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CT FINDINGS IN INITIAL RT-PCR NEGATIVE TESTING COVID 19: BASED ON STUDY IN A LARGEST TERTIARY CARE CENTRE OF CENTRAL INDIA.

Radiodiagnosis

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ABSTRACT

Summary Statement CT imaging findings in patients of suspected 2019-nCoV infection, who have initial negative results of reverse transcription–polymerase chain reaction (RT-PCR) testing.

Objective The purpose of this study is to explore the diagnostic value of CT over RT-PCR in the diagnosis of corona virus disease (COVID-19) pneumonia, especially for patients who have initial negative results of reverse transcription–polymerase chain reaction (RT-PCR) testing.

Materials And Methods Patients with suspected COVID-19 pneumonia from April 1, 2020, to September 30, 2020, were included. They are initially underwent RT-PCR followed by HRCT thorax after 1 day of negative initial RT-PCR testing. The imaging findings were obtained and compared with CT findings of those patients who have confirmed initial reverse transcription–polymerase chain reaction (RT-PCR) testing.

Results Total sixty (40 men, 20 women) patients who have initial negative RT-PCR testing but are highly suspicious for 2019-nCoV infection were included in our study and their age range between 22 years to 70 years. In our study most of the findings were seen involved the multiple(70%) lobes in both lungs. The main CT features were ground-glass opacity (90%) and consolidation (60%) with a sub pleural (100%) and peri hilar or central distribution. The other CT features included air bronchograms (60%), vascular enlargement and interlobular septal thickening (50%), tree in bud appearance and pleural effusions (10%). when CT of patient with initial negative RT-PCR test were compared with CT of patients with initial positive RT-PCR test , it was found that most of the findings like ground glass opacities and consolidatory changes were also likely present in these group (p>0.05).

Conclusion Chest CT is an important tools for screening and diagnosing the patients who are initial negative RT-PCR however they are highly suspicious and having symptoms like 2019-nCoV infection.

INTRODUCTION

Corona virus disease 2019 (COVID-19) outbreak was first reported from Wuhan, China in December 2019. The rapid spread of the COVID-19 associated pneumonia and its urging mortality rate drew intense attention, leading to the World Health Organization to announce a global health emergency on January 30th, 2020. As of September 30, 2020, the total number of confirmed cases is 34,804,348 worldwide with a reported death of 1,030,738 (1), higher than the preliminary reports. The total number of cases in the India has reached 6,549,373 and death of 101,782 and as of September 2020 (2).

Reverse transcriptase polymerase chain reaction (RT-PCR) remains the standard diagnostic reference for COVID-19 infection, but the high false-negative rate(such as insufficient cellular material for detection and improper extraction of nucleic acids from clinical materials) and its restricted availability limit the prompt diagnosis, which can result in a growing number of cases given the contagiousness of the virus (3). High-resolution CT is an important element in the diagnosis of COVID-19 pneumonia. The total number of cases in Nagpur had increased by 81,742 on September, 2020, which indicated that CT had a higher detection rate in patients with disease in the incubation period, especially for those with negative initial RT-PCR results. This finding showed that CT is helpful for early diagnosis, timely isolation, and treatment of COVID-19 pneumonia. Therefore, computed tomography (CT) is the major diagnostic radiologic tool in identifying the COVID-19 associated pneumonia among the suspected cases. Based on WHO online dashboard, as of September 2020 India is the 2nd leading country in the number of cases and mortality rate (1). Recently performed studies suggest that CT could have higher sensitivity than RT-PCR in the diagnosis of COVID-19 associated pneumonia (5-7). Multiple recent studies from China and South Korea revealed that ground-glass opacities (GGO) are the most common finding in COVID-19 associated pneumonia. Both lungs are involved in almost all cases and a peripheral sub pleural distribution is the most reported location. Multiple other radiologic features have also been described, although imaging features are highly nonspecific (5, 8-11).

PRIMARY OBJECTIVES

The primary purpose of this study was to describe the role of CT especially in those patients who have negative initial RT-PCR results however they have clinical symptoms of COVID-19 pneumonia.

MATERIALS AND METHODS

Study Design:- Prospective study.

Study Period:- Six months (from April 1, 2020 to September 30, 2020)

Study Site:- Government Medical College and Hospital, Nagpur.

Sample Size:- Sixty cases (40 men, 20 women). Among these 60 patients 50 patients had positive final RT-PCR results for SARS-CoV-2 in laboratory testing of respiratory secretions obtained by nasopharyngeal or oropharyngeal swab after CT findings confirmation.

Sourc Of Data:- Department of Medicine, Department of Chest medicine and Super Specialty hospital, GMCH , Nagpur.

Sample Collection:- All patients with initial negative RT-PCR testing however have clinical symptoms of COVID-19 pneumonia (Breathlessness, Fever etc.) who came for High Resolution Computed Tomography (HRCT) of lung.

Inclusion Criteria:- Patients with initial negative RT-PCR testing and have clinical symptoms of COVID-19 pneumonia (Breathlessness, Fever etc.).

Exclusion Criteria:- Patients with initial positive RT-PCR testing for COVID-19 pneumonia.

CT Image Data Acquisition

All 60 patients underwent HRCT after 1 day of negative initial RIGHT-PCR testing. Chest CT(HRCT) was performed with the patients in the supine position during end-inspiration without IV contrast administration. All the patients were evaluated with a 256 slice Philips Brilliance iCT CT scanner at 1mm slice thickness, 120 kV tube voltage and 250 mAs tube current-exposure time current.

CT Image Evaluation

All the images were first evaluated by the third year resident which were crossed and finalized by the two eminent radiologist (10 & 15 years of experience). All the images were evaluated & reviewed at the departments own well equipped work station. The final decisions were made by consensus of the two radiologists. All of the unenhanced CT

images were evaluated in preset standard pulmonary (window-width, 1600 HU; window-level, -600 HU) and mediastinal (window-width, 400 HU; window-level, 60 HU) windows. The following CT characteristics of the lesions were evaluated: Distribution (left or right lung, single or multiple lobes, sub pleural or peri bronchial), Attenuation (ground-glass opacities, consolidation), Air-bronchograms ,Vascular enlargement, Interlobular septal thickening, Mediastinal lymphadenopathy (defined as lymph node size ≥ 10 mm in short-axis dimension), Pleural effusion, and Pulmonary fibrosis.

RESULTS

Patient Characteristics:-This study included 60 patients (40 men, 20 women ; age ranges from 22 years to 70 years). Forty-two (70%) patients had a history of exposure to a person with SARS-CoV-2 infection or had been to contaminated Red Zone , Twelve (20%) patient had history of travel to other state, Six (10%) had unknown exposure history .

Laboratory Findings:- It is very variable and includes normal WBC count to Lymphopenia or Leucopenia, Raised LDH, Raised CRP. In our study 36 (60%) had Leucopenia (WBC count, $< 4 \times 10^9$/L), 12(20%) had Lymphopenia (lymphocyte count, $< 1.0 \times 10^9$/L), 12(20%) had raised LDH level. C-Reactive protein is raised in 36(60%) and erythrocyte sedimentation rates were elevated in 18 (30%) patients (Figure-1)
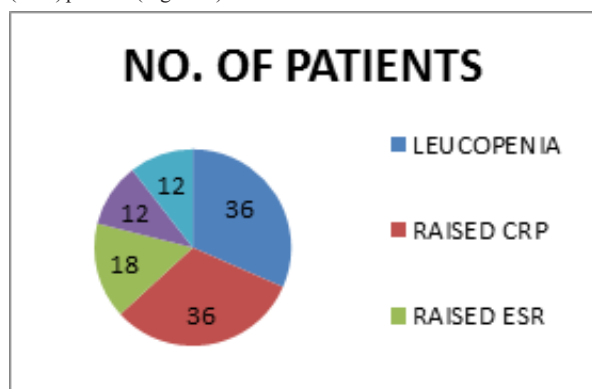

Figure 1:-laboratory Findings In Patients With Initial Negative RT-PCR Test Result

Common Symptoms:- 48(80%) patients had fever, 30(50%) patients had Breathlessness, 24(40%) patients had cough and 12(20%) patients had myalgia (Figure 2).
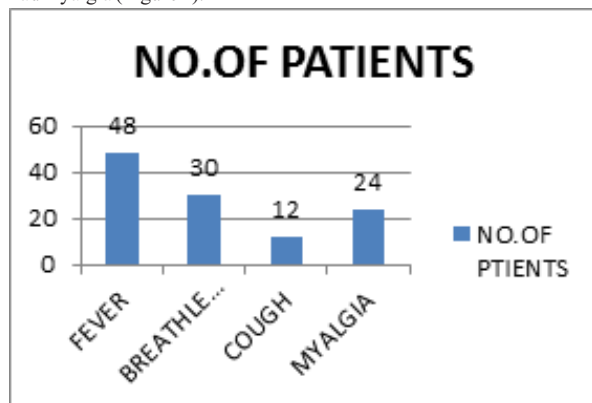

Figure 2:- Clinical Symptoms In Patients With Initial Negative RT-PCR But Highly Suspected For COVID-19 Pneumonia.

Chest CT Features

After complete evaluation and crossed checked of the all the 60 patient's HRCT Chest it is found that lesion were bilateral in 42 (70%) patients, in the left lung 12(20%) and in the right lung 6(10%) patients. In our study it is found that ; in majority 48(80%) of patients the lesions were located in multiple lobes, in 12(20%) patients the lesions were involved the one or two lobes. It is found that most 42(70%) of the lesions were involved the lower lobe. All 54 patients (90%) had ground-glass opacities (FIG 1 A & B) and 36(60%) had consolidation (FIG 2). All 60 patients (100%) had lesions in the sub pleural area, and

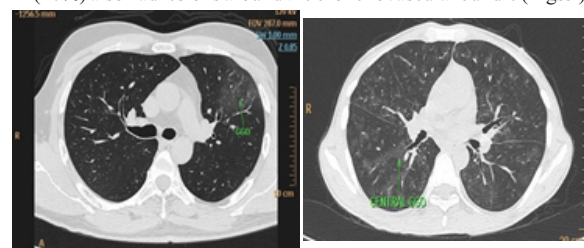24 (40%) also had lesions around the bronchovascular bundle (Figs3).

FIG 1 : 44(A) and 56(B) yr male with history of fever and cough with initial negative RT-PCR result.
A. Axial thin section unenhanced CT shows peripheral or subpleural (arrow) GGO in ant. Segment of left upper lobe.
B.Axial thin section unenhaced CT shows central (arrow) GGO in bilateral lung field.

FIG 2: 36 yr male with fever & myalgia with initial negative RT-PCR result.; Axial thin section unenhanced CT shows Patchy areas of consolidation with surrounding GGO in apico-posterior segment of left upper lobe.
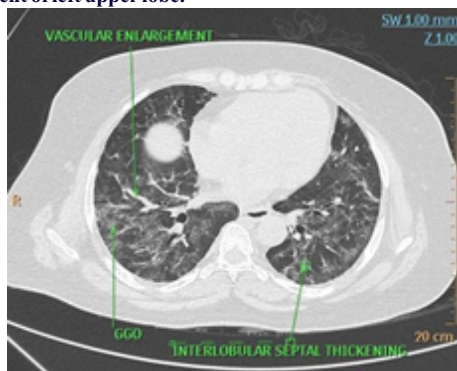

FIG 3: 57 year old female with history of cough and history of contact with initial negative RT-PCR result; Axial thin section unenhaced CT shows multifocal GGO in subpleural region and around bronchovascular bundle.

Other CT Findings Includes:- 36(60%) having air bronchograms (FIG 4) , 50(%) patients having vascular prominence(FIG 5) and interlobular septal thickening (FIG 6). Six (10%) patients having pleural effusion (FIG 7) , six(10%) patients having lymphadenopathy and no patients having pulmonary fibrosis.
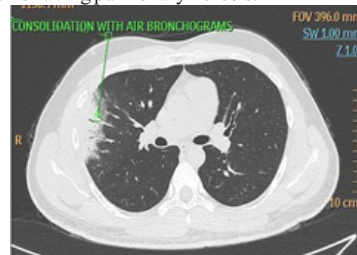

Fig 4: 22 year old male with history of breathlessness and recent history of travel with initial negative RT-PCR result; Axial thin section unenhaced CT shows patchy area of consolidation with air bronchograms and adjacent GGO noted in the apical & posterior segments of right upper lobe.
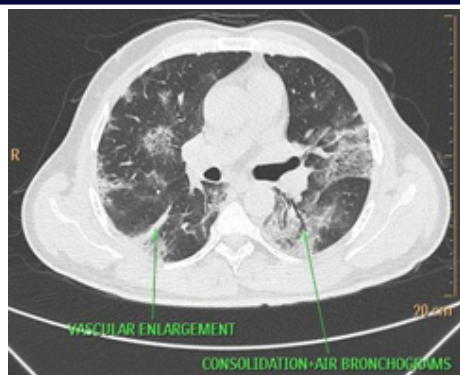
FIG 5: 46 years male with fever & cough with initial negative RT-PCR result; Axial thin section unenhanced CT shows multifocal GGO , patchy areas of consolidation with air bronchograms noted in bilateral lung fields. There is vascular enlargement also noted (Arrow).

Fig 6: 27 year female with history of fever, breathlessness, cough and myalgia with initial negative RT-PCR result ; Axial thin section unenhanced CT shows patchy areas of GGO with interlobular septal thickening in bilateral lung fields(right >left).
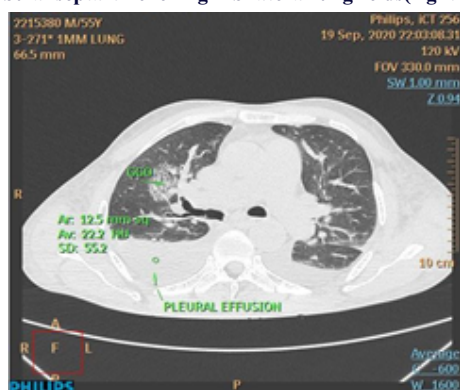

Fig 7: 56 year male with history of fever, cough & myalgia with initial negative RT-PCR result; Axial thin section unenhanced CT shows consolidatory changes with adjacent GGO in right upper lobe and bilateral pleural effusion.

RT-PCR TEST RESULTS AFTER REPETATION OF RT-PCR TESTING-

Among all 60 patients who had initial negative RT-PCR test result ; all 60 patients undergone repeat RT-PCR testing after findings on CT and it is found that results of 50 (83.3%) patients came positive on repeat RT-PCR testing and rest 8(13.3%) patients have imaging findings of superadded bacterial infection like multiple centrilobular nodules with linear branching patterns giving "Tree In Bud" appearance etc.

CT Findings Interpretations:-

When the CT findings of all these 60 patients were obtained and compared with CT findings of those patients who had confirmed positive RT-PCR testing and positive CT chest findings ; it is found that the CT scans findings of these patients who had negative initial RT-PCR testing results had less consolidation in comparison to those had

positive initial RT-PCR test results (p<0.04). The chest CT imaging findings in initial negative RT-PCR patients are almost similar to those with confirmed initial positive RT-PCR patients. Those findings are:- Ground glass opacities, Consolidations, Bilateral or Unilateral lung involvements and Single or Multiple lobes involvements (TABLE 1).

Table 1: HRCT Features In Patients With Initial RT-PCR Negative But Symptoms Of COVID-19 Pneumonia.

HRCT feature	Number/ Percentage of patients(60) with the mentioned feature	
Lesion Distribution:-		
Sub pleural	60	100%
peripheral and central	24	40%
CT sign:-		
Lung change		
GGO	54	90%
Consolidation	36	60%
Vascular enlargement	30	50%
Inter & Intralobular septal	30	50%
thickening	11	18.3%
TIB		
Bronchial change	36	60%
Air bronchograms	6	10%
Lymphadenopathy		

Note-GGO=ground Glass Opacities; TIB= Tree In Bud

DISCUSSION

The RT-PCR test is considered the standard for the diagnosis of COVID-19, but in some cases it can give false-negative results especially in the early stages of the disease. In that case CT findings have confirmed the diagnosis in number of those patients who had initial negative RT-PCR test result with signs and symptoms of COVID-19 infection[12]. In these cases HRCT Chest may be considered as a primary tool for detection of symptomatic but initial RT-PCR testing. In this study, we found differences in CT features between the patients with negative initial RT-PCR results to that who had confirmed positive initial RT-PCR and HRCT results.

In our prospective study of 60 patients, the disease had a high likelihood of bilateral multifocal involvement of the lower lobe of the lung, similar to the findings reported by Chung et al. [13]. However, a small number of patients had involvement of only a single lobe. Han et al. [14] reported that the single lobe usually was the right lower lobe, possibly because its thick and short anatomic features make it easy for the virus to invade. We also found the disease likely to have a sub pleural distribution, possibly because the target cells are located in the lower airway [15]. In addition to above findings , some of the lesions were located around the bronchovascular bundle, which may indicate that the pneumonia can spread along the pulmonary intralobular interstitium and induce an inflammatory reaction. It has been supposed [16] that the lesions start by invading the bronchioles and alveolar epithelium of the cortical lung tissues and extend gradually from the periphery to the center.

Patients with COVID-19 pneumonia usually had ground-glass opacities (95%) and consolidation (72%). That ground-glass opacities were more common is similar to findings in previous studies [13, 17]. Because of the highly homologous sequences between the genomes of SARS-CoV-2 and SARS-CoV [18], it has been speculated that the ground-glass opacities are caused by serous inflammatory exudation from the pulmonary alveoli and that the consolidation is caused by the increased inflammatory exudation. It has also been reported [19] that patients admitted to an ICU are more likely to have large areas of bilateral consolidation on CT scans, whereas patients not needing admission and presenting with milder forms of the illness are more likely to have ground-glass opacities and small areas of consolidation. That is, the disease usually manifests ground-glass opacities in the early stage and then the area of consolidation increases after the disease progresses, which may be predictive of severe complications, such as acute respiratory disease.

Other CT features included air bronchograms, vascular enlargement, and interlobular septal thickening. When there is occurrence of superimposed ground glass opacification, the interlobular septal thickening can form the crazy paving pattern. In our study few of the patients had underlying diseases, such as hypertension and diabetes mellitus.

When we compare the our HRCT chest findings of initial negative RT-PCR patients to those had confirmed positive RT-PCR and HRCT chest findings, we found that the area of consolidation in our patients was smaller. In our study we found that the patients with negative initial RT-PCR results, most of the lesions appeared as ground-glass opacities or opacities mixed with a small area of consolidation, which indicated that the disease was in its early stage. An another recent study [20] had a similar result: all five of the patients in the study had ground- glass opacification, and only two had mixed consolidation. It has been reported [19] that the presence of consolidation lesions suggests an organizing pneumonia pattern of lung injury. A small area of consolidation indicates that the injury to lung tissue is mild, increasing the possibility of negative initial RT-PCR results. In contrast, when the area of consolidation is large, the possibility of negative initial RT-PCR results decreases.

LIMITATIONS:-
First , RT-PCR detection   is affected by many factors, such as laboratory reagents, test method used, and subjective operability.

Second no follow-up CT was performed to observe dynamic changes resulting from treatment.

CONCLUSION:-
In patients of initial negative RT-PCR, there was typical CT findings like bilateral ground glass opacities and consolidation along with sub pleural distribution was found. The less pulmonary consolidation found at CT, the greater was the possibility of initial negative RT-PCR results. Although CT is not proposed for final diagnosis of COVID-19 pneumonia , however it plays a vital role in the diagnosis and nevertheless plays an irreplaceable role. When patients with suspected COVID-19 pneumonia who have epidemiologic history with signs and symptoms and typical CT features have negative initial RT-PCR results then repeated RT-PCR tests and isolation of patients should be considered.

Declaration Of Interest

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