear. The optimal size of the tree is determined by shrinking the tree. This process is repeated on nine further occasions using a different test set on each occasion.The combined results of all ten trials are used to determine the optimal size of the tree. The original tree is then pruned to conform to that optimal size. This process is designed to produce a tree that has good predictive properties when tested with completely new data. The probability that the tree is different from uniform classification amongst the grades of smear positivity was tested by the chi-square statistic.

RESULTS

Twenty-eight of 61 patients were smear positive, whereas remaining 33 were smear negative. In smear positive group, 9 patients had (+), 7 had (2+), 5 had (3+) and 7 had (4+). The mean scores of the HRCT findings and their comparison between smear positive and smear negative patients are summarized in Table-1. There was a significant correlation between radiological extent of disease (global HRCT score) and the degree of smear positivity ($r=0.63$, $p=0.0001$). There were cavities in 27 patients. A significant correlation between the scores of cavities and degree of smear positivity was found ($r=0,62$, $p=0,0001$) (figures-1, 2, 3, 4). Also, there were significant correlations between the degree of smear positivity and mean diameter of cavities, between the degree of smear positivity and the thickness of cavity wall and between the degree of smear positivity and distance of cavity from nearest airway ($r=0.60$, $p= 0.001$, $r=0.42$, $p= 0.03$, $r=-0.65$ and $p=0.001$ respectively). Fifty-seven patients had nodules (figures-2, 3). There was a significant correlation between nodule score and the degree of smear positivity ($r=0.62$, $p=0.0001$) (figure-1). Fifty-seven patients had consolidation and a significant correlation between consolidation score and the degree of smear positivity was found ($r=0.47$, $p=0.0001$) (figures-1, 2, 3, 4). Areas of GGO was detected in 58 patients, and a significant correlation between the degree of smear positivity and GGO scores was found ($r=0.48$, $p=0,0001$) (figures-1, 4). Sixty patients had MNs on their HRCTs and a significant correlation between the degree of smear positivity and MN scores was found ($r=0.46$, $p=0.0001$) (figures-2, 4). Bronchiectasis and/or bronchial wall thickness were detected in 39 patients and a significant correlation between the degree of smear positivity and brochial lesion scores ($r=0.51$, $p=0.0001$) (figure-2).

To determine the components of the total score that contribute to its ability to predict the smear positivity we first develop a classification tree that used total score as the only predictor variable. The resulting pruned tree indicated that when total score is < 26, the probabilities of smear grade 0, 1, 2, 3, and 4 are 0.69, 0.2, 0.04, 0.04, and 0.02 respectively. When the total score is >26 and < 33, the probabilities of smear grade 0, 1, 2, 3, and 4 are 0, 0, 0.8, 0.2 and 0 respectively. When the total score is >33 and < 40, the probabilities of smear grade 0, 1, 2, 3, and 4 are 0, 0, 0.17, 0.33 and 0.5 respectively.

When the total score is >40, the probabilities of smear grade 0, 1, 2, 3, and 4 are 0.4, 0, 0, 0, and 0.6 respectively. The predictive properties of this tree were significantly different from uniform probability distribution amongst grades (p=0.015).

We then developed a classification tree that included all predictor variables except the total score. This tree had predictive properties (p=0.015) that were similar to the previous tree that used total score as the only predictor variable. This tree used three predictor variables: cavity, nodules and bronchial lesions (figure 5). Therefore these three variables are the most important contributors of the predictive properties of the total score.

DISCUSSION

We have shown that smear positive PTB patients have more extensive disease than smear negative ones. We have also shown a significant and a strong correlation between radiological extent of disease based on HRCT and the degree of smear positivity in PTB patients. In addition, a multivariate analysis showed that a total HRCT score lower than 26 was in favor of smear negativity. This result was compatible with the previous findings suggesting existence of air space consolidation, cavitation, nodule and ground-glass opacity are related to smear positivity since our global score was mainly based on these parameters [7,8,12-15]. However in those studies a global score was not used, only existence of the HRCT findings were described. We believe, sputum smear positivity do not depend on only some individual HRCT findings such as consolidation or cavitation, as a whole , all findings might be responsible for sputum smear positivity which we tried to estimate by global HRCT score. On the other hand, a global HRCT score is not the only factor determining smear positivity in PTB patients, since, even though, theoritecally we expected to find a higher correlation coefficient, it was not as high as that we expected. Several reasons might be responsible from this condition, first is the existence of probability endobronchial disease in patients having minimal or moderately extensive disease, second the disease might be radiologically extensive but bronchial involvement might be less than expected, the proximity of the disease to central airways might have an effect and airway dynamics might have a role due to the localization of the disease.

A significant difference was found for nodule scores between smear postive and smear negative patients. In fact, the highest correlation coefficient was between nodules and the degree of smear positivity among the HRCT findings. In multivariate analysis, nodules were the first of the three predictors of total score. Our result is similar to previous studies indicating a relationship between nodules and smear positivity. In addition, in the studies investigating the determination of activity of the PTB, micronodules were also suggested in favor of disease activity [5,12-15]. We did not found a significant difference for MNs between smear positive and smear negative patients. However there was a significant correlation between MNs and smear positivity. It seems there is a conflict between our study and previous studies about the role of MNs, we believe the difference between studies due to the definition of nodules or micronodules which might differ from one study to another. In our study we described nodules as opacities between 4mm and 10mm, MNs defined as lower than 4mm in size. In one study MNs defined as opacities lower than 10mm in size. In this study MNs were found to be closely related to smear positivity. In another study MNs described as opacities between 2 and 4 mm, in the second study no difference were found between smear negative and positive PTB patients for existence of MNs [7,8]. Our results are compatible with findings of the latter study. Combining all of these data, we might suggest that the more the size of a nodule is the more related to smear positivity.

There was a significant difference between smear positive and smear negative patients for cavity scores. In addition, we found a significant correlation between existence and size of cavity/cavities and smear positivity. This finding is an expected finding, in many studies and in textbooks, cavitation was always introduced as an associative feature of infectiousness [1-4,12-15]. Actually, in multivariate analysis, cavities were the second of the three predictors of total score. Cavitation occurs when the caseous necrotic material liquefies and is extruded through the connecting airway [14]. However the rate of existence of cavitation was considerably low among our patients that only 27 patients had cavity/cavities on their HRCTs. In addition, we found that there was a significant correlation between cavity wall thickness and the degree of smear positivity. As much as we screened the current literature we did not find any article suggesting this entity. This relationship might be explained basically by the probability of higher bacillus load in cavities with thicker walls. We also found that the proximity of cavities to main bronchi was another factor determining smear positivity. A negative and significant correlation existed between the distances of the cavity to main bronchi and the degree of smear positivity. This finding, theoretically, was an expected finding that the opening and discharging ingredients of central cavities into airways is easier than peripheral cavities. This finding also might contribute to explain smear negativity in some patients with peripheral cavities on their HRCTs.

We also found a significant difference between smear positive and smear negative patients for consolidation score. There was also a significant correlation between consolidation score and the degree of smear positivity which was a little lower than expected according to previous studies [7,8]. In a previous study it was suggested that air space consolidations consist of centrally located granulomas containing caseation necrosis and marginal nonspecific inflammation. The necrotic material, which drains through the airway, causes bronchial spread of pulmonary tuberculosis [14]. The fact that fluid and necrotic material contain numerous bacilli and are spread via the bronchial route relatively close to central airways might contribute to explain the correlation between consolidation and a positive sputum smear.

A significant difference was found for scores of GGO between smear positive and smear negative PTB patients. We also found that a significant correlation between GGO score and the degree of smear positivity, which is compatible with previous studies [8]. GGO in PTB might reflect nonspecific inflammatory change adjacent to an area of consolidation [14,15]. Even though, this finding may be considered as a şignificant indicator of tuberculous activity, some reports suggest that GGO might be seen as a sign of insufficient treatment [15].

There was a significant difference for bronchial lesion scores between two groups. There was also a significant correlation between bronchial lesion score and the degree of smear positivity. In multivariate analysis, bronchial lesions were the last predictor of total score. These findings were unexpected findings if we consider the bronchial lesion as isolated however in our study almost all of the patients who had bronchial lesions associated consolidation or another abnormality on their HRCTs. We think that bronchial lesion develops secondary to associated abnormality. So our study suggests that isolated bronchial lesion might not be considered as an indicator of smear positivity.

In conclusion, our study suggests that radiological extent of disease based on HRCT findings correlated with the degree of smear positivity in patients with PTB. Different HRCT findings such as nodule, cavitation, ground-glass opacity, consolidation and bronchial lesions are significantly associated with smear-positive PTB. Particularly, nodules, cavities and bronchial lesions might be predictors of smear positivity in patients with PTB. This study also suggests that the thickness of cavity wall and the distance of cavity from central airways might be related to the degree of smear positivity. Overall, this study suggests that HRCT might be useful in evaluating the infectiousness of PTB.

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LEGENDS OF FIGURES

figure-1 Correlations between the degree of smear positivity and some scores of HRCT findings

figure-2. HRCT image of a patient with PTB showing cavities (arrow A), consolidation (arrow B), nodule (arrow C), micronodules (arrow D), bronchial lesions (arrow E) and parenchymal band (arrow F).

figure-3. HRCT image of a patient with PTB showing cavity (arrow A), consolidation (arrow B) and, nodules (arrow C).

figure-4. HRCT image of a patient with PTB showing cavity (arrow A), consolidation (arrow B), GGO between consolidation areas (arrow C) and, micronodules (arrow D).

figure-5. Classification tree to predict grade of smear positivity. At each termination point of the tree branches, the most likely grade is shown, together with the probability for each grade in the second line [(P) signifies the probabilities for smear positivity grades: 0, 1, 2, 3 and 4 respectively, in the parantheses]. For example, if a patient's nodule score is less than three , the likely grade for sputum positivity is 0, with a probability of 84%. However, if a patient's nodule score is three or more , cavity score is three or more, and bronchial lesion score is 4 or more, then the most likely grade for sputum positivity is 4, with a probability of 75%.

Figure

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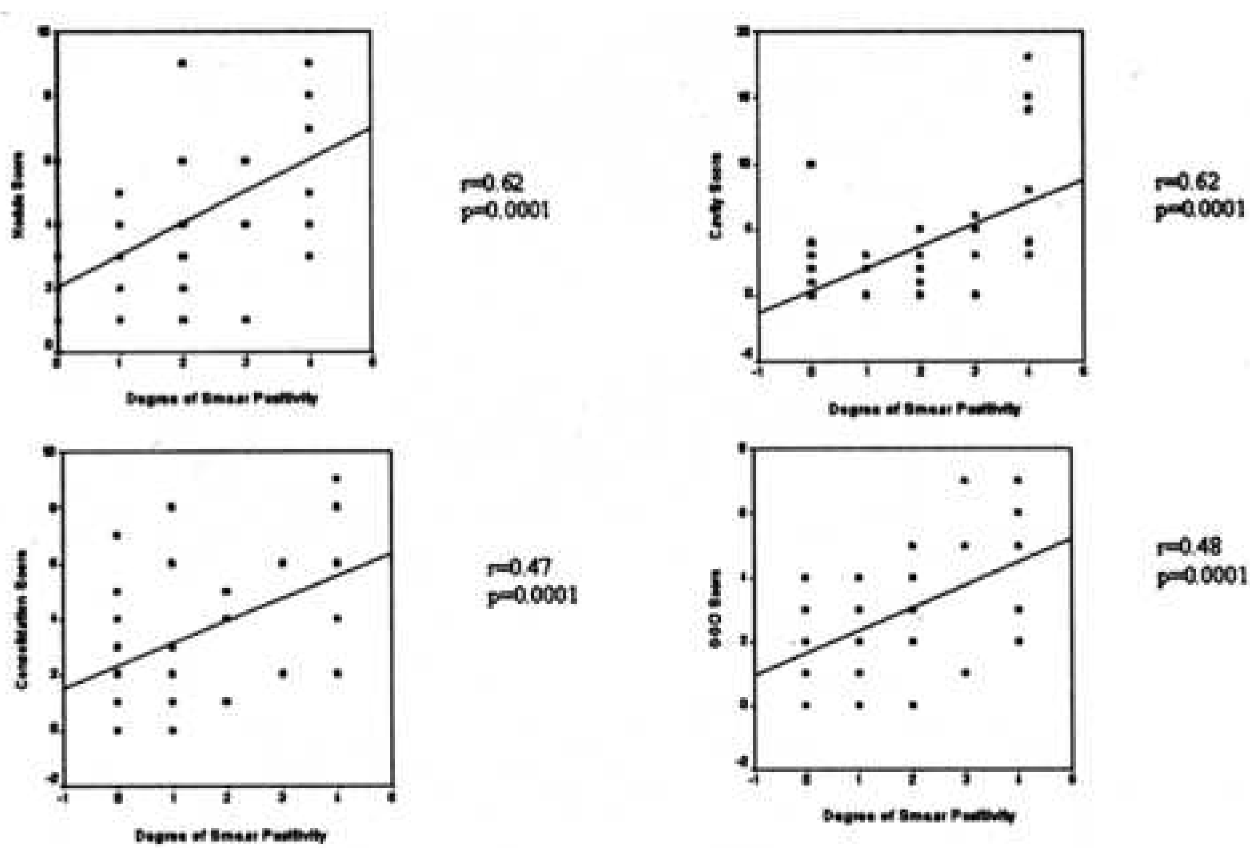

Figure
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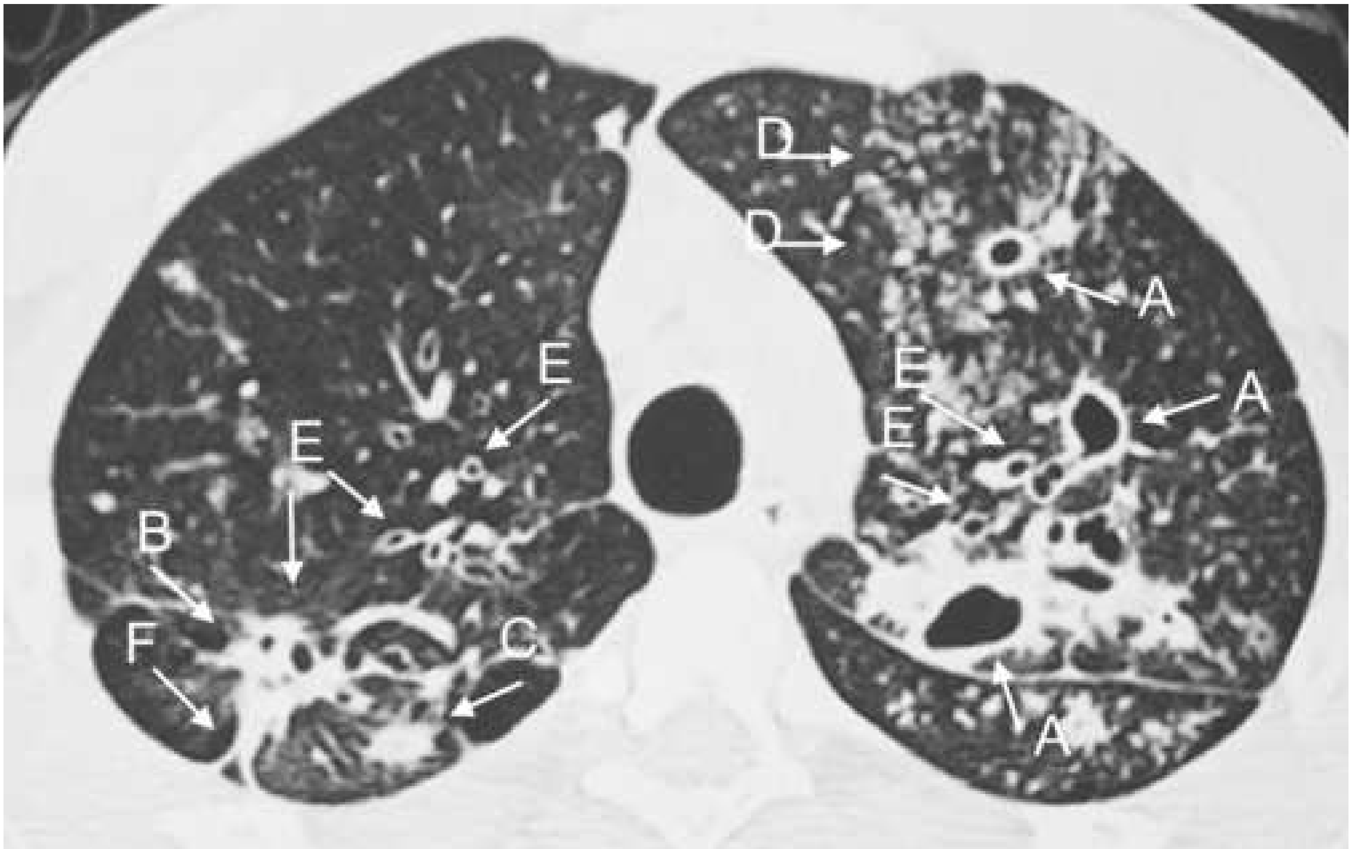

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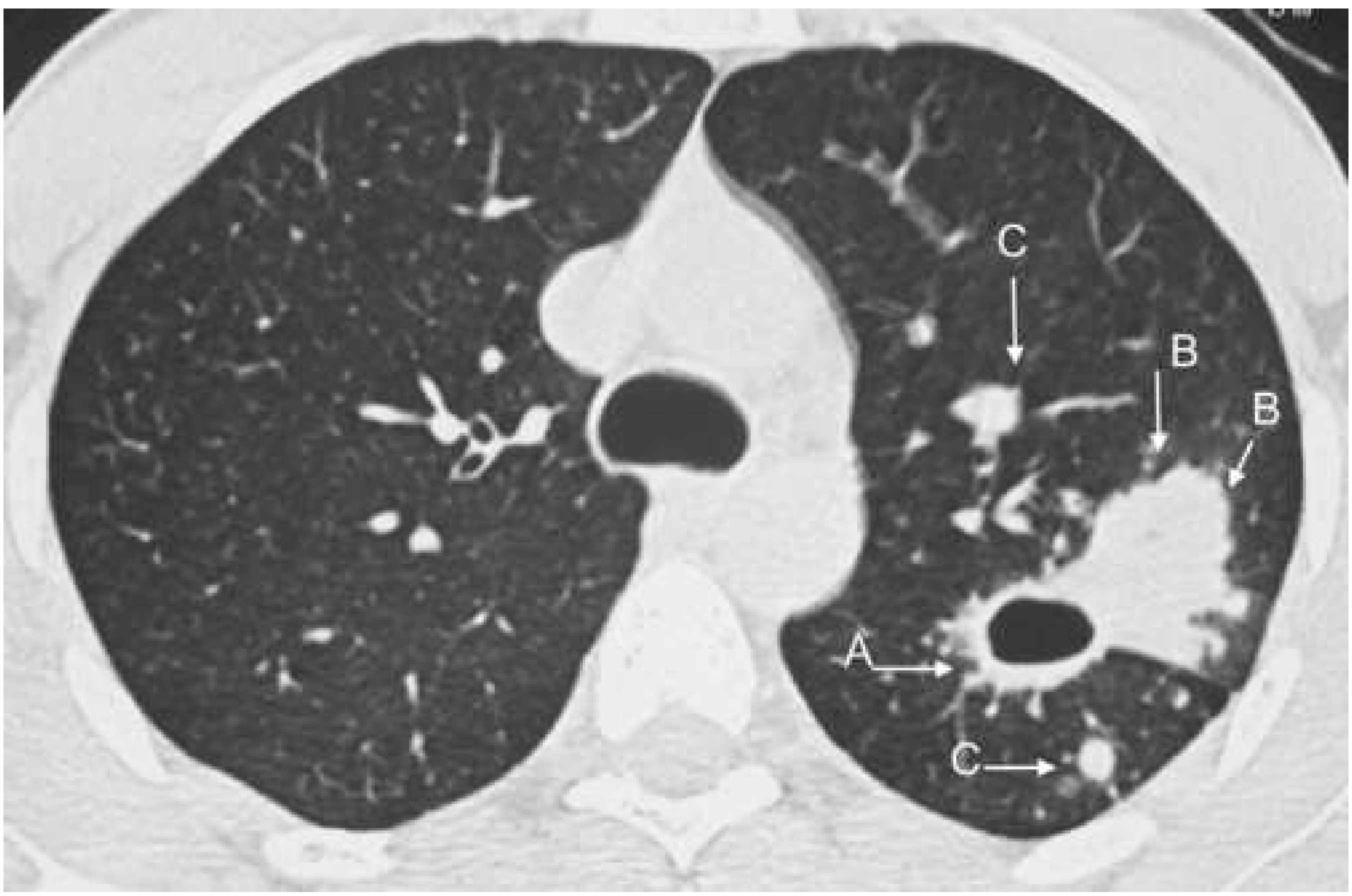

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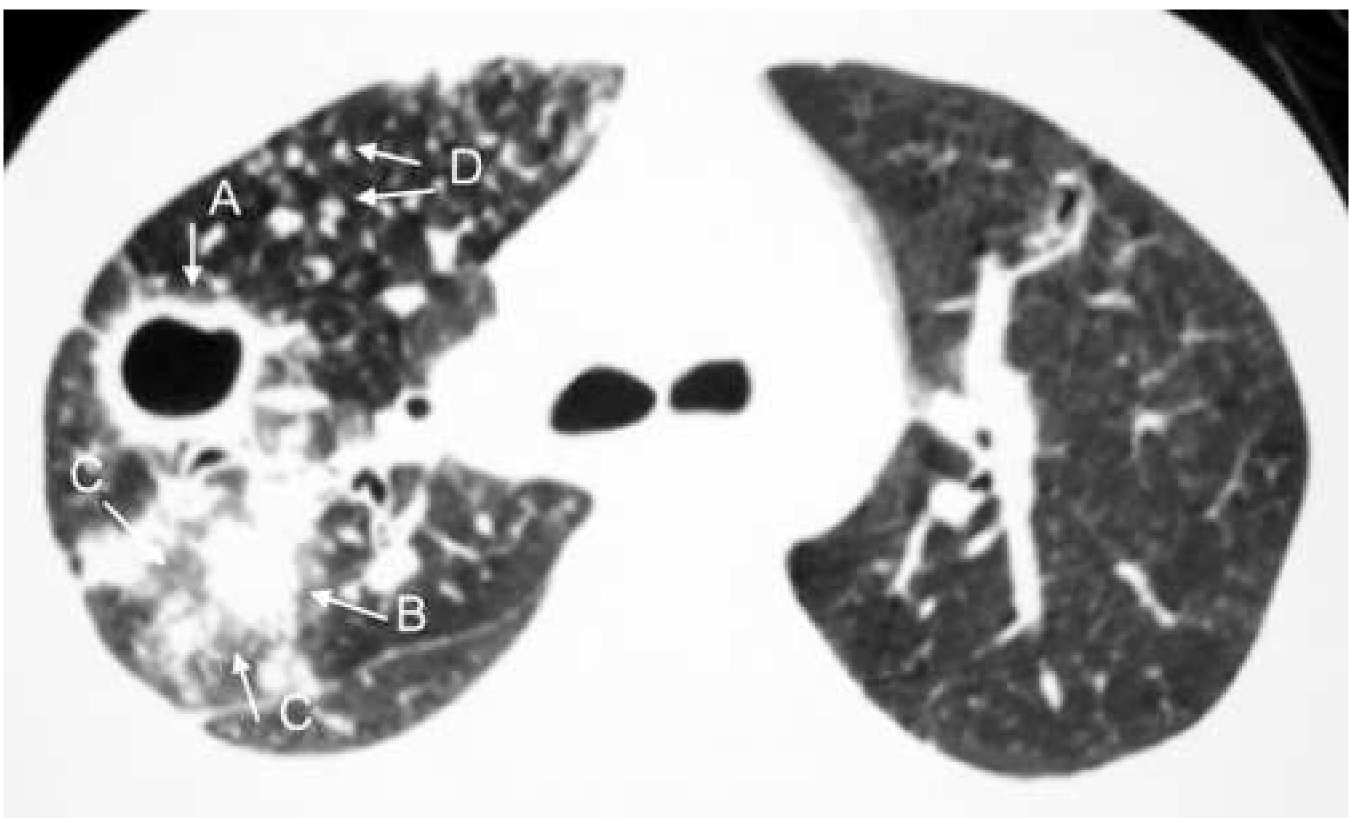

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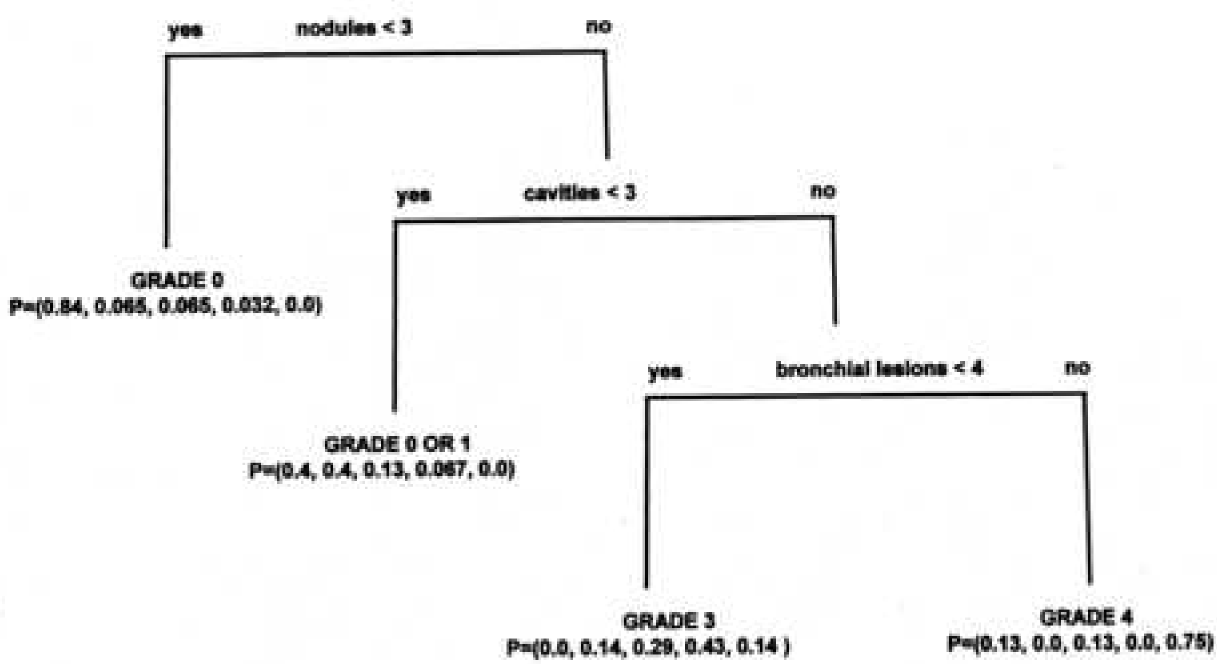

Table-1

Table.1 Comparison of smear positive and smear negative patients for the scores of HRCT findings

	Smear (+)	Smear (-)	
Parameter (Score)	**Mean (SD)**	**Mean (SD)**	**P value**
Cavity	3.9 (4.7)	0.8 (2.0)	0.003
Nodule	4.6 (2.2)	1.9 (1.5)	0.0001
Micronodule	6.1 (3.1)	4.6 (5.7)	0.21
Consolidation	4.1 (2.4)	2.4 (1.6)	0.002
GGO	3.3 (2.1)	1.7 (1.2)	0.001
Bronchial lesion	2.9 (2.7)	0.9 (1.4)	0.001
Band	2.5 (2.5)	1.1 (1.1)	0.007
Total Score	27.3 (13.6)	13.4 (10.2)	0.0001
Cavity Diameter (mm)	66.6 (82.5)	33.3 (32.5)	0.31
Cavity wall thickness (mm)	9.2 (2.8)	6.4 (3.9)	0.054
Cavity Distance (cm)	2.9 (1.1)	4.3 (1.4)	0.016