A STUDY ON ANATOMIC LOCALIZATION PATTERN AND MORPHOLOGICAL FEATURES OF PULMONARY MULTIPLE NODULES AND ITS CORRELATION WITH LUNG DISEASES BY HRCT EVALUATION

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Conflict of interest: NIL
Acknowledgement: MRS. Helen Gracy- Bio statistician, Dr. shivashankari- Research Assistant.

TITLE: A study on anatomic localization pattern and morphological features of pulmonary multiple nodules and its correlation with lung diseases by HRCT evaluation.

ABSTRACT

BACKGROUND: The Fleischner Society's Nomenclature Committee has described a lung nodule as a rounded or irregular opacity that is well or poorly defined and measuring up to 3 cm in size. The lung is made up of network of connective tissue fibers called lung interstitium. Important subsegmental lung units are lung acinus and secondary pulmonary lobule. Pulmonary nodules are distributed in relation to the secondary lobule and have a significant role in the diagnosis of diffuse multinodular disorders. Assessment of the distribution of multiple pulmonary nodules has been a crucial step in the diagnostic process in High resolution CT scan (HRCT) evaluation. The Aim of this study is to assess HRCT anatomic Localization and morphological characters of multiple pulmonary nodules and its correlation with specific lung disease.

MATERIALS AND METHODS: A prospective observational study was conducted with HRCT images of 75 patients with known diagnosis were evaluated by using Multinodular HRCT algorithm. Nodules were placed into four anatomic locations: perilymphatic, random, centrilobular with tree in bud opacity and cetrilobular nodule without tree in bud opacity. Algorithm accuracy was assessed by comparing the anatomic location to that expected location for each specific disease on the basis of reports in the literature.

RESULT: In this study with nodule localization, 24 out of 25 Pulmonary tuberculosis cases had centrilobular nodule with tree in bud opacity distribution pattern with a concordance rate of 96% 12 out of 14 sarcoidosis cases had perilymphatic distribution with a concordance rate of 86%. 5 cases miliary tuberculosis cases had random distribution pattern with the concordance rate of 100%, 9 out of 10 bacterial infection cases had centrilobular nodule with tree in bud opacity distribution pattern with a concordance rate of 90%. 3 out of 4 fungal infection cases had centrilobular nodule with tree in bud opacity distribution pattern with a concordance rate of 75% 7 out of 10 metastatic disease had random distribution pattern with a concordance rate of 70% 3 hypersensitivity pneumonitis cases had centrilobular nodule without tree in bud opacity with a concordance rate of 100%.

CONCLUSION: We conclude that this algorithm is accurate with the anatomic nodule location as expected with patient final diagnosis, reproducible and reliable in Indian population.

KEYWORDS: Multiple nodules, Pulmonary Tuberculosis, Centrilobular Nodules, Perilymphatic Nodules.

1. **INTRODUCTION:** The Fleischner Society's Nomenclature Committee has described a lung nodule as a rounded or irregular opacity that is well or poorly defined and measuring up to 3 cm in size (1). A micronodule is described as opacity smaller than 3mm (1). The lung is made up of network of connective tissue fibers called lung interstitium. The interstitium consists of centrilobular interstitium, peribronchovascualr interstitium, intralobular interstiitum and subpleural interstitium (2). Important subsegmental lung units are lung acinus and secondary pulmonary lobule. According to miller, smallest unit of lung which is surrounded by connective tissue septa is referred to as secondary pulmonary lobule (2,3). For HRCT interpretation, secondary lobule is considered to have three main components 1. Interlobular septa and contiguous subpleural interstitium, 2. Lobular parenchyma and acini, 3. Centrilobular structures (2). Patients with multinodular lung disease usually have innumerable nodules of different sizes. Pulmonary nodules are distributed in relation to the secondary pulmonary lobule and have a significant role in the diagnosis of diffuse multinodular disorders (4). Apart from distribution of nodules, nodule size also taken into consideration especially in diseases like military tuberculosis where nodules are tiny and rarely larger than 5mm. Pulmonary

nodules can occur as diffuse, focal or clustered. Anatomic location of multiple pulmonary nodules is classified into four patterns in relation to secondary pulmonary lobule including perilymphatic distribution, centrilobular with tree in bud opacity distribution, centrilobular without tree in bud opacity distribution (usually consist of ground glass nodular opacity) and random distribution (4). On comparison with conventional CT, Tiny micronodules can be easily detected in MDCT. In this era as the technology advances conventional CT is replaced by MDCT, so multiple pulmonary nodules detection rate is increased. Each pattern of distribution has many disorders as a differential diagnosis (4). Assessment of the distribution of multiple pulmonary nodules has been a crucial step in the diagnostic process in High resolution CT scan (HRCT) evaluation, which has the ability to evaluate diverse patterns of multinodular disease (4). Already there is an HRCT multinodular disease algorithm to provide differential diagnosis. Now our main focus in this study is how the multiple pulmonary nodules distribution pattern in various diseases in Indian population. And whether these diseases follow the distribution pattern in this algorithm or is there any deviation in nodule distribution.

2. Material and Methods

2.1. AIM: The Aim of this study is to assess HRCT anatomic Localization and morphological characters of multiple pulmonary nodules and its correlation with specific lung disease.

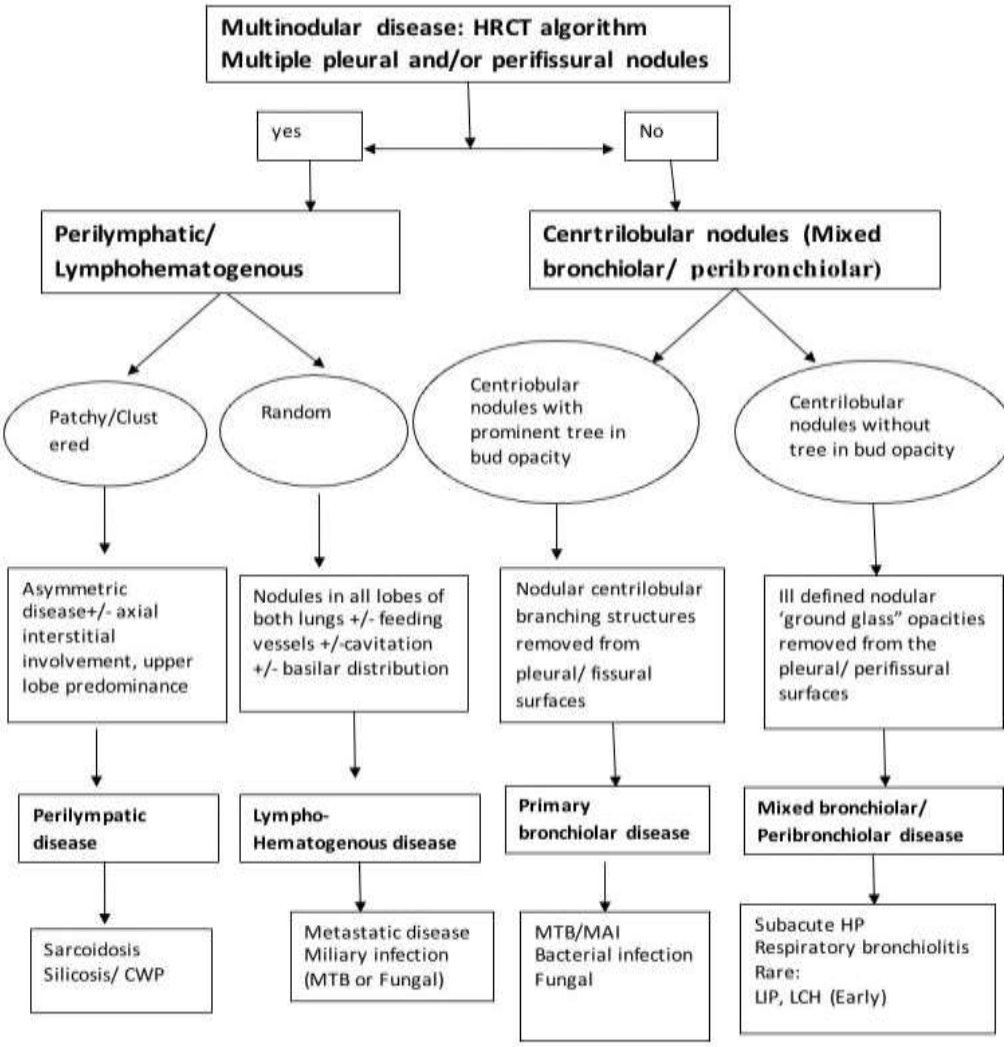
2.2. OBJECTIVE: To study the association of anatomic localization of multiple pulmonary nodules (perilymphatic, centrilobular nodule with tree in bud, centrilobular without tree in bud opacities and Random nodules) with multiple diseases and to evaluate the accuracy of the multinodular disease HRCT algorithm by evaluating interpretative concordance rate of nodule localization in HRCT and patient's final diagnosis.

2.3. Methods: A prospective observational study was conducted in Apollo hospitals Chennai from – with a sample size of. Patients with multiple pulmonary nodules (>2) and size less than or equal to 3cm was included and patients with solitary pulmonary nodule was excluded from the study.

2.4. Methodology: Cases were defined as consecutive patients coming to the Department of Radio-diagnosis with respiratory complaints and undergoing HRCT evaluation. In HRCT scan patients having multiple pulmonary nodules as predominant finding and fulfilling the inclusion criteria are involved in the study after getting written informed consent. All patients are evaluated by Toshiba prime aquilion 160 slices Multi-detector computed tomography machine and dedicated thin section HRCT lung protocol is used for every patient. HRCT findings will be evaluated by radiologist for anatomic localization of pulmonary multiple nodules with associated features and it will be correlated with patient's specific disease diagnosed using various lab investigations, clinical history and ancillary findings in HRCT. Definitive diagnosis made in all patient based on (*a*) AFB culture/ XPERT MTB (n=31), (*b*) Bronchial wash culture positive (n=14), (*c*) Elevated ACE levels (n=14), (d) transbronchial biopsy positive for metastasis (n=11), (e) ANA positive (n=1), (f) Clinical data (*n-=4*). The final study population consists of 75 patients (75 cases; 47 men, 28 women; age range, 16-84 years).

2.5. Localization Algorithm: For the purposes of this study in relation to algorithm application, we divided nodules into one of four anatomic/ distribution types similar to those given by gruden et al study on "Multinodular disease: anatomic localization at thin-section CT—multi-reader evaluation of a simple algorithm"(5) and Raoof et al review article "Pictorial essay: multinodular disease: a high-resolution CT scan diagnostic algorithm" (4) and those distribution types are (*a*) hematogenous or random, (*b*) perilymphatic, (*c*) centrilobular with tree in bud opacity, and (*d*) Centrilobular without tree in bud opacity. For the purposes of this study, Centrilobular nodules are divided into two categories centrilobular nodules with tree in bud opacity and centrilobular nodules without tree in bud opacity. Centrilobular nodules with tree in bud opacity have a distinctive HRCT appearance of impacted bronchioles and this appearance resemble a ''tree-in-bud'' or ''jacks,'' and air-space nodules in relation to other centrilobular nodules. (Ref Figure 1)

Figure 1- HRCT ALGORITHM FOR MULTINODULAR DISEASE (4)



2.6. STATISTICAL ANALYSIS: Continuous variables will be represented by mean± S.D, if they are normally distributed. Non-normally distributed variables will be expressed by median (interquartile range). Categorically variable will be expressed by percentile. Comparison of categorical variables will be done by either chi square test (or) Fischer's exact test. Concordance rate will be computed. Comparison of continuous variables will be assisted by independent sample t test. Data entry will be done by microsoft Excel 2007. Data analysis will be carried out by IBM SPSS statistic for windows version 25.0**.** All p values <0.05 will be considered as statistically significant.

3. RESULTS

In our study, Total 150 patients had been taken and in those 150 patients, 75 patients had final diagnosis and they were included in this study. 75 patients were loss of follow up where final diagnosis could not be made.

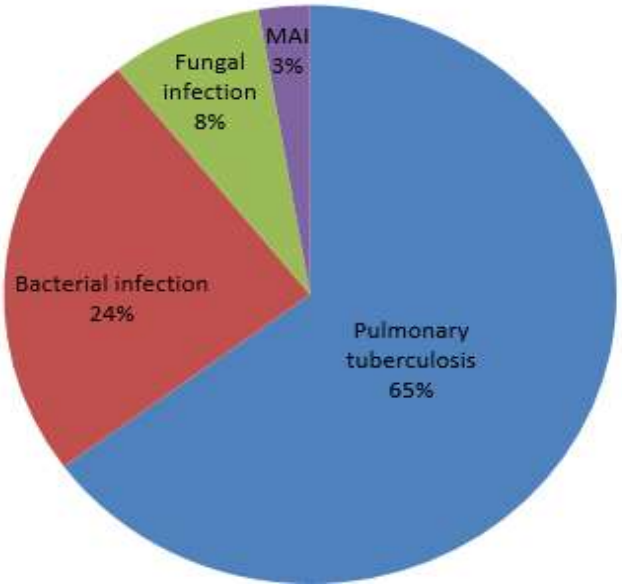
3.1. GENDER DISTRIBUTION:

In our study, Male population is 47 patients (63%) and female population is 28 patients (37%). Most of the disease has male population as predominant population. However, sarcoidosis was predominant in female population.

3.2. AGE GROUP: In this study population, 36 patients (48%) are <50 yrs old and 39 patients (52%) are >50 yrs old.

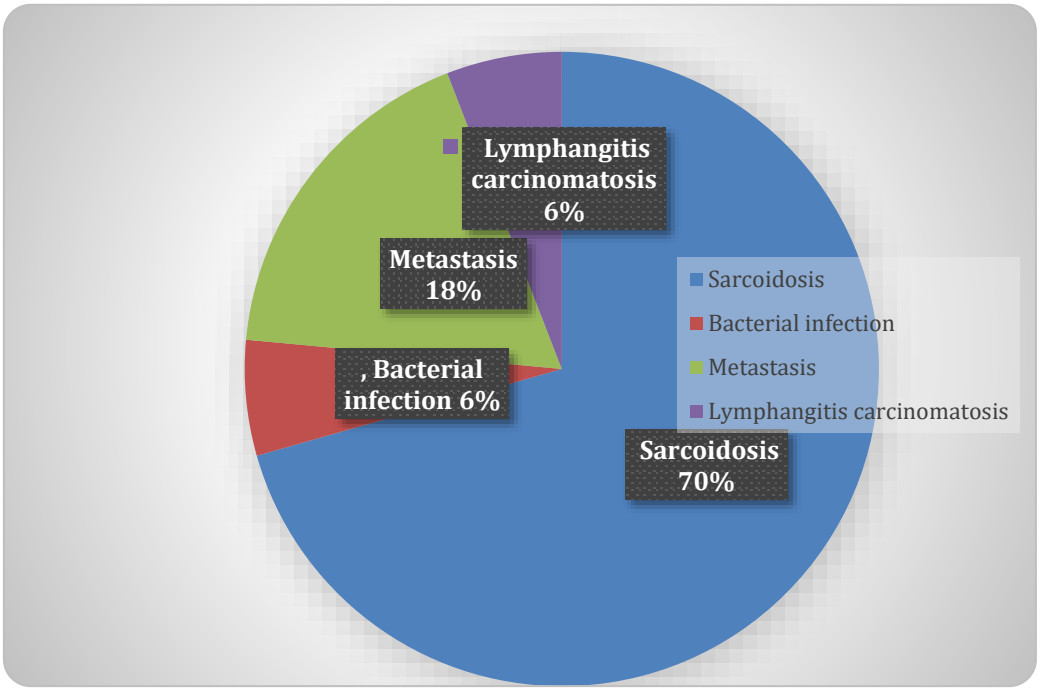
3.3. CENTRILOBULAR NODULES WITH TREE IN BUD OPACITY- Centrilobular nodule with tree in bud opacity. In centrilobular nodule with tree in bud opacity distribution, 24 patient had pulmonary tuberculosis (65%), 9 patient had bacterial infection (24%), 3 patient had fungal infection (8%), 1 patient had mycobacterium avium intercellulare (MAI) (3%). (Ref fig 2)

Figure 2: Centrilobular nodule with tree in bud opacity



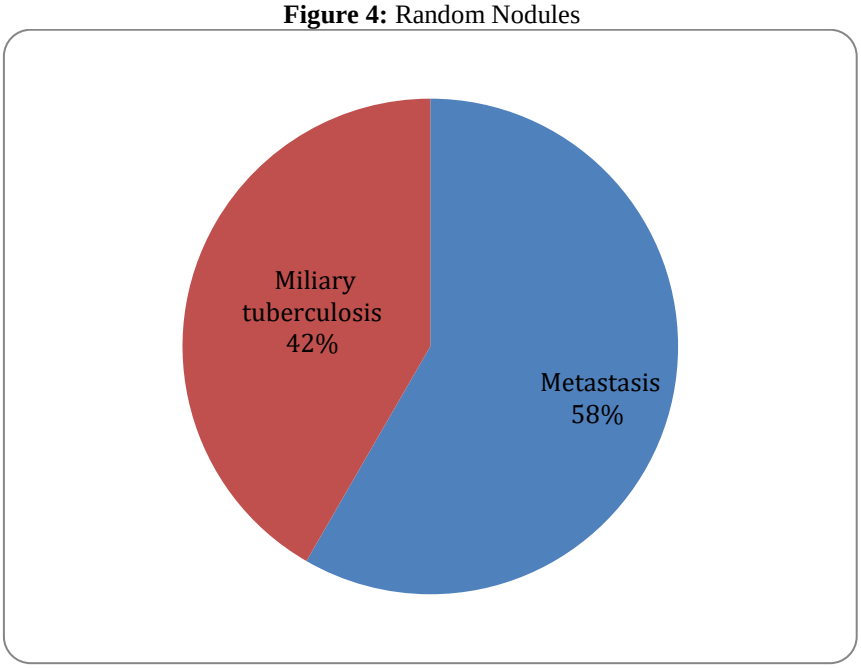
3.4. PERILYMPHATC NODULES: In perilymphatic nodule distribution, 12 patient had sarcoidosis (70%), 3 patient had metastasis (18%), 1 patient had bacterial infection (6%) and 1 patient had lymphangitis carcinomatosis (6%). (Ref fig 3)

Figure 3: Perilymphatic Nodules



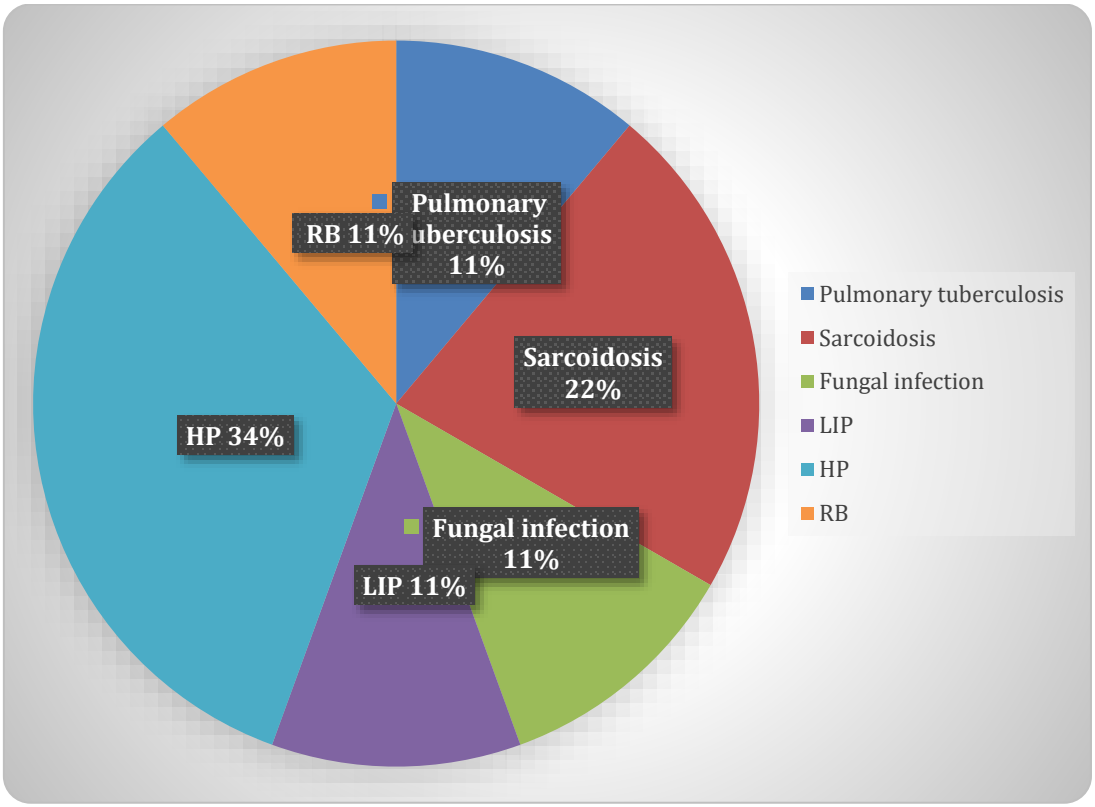
3.5. RANDOM NODULES: In random nodule distribution, 7 patients had metastasis (58%) and 5 patients had miliary tuberculosis (42%) (Ref fig 4)

Figure 4: Random Nodules



3.6. CENTRILOBLAR NODULES WITHOUT TREE IN BUD OPACITY: In centrilobular nodule without tree in bud opacity distribution, 1 patient had pulmonary tuberculosis (11%), 2 patient had sarcoidosis (22%), 1 patient had fungal infection (11%), 1 patient had lymphocytic interstitial pneumonitis (11%), 3 patient had hypersensitive pneumonitis (34%) and 1 patient had respiratory bronchiolitis (11%). (Ref fig 5)

Figure 5: CENTRILOBULAR NODULE WITHOUT TREE IN BUD OPACITY



3.7. NODULE CAVITATION:
Out of 75 patients, Nodule cavitations was absent in 67 patients and nodule cavitation was present in 8 patients. Out of 8 patients 4 patients had pulmonary tuberculosis, 2 patients had military tuberculosis, 1 patient had bacterial infection and 1 patient had fungal infection.

3.8. NODULE MARGIN:
Out of 75 patients in the study, smooth margin was present in 63 patients and irregular margin was present in 12 patients.

3.9. MEDIASTINAL LYMPHADENOPATHY:
Out of 75 patients in this study, Mediasitnal lymphadenopahty was present in 55 patients and lymphadenopathy was absent in 20 patients and all 14 cases of sarcoidosis had hilar lympahadenoapthy.

3.10. INTERPRETATIVE CONCORDANCE RATE:
Out of 75 patients, 67 patient's nodule finding were concordant with final diagnosis and 8 patients nodule finding were discordant with final diagnosis. (Ref table 1)

Table 1- INTERPRETATIVE CONCORDANCE RATE:

	CONCORDANT/DISCORDANT	
Diagnosis	CONCORDANT CASES	DISCORDANT CASES
Pulmonary tuberculosis	24	1
Sarcoidosis	12	2
Miliary tuberculosis	5	0
Bacterial infection	9	1
Fungal infection	3	1
Metastasis	7	3
Lymphocytic interstitial pneumonitis	1	0
Hypersensitive pneumonitis	3	0
Respiratory broncholitis	1	0
Mycobacterium avium intracellulare	1	0
Lymphangitis carcinomatosis	1	0

In our study with nodule localization, 24 out of 25 Pulmonary tuberculosis cases had centrilobular nodule with tree in bud opacity distribution pattern with a concordance rate of 96% and discordance rate of 4%, 12 out of 14 sarcoidosis cases had perilymphatic distribution with a concordance rate of 86% and discordance rate of 14%, 5 cases miliary tuberculosis cases had random distribution pattern with the concordance rate of 100%, 9 out of 10 bacterial infection cases had centrilobular nodule with tree in bud opacity distribution pattern with a concordance rate of 90% and discordance rate of 10%, 3 out of 4 fungal infection cases had centrilobular nodule with tree in bud opacity distribution pattern with a concordance rate of 75% and discordance rate of 25%, 7 out of 10 metastatic disease had random distribution pattern with a concordance rate of 70% and discordance rate of 30%, 1 lymphocytic interstitial pneumonitits case had ccentrilobular nodule distribution pattern with a concordance rate of 100%, 3 hypersensitivity pneumonitis cases had centrilobular nodule without tree in bud opacity with a concordance rate of 100%, 1 respiratory bronchiolitis case had centrilobular nodule without tree in bud opacity with a concordance rate of 100%, 1 mycobacterium avim intracellular case had centrilobular nodule with tree in bud opacity with a concordance rate of 100% and 1lymphangitis carcinomatosis case had perilymphatic distribution pattern with a concordance rate of 100%.

4. **DISCUSSION:** Multiple pulmonary nodules imaging findings can present in various diseases. In this study our primary aim was simply to evaluate the reproducibility and anatomic accuracy of Multinodular disease HRCT algorithm.

   NODULE LOCALIZATION KEY: Based on gruden et al work on "Multinodular disease: anatomic localization at thin-section CT--multileader evaluation of a simple algorithm" (5) and Raoof et al review article "Pictorial essay: multinodular disease: a high-resolution CT scan diagnostic algorithm" (4), nodule localization key was prepared. (Ref table-2)

Table 2- Nodule localization key

DIAGNOSIS	NO OF CASES (n=75)	EXPECTED NODULE LOCATION
Infectious bronchiolitis	40	Centrilobular with tree in bud opacity
Pulmonary tuberculosis	25	NIL
Bacterial infection	10	NIL
Fungal infection	4	NIL

Mycobacterium avium Intracellulare	1	NIL
Metastasis	10	Random
Miliary tuberculosis	5	Random
Sarcoidosis	14	Perilymphatic
Hypersensitivity pneumonitis	3	Centrilobular
Respiratory bronchiolitis	1	Centrilobular
Lymphocytic interstitial pneumonitis	1	Centrilobular
Lymphangitis carcinomatosis	1	Perilymphatic

Reproducibility of the algorithm: We followed the algorithm given in JF gruden et al study and sahil raoof et al review article. Nodules were placed according to this algorithm and this algorithm was reproducible in our institution.

Accuracy of the algorithm: Overall, 220 (90%) of 245 individual interpretations were correct with respect to the nodule localization answer key. Nodules were correctly localized in 67 (90%) of 75 cases with complete concordance when correlated with patient final diagnosis and 8 (10%) of 75 cases were discordant. Complete concordance seen in 24 out of 25 pulmonary tuberculosis, 12 out of 14 sarcoidosis, 9 out of 10 bacterial infections, 3 out of 4 fungal infections, 7 out of 10 metastasis, 5 miliary tuberculosis, 3 hypersensitivity pneumonitis, 1 lymphocytic interstitial pneumonitis, 1 respiratory bronchiolitis, 1 lymphangitis cardcinomatosis and 1 mycobacterium avim intercellulare.

ANATOMIC LOCALIZATION PATTERN OF NODULE: CENTRILOBULAR NODULE WITH TREE IN BUD OPACITY PATTERN: In Pulmonary tuberculosis, out of 25 patients 24 patients had "centrilobular with tree in bud opacity" pattern with a concordance rate of 96% and this finding is in accordance with the study of Im et al (6) study where 95% pulmonary tuberculosis patient had Cenrilobular opacity with tree in bud pattern. Out of 25 patients 1 patient had "centrilobular pattern" without any tree in bud opacity with a discordance rate of 4%. This discordant arose because patient didn't have any ancillary finding and with smoking history, respiratory bronchiolitis was given as possible diagnosis.

In Bacterial infection, out of 10 patients 9 patients had "centrilobular with tree in bud opacity" pattern with a concordance rate of 90% and this finding is in accordance with gruden et al (5) study where 80% bacterial infection had "centrilobular opacity with tree in bud pattern". Out of 10 patients 1 patient had perilymphatic pattern with discordance rate of 10%. This discordant arose because patient presented with subpleural nodules and patient was placed under perilymphatic pattern. In Fungal infection, out of 4 patients, 3 patients had "centrilobular with tree in bud opacity" pattern with a concordance rate of 75%.

PERILYMPHATIC PATTERN: In Sarcoidosis, out of 14 patients, 12 patients had "perilymphatic" pattern with a concordance rate of 86% and this is in accordance with Remy jardin et al (7) study where sarcoidosis patient presented with subpleural nodules. Out of 14 patients, 2 patients had centrilobular pattern with a discordant rate of 14%. This discordant arose because patient had few subpleural nodule and placed in indeterminate arm initially and later placed in centrilobular arm. In lymphangitis carcinomatosis, 1 patient presented with "perilymphatic pattern" with concordance rate of 100% and this is in accordance with Remy jardin et al (7) study where perilymphatic distribution seen in lymphangitis carcinomatosis.

RANDOM PATTERN*:* In metastasis, out of 10 patients 7 patient presented with "random" pattern with a concordance rate of 70% and this is in accordance with gruden et al (5) study where random nodule distribution was seen in metastasis. Out of 10 patients 3 patients presented with "perilymphatic pattern" with a discordant rate of 30%. This discordant arose because only common anatomic distribution pattern is taken in the nodule localization key. Even though in literature it has been mentioned that metastasis can occur as perilymphatic distribution pattern, most common random distribution pattern is taken in nodule localization key. In miliary tuberculosis, out of 5 patients all patients had "random" pattern with concordance rate of 100% and this is in accordance with McGuinness et al (8) study where miliary tuberculosis had random distribution pattern.

CENTRILOBULAR PATTERN WITHOUT TREE IN BUD OPACITY: In Hypersensitivity pneumonitis, out of 3 patients all patients had "centrilobular pattern" with ground glass opacity and concordance rate is 100% and this is in accordance with gruden et al (5) study where hypersensitivity pneumonitis showed centrilobular distribution. There is 100% concordance rate in both lymphocytic interstitial pneumonitits and respiratory bronchiolitis. However, these two diseases study was limited by very low sample size. Large sample size is required to calculate better concordance rate in general population.

- **MORPHOLOGICAL FEATURES**

MARGIN: Out of 75 patients in the study, smooth margin present in 63 patients (84%) and irregular margin present in 12 patients (16%). In a study by Nakatsu et al (9), nodules in sarcoidosis had irregular margin but in our study 10 out of 14 sarcoidosis nodules showed smooth margin. 7 out of 10 metastatic nodules (70%) showed smooth margin and this is in accordance with murata et al (10) study which showed majority of metastatic nodules are well defined and smooth margin.

LYMPHADENOPATHY: In our study mediastinal lymphadenopathy was present in all diseases except respiratory bronchiolitis and lymphocytic interstitial pneumonitis (LIP). All sarcoidosis patients (14 patients) had hilar lymphadenopathy and this is in accordance with muller et al study (11).
NODULE CAVITATION: In this study nodule cavitation was exclusively associated with infectious bronchiolitis (pulmonary tuberculosis, bacterial infection and fungal infection).

CLINICAL IMPORTANCE OF THIS STUDY: This study proves that this algorithm is accurate, reproducible and reliable in Indian population. With this algorithm if a patient present with centrilobular nodule with tree in bud opacity then infectious bronchiolitis should be suspected and sputum analysis can be done in this patient instead of diagnostic procedures like transbronchial biopsy. In patient presenting with random nodules usually transbronchial biopsy may be required for diagnosis. Perilymphatic and centrilobular nodules without tree in bud opacity usually do not require transbronchial biopsy if properly correlated with history.

5. **LIMITATIONS:** For some diseases sample size is small due to limited study period. Many diseases with multiple pulmonary nodules could not be included in the study population due to limited study period. With this multinodular disease nodule distribution algorithm only differential diagnosis are provided based on distribution pattern and it requires other CT ancillary findings and other investigation for specific diagnosis. It was a single centered study without any external validation.

6. **RECOMMENDATION:** Large sample size should be included in the study. Many diseases with pulmonary multiple nodules should be included in the study.

7. **CONCULSION:** This study concludes that this algorithm is accurate with the anatomic nodule location as expected with patient final diagnosis, reproducible and reliable in Indian population. This study data which analyzed extensively different diseases suggest that this HRCT algorithm is a reproducible algorithm to categorize patient with diffuse pulmonary nodules. Majority of individual nodule anatomic location has a high concordance rate with patient final diagnosis. We can standardize the clinical approach to differential diagnosis by using this algorithm. Our study showed that in Indian population most common disease is infectious bronchiolitis and among infectious bronchiolitis, pulmonary tuberculosis is common. Given the wide differential diagnosis for pulmonary multiple nodules, the utilization of an HRCT algorithm of pulmonary multiple nodules is considered an important component of patient evaluation.

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