

**A STUDY OF REVERSE TRANSCRIPTASE-POLYMERASE CHAIN REACTION  
NEGATIVE COVID-19 CASES IN A RURAL TERTIARY HEALTH CARE CENTRE****<sup>1</sup>Taseena Banu R., <sup>2</sup>Chandrashekar T. V., <sup>3\*</sup>Vasantha Kamath, <sup>4</sup>M. J. Jacob and <sup>5</sup>Dharani Mohan**<sup>1,2</sup>Post-Graduate, Department of General Medicine, M.V.J Medical College & Research Hospital, Bangalore.<sup>3</sup>Senior Professor, Department of General Medicine, M.V.J Medical College & Research Hospital, Bangalore.<sup>4</sup>Professor and Head, Department of General Medicine, M.V.J Medical College & Research Hospital, Bangalore.<sup>5</sup>Chief executive Officer, M.V.J Medical College & Research hospital, Bangalore.**\*Corresponding Author: Vasantha Kamath**

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**ABSTRACT**

**Introduction:** It is reported that many 'suspected' cases with typical clinical characteristics of COVID-19 and specific computed tomography (CT) images went undetected by RT-PCR. Our study aims to review the clinical features, laboratory test, radiological results, complications, and management of such patients who are clinical COVID but RT-PCR negative. **Methodology:** It is a descriptive study of RT-PCR negative COVID-19 patients done in a rural tertiary care hospital, Hoskote, Karnataka for a period of 6 months. Out of 1807 who presented with clinical suspicion of COVID-19, 1754 tested positive and 53 patients whose nasopharyngeal swab tested negative for RT-PCR were included in the study. **Result:** Out of 53 patients, median age of patients was 49 years, 31(58.49%) were males and 22 (41.51%) females. Most were in the age group <40years (41.51%). Most common clinical symptom noted in our study was myalgia, productive cough, breathlessness. Diabetes Mellitus (26.42%) was the most common comorbidity in our study. Fatality was seen in 8 cases with a case fatality rate of 15%. **Conclusion:** In patients presenting with clinical symptoms of Covid but with a negative RT-PCR, the diagnosis must not only rely on RT-PCR test results but on the clinical suspicion and on the findings from other tests, most notably chest CT and elevated inflammatory markers.

**KEYWORDS:** RT-PCR swab negative COVID-19, clinical suspicion, Inflammatory markers, CT thorax.**INTRODUCTION**

RT-PCR method is considered as the 'gold standard' for the detection of corona virus with high sensitivity (68-80%), and specificity (90-95%).<sup>[1,7]</sup> An important issue with the RT-PCR test is the risk of eliciting false-negative (33%-40%) and false-positive results. It is reported that many 'suspected' cases with typical clinical characteristics of COVID-19 and specific computed tomography (CT) images went undetected by RT-PCR.<sup>[2]</sup> Even rigorous RT-PCR testing protocols might miss a substantial proportion of SARS-CoV-2 infections, perhaps in part due to difficulties in determining the timing of testing, choice of specimen with respect to viral load kinetics and dynamic genetic variability of the virus per se and its discordance with the primers used for testing. Here we have studied RT-PCR negative covid patients regarding the age, symptoms, investigations, treatment, and outcome.

**MATERIALS AND METHODS**

It is a descriptive study of RT-PCR negative COVID-19 patients done in a rural tertiary care hospital, Hoskote, Karnataka for a period of 6 months.

Out of 1807 who presented with clinical suspicion of COVID-19, 1754 tested positive and 53 patients whose nasopharyngeal swab tested negative for RT-PCR were included in the study.

We defined swab-negative clinical COVID-19 cases as follows: (a) clinical COVID-19 as defined by WHO clinical criteria<sup>[17]</sup> for a suspected case that is acute onset of fever and cough or acute onset of any three or more of the following signs or symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnoea, anorexia/nausea/vomiting, diarrhoea, altered mental status (b) RT-PCR swab-negative.

We defined eligible cases as those who presented with clinical suspicion of COVID-19 or had symptoms compatible with COVID-19, were admitted to hospital and had a SARS-CoV-2 nasopharyngeal swab performed. We collected full demographic characteristics, time course of symptoms, time of presentation and testing, presenting symptoms, final diagnosis, and outcome as well as radiological and laboratory findings for all patients with a negative swab from admission until discharge.

The study cohort of 53 were categorized into Mild, Moderate, and Severe as per the Ministry of Health and Family Welfare guidelines for management of COVID-19. Mild case is defined as those with SpO<sub>2</sub> above 95% and Respiratory rate of <24cpm; Moderate case is defined by SpO<sub>2</sub> between 91-94% and Respiratory rate between 24-30cpm; Severe case is the one with SpO<sub>2</sub> of <90% and Respiratory rate of >30cpm.<sup>[7]</sup>

females. 28(52.83%) of them belonged to a rural demography and the other 25(47.16%) hailed from urban areas. Most were in the age group <40years (41.51%). These patients were categorised as mild, moderate, and severe as per MOHFW based on their respiratory rate and oxygen saturation at presentation. [TABLE 1]

## RESULTS

### Patient Characteristics

Our study cohort had 53 patients, median age of patients was 49 years, 31(58.49%) were males and 22(41.51%)

**Table 1: SEVERITY DISTRIBUTION-Gender and age wise.**

Age group	Male N=31			Female N=22		
	18-40 years (15)	40-60 years (7)	>60 years (9)	18-40 years (7)	40-60 years (6)	>60 years (9)
MILD (10)	3	1	1	2	2	1
MODERATE (18)	6	3	3	1	2	3
SEVERE (25)	6	3	5	4	2	5

### Clinical presentation

#### Median time since symptom onset was 5 days.

Clinical symptoms included fever in 58.39%, arthralgia in 54.96%, myalgia in 83.01%, 18.86% had rhinorrhoea, sore throat was seen in 16.98%, throat pain in 22.64%, dry cough in 47.17%, productive cough in 67.92% and breathlessness in 60.37%, loss of smell in 28.3%, loss or change in taste in 60.37% [TABLE 2]

Clinical signs included temperature >100 F in 67.93%, tachycardia in 60.37%, bradycardia in 13.20% and hypotension in 28.30%. Oxygen saturation >95% and respiratory rate <24cpm in 18.8%, Spo<sub>2</sub> between 90-95% and respiratory rate 25-30cpm in 33.9% and Spo<sub>2</sub> <90% with respiratory rate >30cpm in 47.1%.

**Table 2: Clinical Symptoms and Their Percentages of Occurrence.**

	CLINICAL SYMPTOMS	%Of symptoms N=53	Mild (10)	Moderate (18)	Severe (25)
Constitutional symptoms	Fever	58.49%	10	15	6
	Myalgia	83.01%	9	16	19
	Arthralgia	54.96%	8	13	18
Respiratory symptoms	Rhinorrhoea	18.86%	4	3	3
	Sore throat	16.98%	5	2	2
	Throat pain	22.64%	5	3	4
	Dry cough	47.17%	2	6	17
	Productive cough	67.92%	4	9	23
	dyspnoea	60.37%	0	11	21
	Haemoptysis	3.77%	0	0	2
Gastrointestinal symptoms	Nausea	41.51%	8	8	6
	Vomiting	28.30%	3	5	7
	Pain abdomen	20.75%	1	2	8
	Anorexia	28.30%	8	12	17
Neurological symptoms	Loss of smell	28.30%	6	5	4
	Loss of taste/change in taste	60.37%	7	13	12

### Comorbidity distribution and severity of disease

Various comorbidities such as Diabetes Mellitus (26.42%), Systemic Hypertension (18.87%), Dyslipidaemia (15.09%), Ischaemic heart disease (13.2%), chronic kidney disease (5.66%), Chronic liver disease (1.89%), Chronic obstructive pulmonary disease (18.87%), Bronchial asthma (9.43%), Tobacco smoking (22.64%), Alcohol consumption (15.09%), Obesity

(28.3%) were found in the study group in variable percentages. It was found that severity of disease was much more in those with comorbidities predominantly diabetes, obesity, tobacco smoking, systemic hypertension, COPD, dyslipidaemia, alcohol consumption.

Fatality occurred in 8 cases of which 2 were from moderate category and were obese and among the 6 severe cases who succumbed 3 were diabetic, hypertensive and dyslipidaemia, 2 were known cases of

COPD and the other was a known case of chronic kidney disease.

**Table 3: Comorbidity Distribution And Association With The Severity Of Disease.**

COMORBIDITIES/RISK FACTORS	MILD (10)	MODERATE (18)	SEVERE (25)
Diabetes mellitus	1	5	8
Systemic hypertension	1	2	7
Diabetes mellitus and systemic hypertension	1	3	4
Dyslipidaemia	1	2	5
Ischaemic heart disease	0	3	4
Chronic kidney disease	0	1	2
Chronic liver disease	0	0	1
COPD	0	4	6
Bronchial asthma	0	2	3
Tobacco smoking	0	5	7
Alcohol consumption	0	3	5
Obesity	2	5	8

#### Laboratory parameters

Haematological parameters showed leukopenia in 16.98% and leucocytosis in 28.30%, neutrophilia in 94.33%, lymphopenia in 92.45%, NLR ratio >3.3 in 94.33%, thrombocytopenia in 24.53%, thrombocytosis in 7.54%. 69.81% patients had deranged RFT, 50.3% had

altered LFT. Coagulopathy was seen in 15.09%. Inflammatory markers ESR, CRP, LDH, Serum Ferritin, D-dimer were elevated in all 53 patients in variable ranges and correlating with the severity of disease. [TABLE 4]

**Table 4: Laboratory Findings.**

		% Of cases n=53	MILD (10)	MODERATE (18)	SEVERE (25)
Lymphocytes	lymphopenia	92.45%	10	16	23
NLR	>3.3	94.33%	10	17	23
PLT	<1.5lakh	24.53%	3	5	5
	1.5-4 lakh	67.92%	7	13	16
	>4 lakh	7.54%	0	0	4
Renal function test	Altered	69.81%	10	13	14
Liver function test	Altered	49.01%	3	7	16
		50.94%	3	8	16
ESR	<20mm/hr	5.66%	2	1	0
	>20mm/hr	94.34%	8	17	25
CRP	6-20mg/dl	22.64%	10	2	0
	20-50mg/dl	28.30%	0	15	0
	>50mg/dl	49.05%	0	1	25
LDH	<300mg/dl	20.75%	8	3	0
	300-400mg/dl	32.07%	2	13	2
	>400mg/dl	49.05%	0	3	23
D-DIMER	<500mg/dl	20.75%	9	2	0
	500-1000	35.85%	1	15	3
	>1000	43.4%	0	1	22
SR. FERRITIN	<500	22.64%	8	3	1
	>500mcg/dl	33.96%	2	13	3
	>800	43.39%	0	2	21

#### Radiological findings

Chest radiograms were normal in 5.66% of mild cases; peripheral opacities were seen in 37.73% in 7 mild cases,

11 moderate cases and 2 of severe category cases; bilateral basal zone opacities were seen in 24.53% that is in 6 moderate cases and 7 severe cases; diffuse non

homogenous opacities were seen in 32.7% that is in 1 moderate case and 16 severe cases.

On HRCT chest all 53 patients were designated as CORADS 5 and CT severity score ranged between 1-10 in 80% of mild clinical category; Score ranged 10-15 in 20% of mild category, 77.78% of moderate category and

24% of severe category. Score between 15-25 was seen in 22.22% of moderate category and 76% of severe category. [TABLE 5]

Severe cases had severe CT-score and bilateral opacities on chest radiogram.

**Table 5-Radiological findings.**

Chest x-ray findings		Normal	Lobar opacity	Peripheral opacifications	Basal zone opacities	Diffuse non-homogenous opacities
% Of cases	N=53	5.66%	0%	37.73%	24.53%	32.07%
MILD (10)	10	3	0	7	0	0
MODERATE (18)	18	0	0	11	6	1
SEVERE (25)	25	0	0	2	7	16

CT SEVERITY SCORE	1-10	11-15	15-25
MILD	8	2	0
MODERATE	0	14	4
SEVERE	0	6	19

### ECG Findings

Out of 53 patients, sinus tachycardia was seen in 43 of them despite a normal haemoglobin, sinus bradycardia in 8 and 2 patients had STEMI associated with positive cardiac markers i, e troponin I.

Among 53 patients, who were RT-PCR negative COVID-19, fatality was seen in 8 patients with a case fatality rate of 15%. Out of 8 patients who succumbed, 5 were males and 3 were females. Youngest and oldest was 38years and 68years, respectively. Among 8 patients who succumbed, all had comorbidities, 6 belonged to the severe category and 2 from moderate category. The most common comorbidity associated was Diabetes Mellitus, systemic hypertension and dyslipidaemia followed by obesity. The most common cause of death was ARDS, followed by ACS.

### DISCUSSION

When the COVID-19 pandemic began, Real time reverse-transcriptase polymerase chain reaction (Rt-PCR) test was the first to be developed and widely deployed, and it remained the primary tool used for diagnosis of COVID-19. A Rt-PCR assay uses RNA for in vitro nucleic acid amplification and utilizes reverse transcriptase, an RNA dependent DNA polymerase that catalyses DNA synthesis using RNA as template producing a more stable end product known as complementary DNA (c DNA) which acts as a template for ds DNA synthesis and PCR amplification. SARS-CoV-2 RT-PCR thus detects viral RNA; a positive result is highly specific for the presence of the virus. The sensitivity of these tests is not uniform, and is affected not only by the assay itself, but also the limit of detection, viral inoculum, viral dynamics that differ in different anatomic sites of the patients throughout the natural history of COVID-19, like RT-PCR for SARS-

COV 2 is positive when tested in throat/nasal swab during the 1<sup>st</sup> week of symptom onset as maximum viral shedding occurs in the upper respiratory tract during this period. It is negative when it involves lower respiratory tract and causes pneumonia when it is advisable to do RT-PCR of sputum or Broncho- Alveolar Lavage Fluid.<sup>[5, 6]</sup> While BAL provides the optimal material in terms of testing sensitivity (93%), the nasopharyngeal swab is considered the sample of choice in the everyday clinical practice (63% sensitivity).<sup>[8,9]</sup>

Genetic diversity and rapid evolution of this novel coronavirus have been observed in different studies and it is well known that results from real-time RT-PCR using primers in different genes can be affected by the variation of viral RNA sequences.<sup>[3,4]</sup> False-negative results may occur by mutations in the primer and probe target regions in the SARS-CoV-2 genome, these variants are termed the “escape variants”.

RT-PCR is false negative in 33%–40% of COVID patients, and CT chest shows abnormalities among 40%–50% of such cases. CT chest shows significant changes in 55%–60% of patients with no symptoms, also patients with positive RT-PCR can show normal CT chest in 12%–15% of patients. However, it is positive in 85%–90% of patients with positive PCR.<sup>[11]</sup> Hence, the diagnostic accuracy of Rt-PCR upper respiratory tract swabs is increasingly being questioned. Maximum viral shedding occurs just before and up to one week after the symptom onset. Repeat RT-PCR testing can serve to widen the window of opportunity for detecting viral shedding and minimize suboptimal sample collection. Hence, early sampling minimizes false-negative results. Beyond 10 days of symptoms, Rt-PCR should be tested on sputum and bronchoalveolar lavage.<sup>[11, 13]</sup>

Previously WHO defined a confirmed case as a person with laboratory confirmation of COVID-19 infection and cases where laboratory confirmation is not done or inconclusive were recognized as probable cases however those with strong clinical features, but negative testing was not recognized. Recent changes to WHO case

definitions now allow probable cases to include patients who meet clinical and epidemiological criteria or patients with severe acute respiratory illness who have typical chest imaging features or unexplained anosmia or ageusia and do not stipulate the results of any performed laboratory testing.

Acknowledging this, some patients with strong features of COVID-19 receive a clinical diagnosis of COVID-19 despite a negative swab result. This clinical approach is being further recognized in the admission criteria of some clinical trials who permit recruitment of these patients<sup>10</sup>. For example in the recently reported RECOVERY trial 10% of those randomized to dexamethasone had a negative swab at the time of randomization.<sup>[19]</sup>

Wang et al. recently examined 1070 specimens collected from 205 patients with COVID-19. In his study, bronchoalveolar lavage fluid guaranteed the highest positive rate (93.3%), followed by sputum (72.1%), nasal swabs (62.5%), in contrast to our study where all samples were from nasopharynx and oropharynx.<sup>[10]</sup>

There have been a few publications in which the RT-PCR negative COVID-19 cases, have been studied, for example Di Paolo et al<sup>[14]</sup> studied 16 such COVID cases where the median age was 59.2 years, 68.75% were males and 31.25% were females in comparison to our study which included 53 (out of 1087 patients), with a median age being 49 years, 58.49% were males and 41.51% were females.

In their study the severity of the disease on admission was mild in 71.05%, moderate in 21.05% and severe in 7.89% of the cases respectively whereas in our study 18.86% patients were mild, 33.96% were moderate and 47.17% cases were severe. 63.15% sought medical care after 6 or more days with symptoms in contrast to our study time between onset of symptoms and presentation to health facility was 5 days.

In a similar study, fever and dyspnoea were the most predominant symptoms found in 87.5% patients, followed by cough in 43.7% and Gastrointestinal symptoms in 12.5% patients, respectively. Whereas in our study, myalgia (83.01%), cough (67.92%) and dyspnoea (60.37%), gastrointestinal manifestations were seen in 41.5% were the most common symptoms.

In a recent study<sup>[15]</sup> Diabetes Mellitus was found to be the most common comorbidity (34.21%) associated with RT-PCR negative COVID-19 patients, whereas our study which had obesity in 28.3% followed by diabetes in 26.42%.

Mean duration of hospital stay in our study was 25 days.

In a study done by Paolo SRC et al<sup>[15]</sup> in Mexico, all patients with COVID like symptoms but RT-PCR

negative had characteristic lymphopenia, significantly increased NLR, and elevated inflammatory markers similar to our study. In addition, our study also reported thrombocytopenia in 24.53% patients without bleeding manifestations, altered RFT and LFT in 69.81% and 50.3% patients, respectively.

In a multicentre case control study conducted in France<sup>[16]</sup> Chest radiographs showed bilateral patchy opacities in 12 patients, interstitial abnormalities in 7, ground-glass opacities in 4, local patchy opacities in 1, and normal chest x-ray in 1 patient. CT scan of the chest was obtained in 75 cases, 69 among them showed ground-glass opacities; interstitial abnormalities were seen in 4 patients, and the results were normal in 1 patient, when compared to our study chest radiograph was normal in 5.66% of mild cases; Bilateral peripheral opacities were seen in 37.73% among 7 mild cases, 11 moderate cases and 2 severe category cases; bilateral basal zone opacities were seen in 24.53% that is in 6 moderate cases and 7 severe cases; diffuse non-homogenous opacities were seen in 32.7% that is in 1 moderate case and 16 severe cases. On HRCT chest all 53 patients were designated as CORADS 5 and CT severity scores ranged between 1-10 in 80% of mild category; score between 10-15 in 20% of mild category, 77.78% of moderate category and 24% of severe category; score between 15-25 in 22.22% of moderate category and 76% of severe category, respectively. Another study utilizing both chest computerized tomography imaging (CT) and RT-PCR testing in patients with suspected COVID-19 found 75% of cases with a negative RT-PCR test had CT findings suggestive of COVID-19.<sup>[18]</sup>

In a recent study<sup>[20]</sup>, Oxygen supplementation was required in 46.8% in the form of mechanical ventilation in 13.8% and inhalational oxygen in 33% and 53.2% did not require oxygen supplementation. Whereas in our study oxygen supplementation was required in 81.13%, High flow nasal oxygen in 9.43%, non-invasive ventilation in 30.8% and invasive ventilation in 7.54% patients, respectively.

Our study witnessed, recovery in 84.9% and fatality in 15% patients in comparison to the above study where the registered mortality was 16%.<sup>[20]</sup>

## CONCLUSION

When a patient presents with typical symptoms of Covid with a negative RT-PCR we have to consider them like Covid-19 as the outcomes of these patients did not differ from rest of the COVID-19 population since they shared similar characteristics like lymphopenia, raised NLR, elevation of inflammatory markers as well as a tomographic COVID-19 score of severe illness, however we suggest that the Patients with a first negative RT-PCR test for COVID-19, the diagnosis must rest not only on RT-PCR test results but also on the clinical presentation



and on the findings from other tests, most notably chest CT and elevated inflammatory markers.

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