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Research Article

A STUDY OF RT-PCR NEGATIVE COVID-19 CASES IN A TERTIARY RURAL HEALTH CARE CENTRE

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ABSTRACT

Introduction: Reports say that many "suspected" cases with archetypal clinical characteristics of COVID-19 and characteristic computed tomography (CT) images went undetected by RT-PCR due to late testing, escape variants and lack of sputum samples through BAL . This study directs to assess the clinical features, laboratory tests, radiological results, complications, and management of these patients who are COVID cases clinically but were 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 9 months. A total of 2281 cases who presented with COVID-19 symptoms were included in this study, out of which 2204 were tested positive and 77 patients were tested negative for COVID.

Result: Out of these 77 patients, 46(59.74%) were males, and 31(40.25%) were females and the mean average age was 46years. Most were in the age group of less than 40 years. The most frequent clinical symptoms noted in our study were myalgia, productive cough, breathlessness, Diabetes mellitus (27.27%) being the most common co-morbidity with a fatality rate of 12.98%.**Conclusion:** In patients presenting with clinical symptoms of COVID-19 but with a negative RT-PCR, the diagnosis must rely not only on RT-PCR test results but also on the clinical findings of chest CT and elevated inflammatory markers, and such patients need to be treated with standard COVID-19 protocol.

INTRODUCTION

The RT-PCR method is considered the 'gold standard for detecting coronavirus with high sensitivity (68-80%) and specificity (90-95%). [1,2] An important matter in question with the RT-PCR test is the risk of eliciting false-negative (33%–40%) and false-positive results[1]. 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.[3] Even meticulous RT-PCR testing protocols might miss a considerable proportion of SARS-CoV-2 infections, perhaps in part due to difficulties in determining the timing of testing, choice of the specimen concerning 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-19 patients concerning clinical spectrum, laboratory parameters, radiological features, severity distribution, and outcome.

Aims and Objectives

1. To study the clinical spectrum of RT-PCR negative COVID cases.
2. To show the biochemical and radiological correlation to the disease severity in RT-PCR negative COVID cases.

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 9 months.

Out of 2281 patients presenting with clinical suspicion of COVID-19, 2204 tested positive and 77 patients that tested negative for nasopharyngeal swab 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 [4] 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, diarrhea, altered mental status (b) RT-PCR swab-negative (c) Raised inflammatory markers ESR, CRP, D-dimer, Serum Ferritin, LDH. (d)HRCT thorax showing CORADS 5.

We defined eligible cases as those who presented with clinical suspicion of COVID-19 or had symptoms compatible with

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COVID-19, and were admitted to the hospital and had a SARS-CoV-2 nasopharyngeal swab performed. We collected full demographic characteristics, the 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.[6]

The study cohort of 77 was categorized into Mild, Moderate, and Severe as per the Ministry of Health and Family Welfare guidelines for the management of COVID-19. The mild case is defined as those with SpO2 above 95% and Respiratory rate of < 24cpm; Moderate case is defined by SpO2 between 90-95% and Respiratory rate between 24-30cpm; Severe case is the one with SpO2 of <90% and Respiratory rate of >30cpm. [6,7]

Exclusion criteria: Patients with co-infections such as dengue, malaria, Leptospira, Rickettsial fever, Enteric fever with COVID, Other lung parenchymal infections such as pneumonia due to influenza(flu), measles, interstitial lung diseases, pulomonary edema of cardiac cause that had CORADS <5 on HRCT thorax.

Statistical analysis: Frequency of occurrence of clinical findings, hematological and radiological findings in each category was calculated. Median and interquartile range of age and duration of symptoms was calculated

P value of significance is calculated using chi-square test or t - test wherever applicable.
Institutional ethical committee clearance was taken.

RESULTS

Patient Characteristics

Our study cohort had 77 patients, the median age of patients was 46 years, IQR1 -28 IQR3-63 interquartile range is 35 years, 46(59.74%) were males, and 31(40.25%) were females. 46(58.75%) of them belonged to rural demography and the other 31(40.25%) hailed from urban areas. Most were in the age group of less than 40years (40.26%).

These patients were categorized as mild, moderate, and severe as per MOHFW[6,7] based on their respiratory rate and oxygen saturation at presentation. **[Table 1]**

Statistical analysis was done using the Chi-square test for severity and gender correlation however, the p-value(0.85) was not statistically significant.

The age and severity correlation was also analyzed using the chi-square test and the p-value was 0.49, which is not statistically significant. And the p-value for the occurrence of severe disease in age >61 years was 0.0133.

Clinical presentation

Median time since symptom onset was 6 days.IQR1-5,IQR3-9 and interquartile range is 4. Clinical symptoms included fever in 66.23%, arthralgia in 74.02%, myalgia in 85.71%, 25.97% had rhinorrhoea, sore throat was seen in 25.97%, throat pain in 28.57%, dry cough in 41.55%, productive cough in 71.42% and breathlessness in 61.03%, loss of smell in 28.57%, loss or change in taste in 55.84%

Clinical signs included temperature >100♌F in 54.93%, tachycardia in 72.72%, bradycardia in 14.28% and hypotension in 28.30%. Oxygen saturation >95% and respiratory rate <24cpm in 18.18%, Spo2 between 90-95% and respiratory rate 25-30cpm in 31.16% and Spo2 <90% with respiratory rate >30cpm in 50.64%**.**

Comorbidity distribution and severity of disease

Various comorbidities such as Diabetes Mellitus (27.27%), Systemic Hypertension (20.77%), Dyslipidaemia (16.88%), Ischaemic heart disease (10.38%), chronic kidney disease (3.89%), chronic liver disease (2.59%), Chronic obstructive pulmonary disease (18.18%), Bronchial asthma (7.79%), Tobacco smoking (23.37%), Alcohol consumption (16.88%), Obesity (28.57%) were found in the study group in variable percentages.

Table 1 Severity Distribution-Gender and age-wise.

Gender	Male N=46			Female N=31		
Age group	18-40 years (n-22)	41-60 years (n-12)	>60 years (n-12)	18-40 years (n-9)	41-60 years (n-8)	>60 years (n-14)
Mild	5(22.73%)	1(8.33%)	1(8.33%)	3(33.33%)	2(25%)	2(14.28%)
Moderate	9(40.9%	4(33.33%)	4(25%)	1(11.11%)	3(37.5%)	4(28.57%)
Severe	8(36.36%	7(58.33%)	7(66.67%)	5(55.55%)	3(37.5%)	8(57.14%)

Table 2 CLINICAL SYMPTOMS and their percentages of occurrence

	Clinical symptoms	% of symptoms N= 77	Mild (n-14)	Moderate (n-24)	Severe (n-39)
Constitutional symptoms	Fever	51(66.23%)	14(100%)	21(87.5%)	16(41.02%)
	Myalgia	66(85.71%)	13(92.85%)	22(91.67%)	31(79.48%)
	Arthralgia	59(74.02%)	11(78.57%)	17(70.83%)	31(79.48%)
Respiratory symptoms	Rhinorrhoea	20(25.97%)	6(42.85%)	6(25%)	8(20.51%)
	Sore throat	20(25.97%)	7(50%)	5(20.83%)	8(20.51%)
	Throat pain	22(28.57%)	7(50%)	6(25%)	9(23.08%)
	Dry cough	32(41.55%)	3(21.43%)	7(29.17%)	22(56.41%)
	Productive cough	55(71.42%)	7(50%)	14(58.33%)	34(87.18%)
	dyspnoea	47(61.03%)	0(0%)	13(54.17%)	34(87.18%)
	Haemoptysis	4(5.13%)	0(0%)	1(4.17%)	3(7.69%)
Gastrointestinal symptoms	Nausea	31(40.25%)	10(71.43%)	11(45.83%)	10(25.64%)
	Vomiting	15(19.49%)	3(21.43%)	5(20.83%)	7(17.95%)
	Pain abdomen	14(18.44%)	1(7.14%)	3(12.5%)	10(25.64%)
	Anorexia	40(51.94%)	9(64.3%)	13(54.17%)	18(46.15%)
Neurological symptoms	Loss of smell	22(28.57%)	7(50%)	7(29.17%)	8(20.51%)
	Loss of taste/change in taste	43(55.84%)	8(57.14%)	16(66.67%)	19(48.72%)

It was found that the severity of disease was much more in those with comorbidities predominantly diabetes, obesity, tobacco smoking, systemic hypertension, COPD, dyslipidemia, alcohol consumption.

The fatality occurred in 10 cases of which 2 were from the moderate category and were obese and among the 8 severe cases who succumbed 4 were diabetic, hypertensive, and dyslipidemia, 3 were known cases of COPD and the other was a known case of chronic kidney disease.

On HRCT chest all 77 patients were designated as CORADS 5 and CT severity score ranged between 1-10 in 78.57% of mild clinical category; Score ranged 11-15 in 21.43% of the mild category, 75% of the moderate category, and 23% of the severe category. A score between 16-25 was seen in 25% of the moderate category and 76.92% of the severe category. **[Table 5]**

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

Table 3 Comorbidity Distribution and Association with The Severity of Disease

Comorbidities/Risk Factors	Mild (n-14)	Moderate (n-24)	Severe (n-39)	Total (N-77)
Diabetes mellitus	2(14.28%)	7(29.17%)	12(30.77%)	21(27.27%)
Systemic hypertension	1(7.14%)	4(16.67%)	11(28.2%)	16(20.78%)
Diabetes mellitus and systemic hypertension	1(7.14%)	3(12.5%)	6(15.38%)	10(12.99%)
Dyslipidaemia	1(7.14%)	3(12.5%)	7(17.99%)	11(14.28%)
Ischaemic heart disease	0(0%)	3(12.5%)	5(12.82%)	8(10.39%)
Chronic kidney disease	0(0%)	1(4.16%)	2(5.13%)	3(3.89%)
Chronic liver disease	0(0%)	0(0%)	2(5.13%)	2(2.6%)
COPD	0(0%)	5(20.83%)	8(20.51%)	13(16.88%)
Bronchial asthma	1(7.14%)	2(8.33%)	3(7.69%)	6(7.8%)
Tobacco smoking	0(0%)	7(29.17%)	11(28.20%)	18(23.37%)
Alcohol consumption	1(7.14%)	4(16.67%)	8(20.51%)	13(16.88%)
Obesity	2(14.28%)	7(29.17%)	13(33.33%)	22(28.57%)

Laboratory parameters

Haematological parameters showed leukopenia in 14.68% and leucocytosis in 26.30%, neutrophilia in 94.33%, lymphopenia in 89.61%, NLR ratio >3.3 in 92.20%, thrombocytopenia in 22.07%, thrombocytosis in 7.79%. 54.54%of patients had deranged RFT, 42.85% had altered LFT. Coagulopathy was seen in 19.48%. Inflammatory markers ESR, CRP, LDH, Serum Ferritin, D-dimer were elevated in all 77 patients in variable ranges and correlated with the disease's severity. **[Table 4]**

ECG Findings

Out of 77 patients, sinus tachycardia was seen in 56 of them despite normal hemoglobin, sinus bradycardia in 10 and 2 patients had STEMI associated with positive cardiac markers I,e troponin I.

Among 77 patients, who were RT-PCR negative COVID-19, the fatality was seen in 10 patients with a case fatality rate of 12.98%. Out of 10 patients who succumbed, 7 were males and 3 were females.

Table 4 Laboratory Findings

Parameters	variation	% of cases N=77	MILD (n-14)	MODERATE (n-24)	SEVERE (n-39)
Lymphocytes	lymphopenia	69(89.61%)	13(92.86%)	21(87.5%)	35(89.74%)
NLR	>3.3	71(92.20%)	13(92.86%)	22(91.67%)	36(92.3%)
PLT	<1.5lakh	17(22.07%)	4(28.57%)	6(25%)	7(17.95%)
	1.5-4 lakh	56(72.72%)	10(71.43%)	17(70.83%)	29(74.36%)
	>4 lakh	6(7.79%)	(0%)	1(4.17%)	5(12.82%)
Renal function test	Altered	42(54.54%)	10(71.43%)	14(58.33%)	18(46.15%)
Liver function test	Altered	32(41.55%)	3(21.43%)	8(33.33%)	21(53.85%)
ESR	0-20mm/hr	6(7.79%)	3(21.43%)	2(8.3%)	1(2.56%)
	>20mm/hr	71(92.20%)	11(78.57%)	22(91.67%%)	38(97.43%)
CRP	6-20mg/dl	21(27.27%)	13(92.86%)	4(16.67%)	4(10.26%)
	21-50mg/dl	31(27.26%)	11(7.14%)	18(75%)	2(5.13%)
	>50mg/dl	35(45.45%)	(0%)	2(8.33%)	33(84.61%)
LDH	<300mg/dl	14(18.19%)	10(71.42%)	4(16.67%)	(0%)
	300-400mg/dl	26(33.76%)	4(28.57%)	16(66.67%)	6(15.38%)
	>400mg/dl	38(49.35%)	(0%)	5(20.83%)	33(84.61%)
D-DIMER	<500mg/dl	15(19.48%)	12(85.71%)	3(12.5%)	(0%)
	500-1000	26(33.76%)	2(14.28%)	19(79.17%)	5(12.82%)
	>1000	36(46.75%)	(0%)	2(8.33%)	34(87.18%)
Serum FERRITIN	<500mcg/dl	19(24.67%)	12(85.71%)	5(20.83%)	2(5.13%)
	500-800	24(31.16%)	2(14.28%)	16(66.66%)	6(15.38%)
	>800	34(44.15%)	(0%)	3(12.5%)	31(79.49%)

Radiological findings

Chest radiograms were normal in 5.19% of mild cases; peripheral opacities were seen in 38.96% in 9 mild cases, 15 moderate cases, and 6 of severe category cases; bilateral basal zone opacities were seen in 23.37% that is in 1 mild case, 8 moderate cases and 9 severe cases; diffuse non-homogenous opacities were seen in 32.46% that is in 1 moderate case and 24 severe cases.

The youngest and oldest were 38years and 78years, respectively. Among 10 patients who succumbed, all had comorbidities, 8 belonged to the severe category and 2 from the moderate category. The most common comorbidity associated was Diabetes Mellitus, systemic hypertension, and dyslipidemia followed by obesity. The most common cause of death was ARDS, followed by ACS.

Table 5 Radiological findings

(a)Chest X-ray Findings in the study group:

Chest x-ray findings	Normal	Lobar opacity	Peripheral opacifications	Basal zone opacities	Diffuse non-homogenous opacities
% of cases N=77	(5.19%)	(0%)	(38.96%)	(23.37%)	(32.46%
MILD (n-14)	4(28.57%)	(0%)	9(64.28%)	1(7.14%)	(0%)
MODERATE (n-24)	0(0%)	(0%)	15(62.5%)	8(33.33%)	1(4.17%)
SEVERE (n-39)	0(0%)	(0%)	6(15.38%)	9(23.07%)	24(61.54%)

(b) CT severity scoring in the study group:

CT SEVERITY SCORE	1-10	11-15	15-25
MILD(n-14)	11(78.57%)	3(21.42%)	(0%)
MODERATE(n-24)	(0%)	18(75%)	6(25%)
SEVERE(n-39)	(0%)	9(23.07%)	30(76.92%)

DISCUSSION

When the COVID-19 pandemic began, the 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. An RT-PCR assay uses RNA for in vitro nucleic acid amplification and utilizes reverse transcriptase, a RNA dependent DNA polymerase that catalyses DNA synthesis using RNA as a 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 1stweek of symptom onset as maximum viral shedding occurs in the upper respiratory tract during this period. It is negative when it involves the lower respiratory tract and causes pneumonia when it is advisable to do RT-PCR of sputum or Broncho-Alveolar Lavage Fluid. [8,9] While BAL provides the optimal material in terms of testing sensitivity (93%), the nasopharyngeal swab is considered the sample of choice in everyday clinical practice (63% sensitivity) during the initial phase of illness. [10,11]

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. Though the RT-PCR test is considered to be the 'gold standard for detecting covid-19, amid the emergence of the Omicron variant, the focus has gone beyond just its utility as a highly accurate identifier of infection. [12,13] 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 a 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 RT-PCR [1]. 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. [14,15]

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.[16]

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 that permit the recruitment of these patients. For example, in the recently reported RECOVERY trial, 10% of those randomized to dexamethasone had a negative swab at the time of randomization [17].

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%), and nasal swabs (62.5%), in contrast to our study where all samples were from nasopharynx and oropharynx. [18]

There have been a few publications in which the RT PCR negative COVID-19 cases, have been studied, for example, Di Paolo *et al* [15] 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 77 (out of 2281 patients), with the median age being 46 years, 59.74% were males and 40.25% were females.

In a study by Paolo SRC[19] 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 18.18% of patients were mild, 31.16% 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 the onset of symptoms and presentation to health facility was 6 days.

In a similar study[15], fever and dyspnoea were the most predominant symptoms found in 87.5% of patients, followed by cough in 43.7% and Gastrointestinal symptoms in 12.5% of patients, respectively. Whereas in our study, myalgia (85.71%), cough (66.72%), and dyspnoea (61.03%), gastrointestinal manifestations in (42.65%) were the most common symptoms.

In a recent study [19] Diabetes Mellitus was found to be the most common comorbidity (34.21%) associated with RT-PCR negative COVID-19 patients, whereas our study had obesity in 28.5% followed by diabetes in 27.27%.

The mean duration of hospital stay in our study was 25 days.
In a study done by Paolo SRC *et al*[19] 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 22.07% of patients without bleeding manifestations, altered RFT, and LFT in 54.54% and 42.85% patients, respectively.

Many studies are case-control studies[15,20] comparing RT-PCR positive and RT-PCR negative studies showing both cases had increased inflammatory markers correlating with the severity, whereas our study is a descriptive study of RT-PCR negative cases only.

In a multicentre case-controlstudy conducted in France[20], 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 done 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 5.16% of mild cases; Bilateral peripheral opacities were seen in 38.96% among 9 mild cases,15 moderate cases and 6 severe category cases; bilateral basal zone opacities were seen in 23.37% that is in 1 mild case, 8 moderate cases and 9 severe cases; diffuse non-homogenous opacities were seen in 32.46% that is in 1 moderate case and 24 severe cases. On HRCT chest all 77 patients were designated as CORADS 5 and CT severity scores ranged between 1-10 in 78.57% of mild category; a score between 10-15 in 21.43% of the mild category, 75% of the moderate category, and 23% of severe category; a score between 15-25 in 25% of moderate category and 76.92% of the severe category, respectively. Another study employing 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[21]

In a recent study [22], 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 81.81%, High flow nasal oxygen in 12.98%, non-invasive ventilation in 28.19%, and invasive ventilation in 7.02% of patients, respectively.
Our study witnessed recovery in 87.01% and fatality in 12.98% of patients in comparison to a similar study with recovery in 84.9% and fatality in 15%[23].

CONCLUSION

When a patient presents with classic symptoms of COVID-19 with a negative RT-PCR[24] we have to consider them like COVID-19 as the outcomes did not vary from the rest of the COVID-19 population since they shared similar characteristics like lymphopenia, raised NLR, the elevation of inflammatory markers as well as a tomographic COVID-19 score of severe illness.

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