Original Article

HRCT Spectrum in Initially COVID-19 RT-PCR Negative Patients

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[1,3] Analysis/Interpretation/Discussion
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Abstract

Objective: To analyze the radiological spectrum of HRCT in COVID-19 patients, clinically symptomatic but initially having negative RT-PCR.

Study Design: Prospective cross-sectional descriptive study.

Place and Duration of Study: Radiology and Medicine Department, DHQ Hospital Rawalpindi, from June to November 2020

Materials and Methods: The study included 90 patients presenting with clinical symptoms of COVID-19 but with negative RT-PCR. All patients underwent chest computed tomography (CT). Patients having non-COVID-19 HRCT features with negative RT-PCR were excluded from the study.

Results: Out of 90 symptomatic, RT-PCR negative patients, 7 had normal chest CT. According to BSTI classification, 50 patients showed classic, 11 had probable and 22 had indeterminate features. Unilateral changes were in 8 (8.9%) and bilateral in 75 (83.3%). The most common finding was a mixed pattern of peripherally distributed GGN and bronchocentric nodules in 37 (41.1%) patients. Consolidations were in 19 (21.1%), pure ground-glass haze in 13 (14.4%), crazy paving in 4 (4.4%), fuzzy bands and arcades in 7 (7.8%), and subtle gravitational GGH in 3 (3.3%) patients. CT-SS classified 69 (76.7%) patients as mild, 10 (11.1%) as moderate and 4 (4.4%) as severe disease.

Conclusions: HRCT with CTSS is an important tool for diagnosing and prognosticating COVID-19 infection despite negative RT-PCR, timely identifying and isolating COVID-19 cohorts preventing cross-infection and also aiding in prompt symptomatic management.

Keywords: COVID-19, computed tomography, RT-PCR, cross-infection, CT-SS.

Introduction

Coronavirus pandemic has caused turmoil all over the world causing disastrous effects worldwide. COVID-19 has various clinical presentations and radiologically it has a typical appearance according to which it could be classified as classic, probable, intermediate and Non-COVID-19.[1] Despite efforts from national disaster management to provide faster and accurate RT-PCR testing, the literature suggests the sensitivity of diagnosis of COVID-19 infection by RT-PCR assays is 60% and by HRCT 93%.[2] Performing CT for sick patients with negative COVID-19 RT-PCR became essential to triage patients to the COVID-19 unit. A standard protocol was decided to perform CT of only those patients who had negative RT-PCR test and utilizing the use of CT in the rapid triage for effective timely identification of COVID-19 cohorts. It also meant that if CT is typical, the RT-PCR test will need to be repeated, thus preventing clinicians to discharge patients labelling them as COVID-19 negative. The rationale of our study is to recognize the typical and classic features of COVID-19 on HRCT despite negative RT-PCR assay so these patients could be isolated timely to prevent cross-infection and also to assess CT severity score (CT-SS) in categorizing the disease into mild, moderate and severe so they can be managed accordingly. The study is an effort to analyze the radiological spectrum of HRCT in COVID-19 patients, clinically symptomatic but initially having negative RT-PCR

Materials and Methods

A prospective descriptive study was conducted after approval from institutional review board Rawalpindi Medical University, on 90 patients selected by non-probability convenient sampling, from June to November 2020, in Radiology and Medicine Department, District Head Quarters Hospital Rawalpindi who had presented with classical clinical symptoms of COVID-19 infection but their polymerase chain reaction (PCR) for COVID-19 was negative. All these patients underwent high resolution computed tomography (HRCT) of the chest by Toshiba Aquilion 16 slice CT scanner with 120 kVp, 100 to 200 mAs, 350 mm FOV and a slice thickness of 0.6-1.25 mm. For each patient HRCT was evaluated for features of COVID-19 ground-glass haze, consolidation, crazy paving, nodules, cavitations, effusions, axial or peripheral distribution of lesions, lobes involved) and then these patients were classified according to the British Society of Thoracic Imaging (BSTI) Classification of COVID-19 as Classic COVID-19 (100% confidence for COVID-19) if there was lower lobe predominant, peripheral, multiple, bilateral foci of ground glass haze ± Crazy-paving, peripheral consolidation with or without air bronchograms or reverse halo/ perilobular pattern. They were classified as Probable COVID-19 (71-99% confidence for COVID-19) if lower lobe predominant, the mix of bronchocentric and peripheral consolidation, reverse halo/ perilobular pattern and GGO scarce was observed. If the clinical context is wrong or suggests an alternative diagnosis (e.g. an interstitial lung disease in a connective tissue disease setting) or HRCT showing lobar pneumonia, cavitating infections, tree-in bud/ centrilobular nodules, lymphadenopathy, effusions, established pulmonary fibrosis, then the patient was labelled as non-COVID-19 and was excluded from the study. If the patient did not fit into the classic or probable or non-COVID-19 category, then they were classified as indeterminate COVID-19 (< 70% confidence for COVID-19). A repeat PCR test or serology was sent of all these patients for laboratory confirmation of infection with Covid-19. [1] A CT severity score (CT-SS) of all these patients was also calculated by adding up individual scores from 20 regions of both lungs based on the extent of involvement of each of these lung regions, score assigned 0, 1, or 2 respectively if 0%, less than 50% or more than 50% involvement, score ranging from 0-40.[3] All patients were followed up after 6 weeks for any residual symptoms. Age, co-morbids, symptoms were analyzed as frequencies and percentages. HRCT findings were categorized according to BSTI classification and a CT-SS was assigned. The data was collected with the help of a proforma and was recorded in a Microsoft office excel worksheet.

Results

A total of 90 cohorts, 35 (38.9%) were females and 55 (61.1%) were males. The mean age of patients was calculated to be 45.06 (range 23-95 years). Most of the patients that is 57 (63.3%) presented with mixed symptomology of cough, shortness of breath, body aches, GI disturbances or altered consciousness with or without fever. Fever was the only presenting complaint in 13 (14.4%) patients, shortness of breath was the only symptom in 7 (7.8%) patients, 9 (10%) patients presented with a cough only, 2 (2.2%) patients complained of body aches, 1(1.1%) patient presented

with chest tightness and 1 (1.1%) patient presented with diarrhoea.

Out of these 90 symptomatic and RT-PCR negative patients, 7 had normal chest CT but they underwent a repeat RT-PCR test due to strong clinical suspicion and all of them were confirmed as COVID-19 infected on subsequent RT- PCR test. HRCT of 50 patients showed classic BSTI COVID-19 features. 11 patients had probable BSTI COVID-19. Indeterminate BSTI features were seen in 22 patients. Unilateral lung parenchymal involvement was seen in 8 (8.9%) patients in contrast to 75 (83.3%) patients who had bilateral involvement. A mixed pattern of multilobular, peripherally located, bronchocentric ground-glass nodules (Figure 1a), bands or nodular consolidates (Figure 1b) was seen in 37 (41.1%) patients, 19 (21.1%) patients developed consolidations as predominant finding, 13 (14.4%) patients showed peripherally distributed pure ground-glass haze only. Crazy paving (Figure 1c) was seen in 4 (4.4%) patients. Fuzzy arcades and subpleural bands (Figure 2a) were observed in 7 (7.8%) patients and 3 (3.3%) patients showed indeterminate features of subtle ground-glass haze in gravitational distribution with classical vascular prominence. Vascular prominence was seen in relation to lung parenchymal abnormality almost in all patients (Figure 3a). In addition to these features, we also observed bronchioloectasis along with ground glass haze (Figure 2b and 2c) in 7 patients. 2 patients had pre-existing interstitial disease and 2 patients had previous changes of tuberculosis infection. We had only 1 case with a reverse halo sign (Figure 3b). 2 patients developed pleural effusion. None of the patients showed enlarged lymph nodes but sub centimetre mediastinal lymph nodes were seen in all the patients. Results are summarized in Table 1.

Table 1: Characteristics of COVID-19 on High-Resolution CT Chest

CHARACTERISTIC			*NO. OF PATIENTS (N=90)*
Age (years)	Mean with SD	45.056 +/- 11.97	
	Range	23-95	
Gender	Male		35 (38.9%)
	Female		55 (61.1%)
Symptoms	Mixed symptoms		57 (63.3%)
	Fever only		13 (14.4%)
	Shortness of breath only		7 (7.8%)
	Cough only		9 (10%)
	Body aches only		2 (2.2%)
	Chest tightness only		1 (1.1%)
	Diarrhea only		1 (1.1%)
Imaging Characteristics			
Laterality	Normal		7 (7.8%)
	Bilateral		75 (83.3%)
	Unilateral		8 (8.9%)
Lung Parenchymal Pattern According to BSTI	Normal		7 (7.8%)
	Classic		50 (55.6%)
	Probable		11 (12.2%)
	Indeterminate		22 (24.4%)
Lung parenchymal Patterns	Normal		7 (7.8%)
	Mixed GGN and consolidates		37 (41.1%)
	Pure Consolidations		19 (21.1%)
	Pure Ground glass haze		13 (14.4%)
	Fuzzy Bands		7 (7.8%)
	GGH with crazy paving		4 (4.4%)
	Gravitational ground-glass haze		3 (3.3%)
	Vascular Prominence		83 (92.2%)
	Bronchioloectasis		7 (7.8%)
Additional Imaging Features	Reverse halo		1 (1.1%)
	Pre existing ILD		2 (2.2%)

	Pre-existing Tuberculosis		2 (2.2%)		
	Pleural effusion		2 (2.2%)		
	Lymphadenopathy		0		
CT Severity Score			**Clinical Outcome**		
			Recovered	Residual Disease	Died
	Normal	7 (7.8%)	7	0	0
	Mild	69 (76.7%)	62	7	0
	Moderate	10 (11.1%)	5	4	1
	Severe	4 (4.4%)	0	2	2

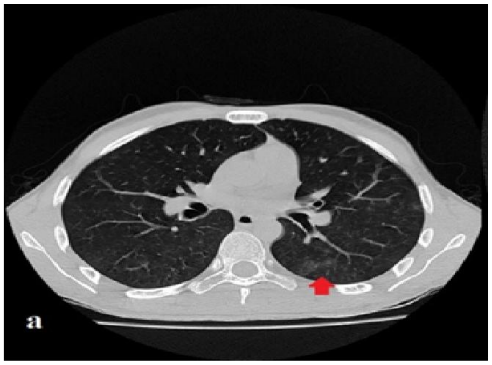

Figure 1a: Subtle bronchocentric ground-glass nodules (arrow)

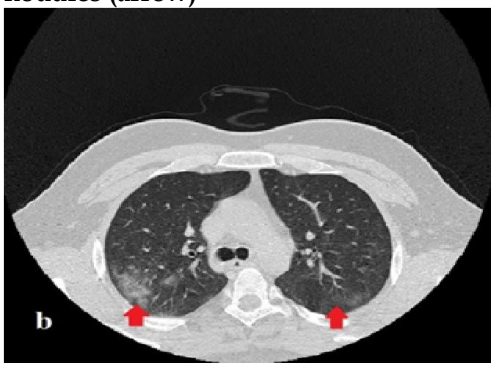

Figure 1b: Bronchocentric ground glass nodules and nodular consolidates (arrows)

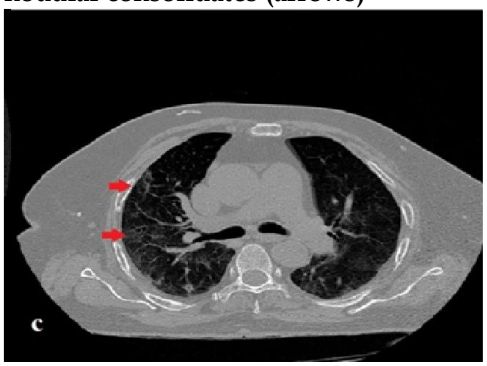

Figure 1c: Crazy paving with ground glass haze

Figure 2a: Fuzzy arcades and subpleural bands (arrow)

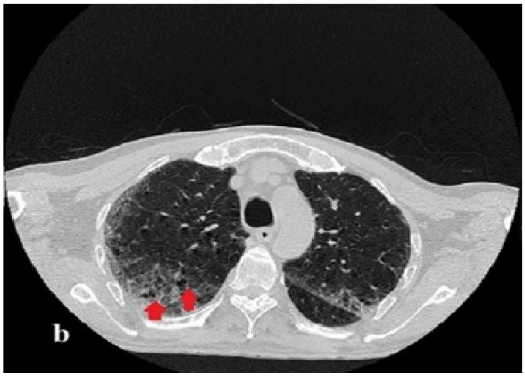

Figure 2b: Ground glass haze with bronchioloectasis (arrows)

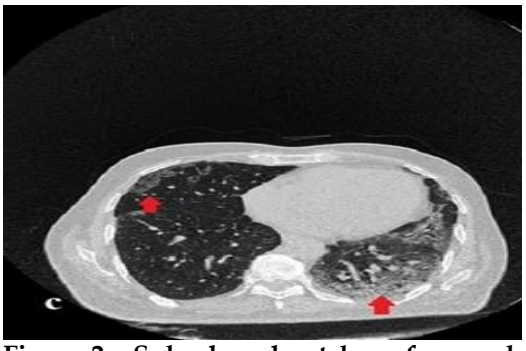

Figure 2c: Sub pleural patches of ground glass haze and bronchioloectasis (arrows)

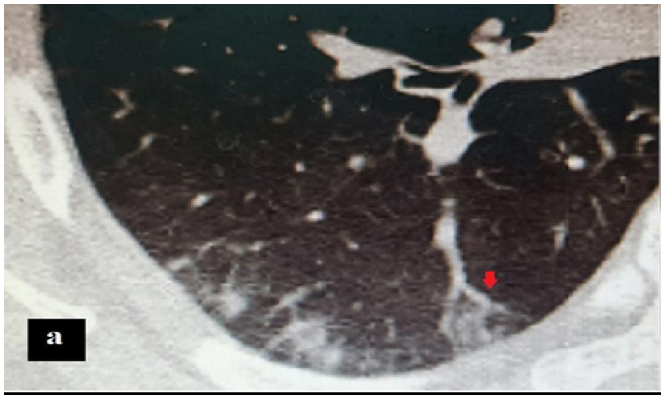

Figure 3a: Peripheral nodule with vessel prominence (arrow)

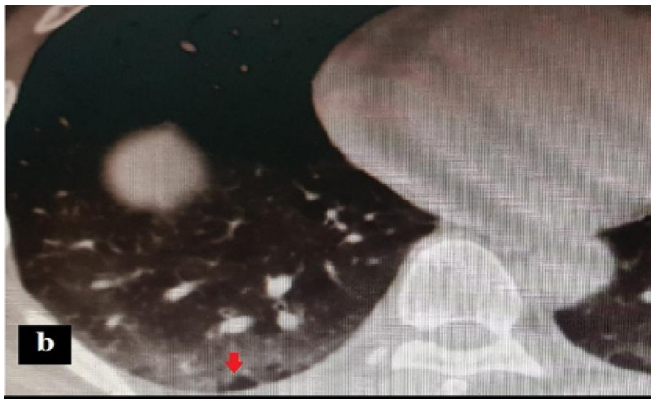

Figure 3b: Subtle haze peripherally and gravitational distribution with reverse halo (arrows)

All these patients initially RT-PCR negative, diagnosed as COVID-19 by HRCT were then retested for laboratory diagnosis, and there were 17 (18.89%) patients who had persistent negative RT-PCR tests on subsequent testing, despite supportive CT features and classic clinical features. The rest of the patients on subsequent testing either showed positive antibody titre or 1st or 2nd subsequent positive RT-PCR.

We also categorized patients according to CT severity score and followed them up after 4 weeks. We observed 69 (76.7%) patients had mild having CT severity score up to 20/40, 2 of them died, 5 had mild residual cough and breathlessness and the rest of them recovered uneventfully on follow up. Ten (11.1%) patients had moderate disease, having CTSS from 21 to 30/40 and amongst them, 4 had mild residual shortness of breath and 1 of them died. Four (4.4%) patients had severe disease having CTSS more than 30/40, amongst them 2 died, and 2 had severe oxygen-dependent breathlessness, as summarised in Figure 4.

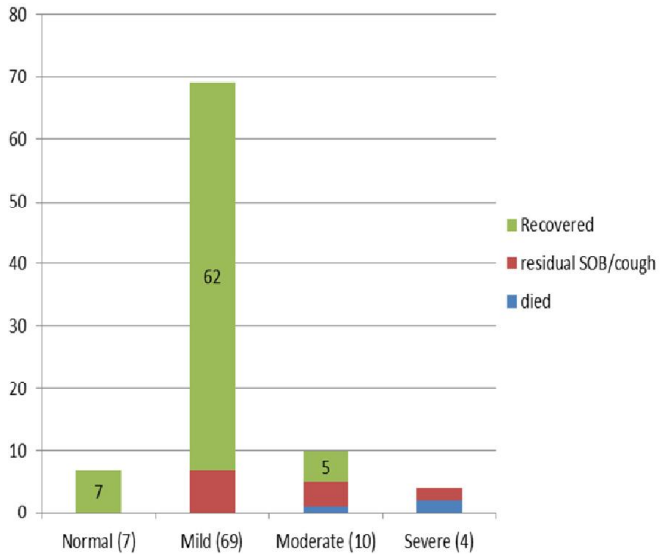

Figure 4: Disease severity and patient prognosis according to CT severity score (CT-SS)

Discussion

The current study showed 17 (18.9%) patients having false negative RT-PCR with findings on HRCT. Recent various studies suggest relatively low efficiency of RT-PCR as compared to HRCT. Inadequate or inappropriate sampling, low viral load in patients or viral mutations are few reasons contributing to the low efficiency of PCR test. Fang et al reported higher sensitivity of chest CT (98%) as compared to RT-PCR (71%).[4] Ai et al reported that 97% of RT-PCR positive patients show positive findings on the chest. [2] A study by Italian researchers evaluated 158 patients and found HRCT to be 97% sensitive.[5] Similarly Dangis et al conducted a study in Belgium and found the sensitivity of CT to be around 87%.[6] In RT-PCR negative patients HRCT is a rapid and reliable diagnostic modality to identify and quarantine Covid-19 cohorts compared to serological tests which are more accurate if samples are assessed 20 days after the first symptom.[7] In Pakistan we also experienced numerous symptomatic patients with repetitive negative RT-PCR which posed a clinical concern not just regarding their clinical treatment but also triaging them to Covid-19 isolations and quarantine. Various international imaging societies including the American College of Radiology, the British Society of Thoracic Imaging, the Fleischner Society and others, recommend the use of CT not only to evaluate and prognosticate RT-PCR confirmed Covid-19 patients but also to diagnose patients of COVID disease.[8,9,10] Radiology society of Pakistan also fully endorsed

international societies and proposed CT as a diagnostic tool for COVID-19.[11]

In our study, we also evaluated different spectrums of COVID-19 infection. We observed a mixed pattern of peripherally distributed ground-glass nodules (GGN) and bronchocentric nodules was the most common parenchymal feature, seen in 41.1% of patients. Patients showing GGN were those who presented early in the course of the disease and these patients also showed relatively lower CT-SS. Consolidations were seen as a predominant finding in 21.1% of patients and these patients were those who presented late with higher severity scores. 14.4% of patients had pure classical GGH. This is comparable to a recent study by Parry et al which demonstrated a mixed pattern in 41.2%, and pure GGH in 29%.[12] A local study by Khaliq et al, found a predominant ground-glass pattern in 88% and predominant consolidations in 52% of patients.[13] A study by Zhou et al showed reverse halo in 4% of patients whereas we just had 1.1 %.[14] Patients with unilateral lung involvement were seen less frequently in our study, only in 8.9% of cases as compared to 83.3 % of cases bilaterally and previous studies also supported that bilateral involvement is more common.[12, 13]

There were a few limitations in our study. Firstly the study was conducted in a public sector hospital of a developing country and a dedicated CT machine was not available for COVID-19 patients hence a standard protocol was followed to evaluate only those patients on CT who were clinical COVID-19 suspects with negative RT-PCR and needed a diagnosis. This not only created a selection bias but also CT features of RT-PCR negative patients was not compared with RT-PCR positive patients. Secondly, our sample size was also small as our study required subsequent serological or PCR confirmation and some patients were lost to follow up. Thirdly we didn't compare and correlated CT features and CT-SS with inflammatory markers which are in plan for future study.

Conclusion

It is concluded that CT has typical features of COVID-19 on HRCT and it is an important tool for diagnosing COVID-19 infection despite negative COVID-19 RT-PCR assay so these patients could be isolated timely to prevent cross-infection. Furthermore, CT severity score (CT-SS) helps in prognosticating patients and categorises disease into mild, moderate and severe, aiding clinicians for appropriate treatment.

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