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Coronavirus Pandemic

Persistence of SARS-CoV-2 in COVID-19 patients during the second wave of the pandemic in India

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Abstract

Introduction: India witnessed the catastrophic second wave of COVID-19 during the summer months of 2021. Many patients with non-resolution of symptoms admitted to dedicated COVID-19 treatment centers required prolonged inpatient care which led to the unavailability of beds for other COVID-19 patients. The objective of this study was to determine the duration of SARS-CoV-2 positivity in moderate and severe COVID-19 patients requiring long-term pulmonary care as well as to find out the association between different variables with the persistence of the virus.

Methodology: A retrospective chart review of clinical and laboratory data of patients with moderate and severe COVID-19 between 1st April 2021 and 15th July 2021 admitted for more than 28 days and requiring long-term pulmonary care was carried out at National Cancer Institute, AIIMS, India. SARS-CoV-2 RNA was detected with real-time reverse transcriptase-polymerase chain reaction-based tests. Data from all consecutively included patients satisfying the selection criteria were presented temporally and analyzed by Fisher's exact test ($p < 0.05$).

Results: All 51 patients tested positive for SARS-CoV-2 RNA at the 5th week of initial laboratory confirmation of COVID-19. The majority of the patients (38; 74.5%) remained positive for viral RNA till the 6th week and the median duration of viral positivity was 45 days. The clinical presentation of SARI at admission was significantly higher among patients with viral persistence till the 6th week ($p < 0.05$).

Conclusions: The median duration of the viral positivity was 45 days and SARI at admission was significantly associated with viral persistence till the 6th week.

Key words: SARS-CoV-2; COVID-19; second wave; pandemic; persistence.

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Introduction

A massive second wave of COVID-19 disease hit India and swept all over the country rapidly during the summer months of 2021. The sheer magnitude of the disease took everyone by surprise after the initial triumph over the first wave. The healthcare system was completely overwhelmed with more than 0.4 million daily new cases reported during mid of May 2021 [1]. A higher transmissibility rate of the SARS-CoV-2 variants along with poor regulatory and preventive public health measures was attributed to the crisis [2]. The proportion of severe acute respiratory infection (SARI) cases was considerably higher during the second wave than in the first wave and the requirement for mechanical ventilation and medical oxygen also had risen [3]. While many patients were waiting for admission, the admitted severe COVID-19 patients required inpatient care for a long duration in the hospitals. Under such circumstances, patients with persistent symptoms requiring long-term inpatient care were to be shifted to the non-COVID-19 pulmonary care center. Repeat molecular testing was sought in these patients. The repeat molecular testing in such patients seemed important to know the duration for which these patients might pose the risk of infection to other susceptible individuals including the healthcare workers [4].

There were some preliminary reports of research on SARS-CoV-2 RNA persistence in COVID-19, conducted during the early months of the long COVID-19 pandemic. Few of these reports focused on persistent viral positivity in mild or asymptomatic patients while

the others included patients in the convalescent phase [4-7]. A handful of the case reports also mentioned the long persistence of the virus in clinical specimens in COVID-19 patients [8-9]. However, none of these published works exclusively investigated the persistent viral positivity in patients with continuing symptoms requiring long-term care. Investigating the persistent viral positivity detected with molecular testing would not only provide useful insight into the duration of infectiousness in the patients with non-resolving symptoms but also would indicate the appropriate time for repeat testing in these patients. The latter might be helpful to lessen the burden of the testing from already overburdened laboratories struggling with limited availability of resources. Moreover, investigating the association between different variables and long-term persistence of the virus might provide useful hints towards key factors involved in SARS-CoV-2 viral persistence in the human body for further research.

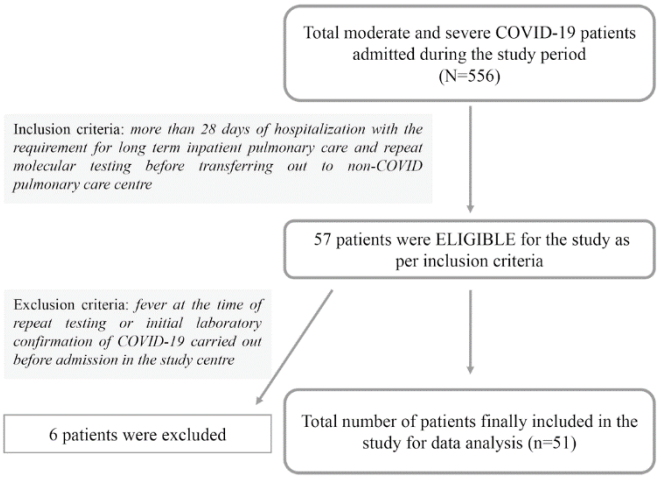
Therefore, in this study, we endeavoured to determine the duration of SARS-CoV-2 positivity in moderate and severe COVID-19 patients requiring long-term pulmonary care and to find out the possible association between the persistence of the virus and different demographic or clinical variables.

Methodology

Study setting

The present retrospective cross-sectional study was conducted in the National Cancer Institute-Jhajjar, which is an allied tertiary care hospital under the All India Institute of Medical Sciences (AIIMS, New Delhi), and has served as a dedicated COVID-19 treatment center during the second wave in India.

Figure 1. Flow diagram showing the approach of selection of patients for the study.



Study population and selection of patients

The study population consists of moderate and severe COVID-19 patients (N = 556) admitted to the study center between 1st April 2021 and 15th July 2021. The severity of the disease was assessed by the clinical manifestations of the patients as suggested in the clinical management protocol for COVID-19 published by the Ministry of Health and Family Welfare, Government of India [10]. Patients with the presence of clinical features of dyspnea and/or hypoxia, cough, fever, including SpO_2 90 to ≤ 93% on room air, respiratory rate ≥ 24 per minute were categorized as moderate COVID-19 patients, whereas patients with clinical signs of pneumonia plus one of the following: respiratory rate > 30 per minute, severe respiratory distress, SpO_2 < 90% on room air were categorized as severe COVID-19 patients.

Those patients with moderate to severe disease admitted to the hospital for more than 28 days duration with the requirement for long-term inpatient pulmonary care as evidenced by the persistence of breathlessness and/or inability to maintain target SpO_2 without supplemental oxygen, for whom repeat molecular testing for SARS-COV-2 was carried out before transferring to the non-COVID pulmonology care ward in accordance to the institutional policy, were eligible for the study.

Patients with the presence of fever at the time of repeat testing and patients for whom the initial laboratory confirmation of COVID-19 with molecular tests was carried out outside the study center before admission, were excluded from the study.

A consecutive sampling technique was applied to include all the admitted patients (n = 51) during the study period, following the selection criteria (Figure 1).

Collection of specimens

Both nasopharyngeal and oropharyngeal swab specimens were collected by trained nursing officers or resident doctors in viral transport medium (VTM) from all patients and sent immediately to the COVID-19 testing laboratory under the Department of Microbiology.

The timing of the repeat testing was decided by the treating clinician considering the clinical status of the patient before transferring to the long-term pulmonology care center. At least seven days of the interval was maintained for all patients between the two repeat molecular tests.

Laboratory diagnosis

The initial laboratory confirmation of the patients during admission was carried out with real-time reverse transcriptase-polymerase chain reaction (rRT PCR) tests like commercially available Indian Council of Medical Research (ICMR) recommended cartridge-based nucleic acid amplification tests like Truenat™ SARS CoV-2 (Molbio Diagnostics, Goa, India) or Xpert Xpress SARS-CoV-2 (Cepheid, Sunnyvale, CA, USA) in nasopharyngeal and oropharyngeal swab specimens collected in VTM).

The repeat testing for the patients was carried out in Xpert Xpress SARS-CoV-2 (Cepheid, Sunnyvale, CA, USA) in nasopharyngeal and oropharyngeal swab specimens collected in VTM.

Data collection

Date of admission, date of first laboratory confirmation with SARS-COV-2 molecular testing, demographic and the current clinical details of the patients, and the reports were obtained from the ICMR sample registration form submitted at the time of testing and the AIIMS eHospital portal, a web-based hospital management system developed by National Informatics Centre (NIC, India).

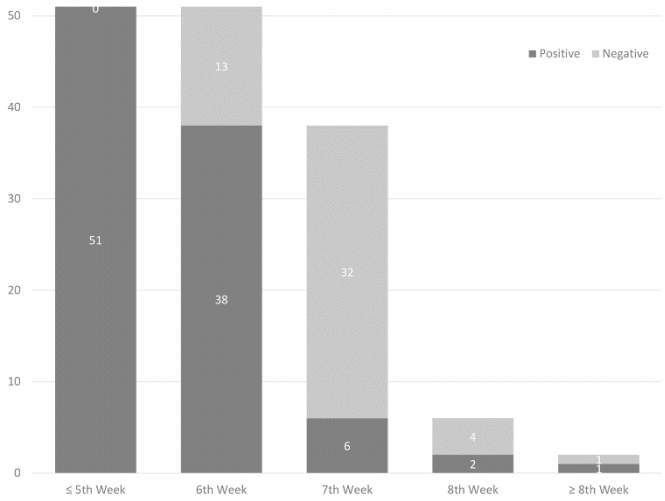
Statistical analysis

Fisher's exact test was used to find the relationship between two variables. Further, the odds ratio was calculated, if statistical significance existed between two categorical variables in cross-tab analysis. All statistical analysis was performed using Medcalc for Windows 19.5 (Medcalc software, Ostend, Belgium). The level of statistical significance was set as $p< 0.05$.

Ethical permission

The permission for conducting this work was obtained from Institute Ethics Committee, All India Institute of Medical Sciences, New Delhi (IEC 765/2021).

Figure 2. Temporal presentation of SARS-CoV-2 viral status in repeat molecular testing in patients included in the study [Colours of the bars represent either SARS-CoV-2 positive result (dark gray) or negative result (light gray) in repeat testing against time. The numbers on the bars denote the number of the patients with SARS-CoV-2 persistence (positive result) or clearance (negative result)].



Results

Descriptive statistics

Data from a total of 51 patients, who satisfied the selection criteria, were analysed. The age of the patients ranged from 17 to 91 years (median 46 years; interquartile range, 37-56 years) and 31 (60.78%) were males. Majority of the patients (34, 66.67%) presented with symptoms of SARI, followed by symptoms suggestive of ILI i.e., influenza-like illness (13 patients, 25.49%). Only 7 (13.73%) of the 51 patients were immunized with at least one dose of the COVID-19 vaccine before the present course of illness. Forty-three patients (84.31%) did not receive any COVID-19 vaccine whereas data on COVID-19 vaccination could not be retrieved for one patient.

Repeat molecular testing: All 51 patients included in the study had the presence of SARS-CoV-2 RNA in their oropharyngeal and/or nasopharyngeal swab specimens at the 5th week after the initial laboratory confirmation of COVID-19. In the 6th week, 38 (74.5%) patients had the presence of SARS-CoV-2 RNA, and the remaining 13 (25.5%) patients were tested negative. In the 7th and 8th week, the presence of SARS-CoV-2 RNA could be documented in only 6 (11.76%) and 2 (3.92%) patients, respectively. SARS-CoV-2 RNA could be documented in the specimen at the 9th week in 1 patient (1.96%). Figure 2 depicts the SARS-CoV-2 viral status in repeat molecular testing in patients over time. The length of each bar corresponds to the proportion of patients undergoing repeat testing over successive weeks and different colors of the bars represent SARS-CoV-2 viral detection status (either positive or negative) in repeat testing. It can be observed from the graph that the majority of the patients remained positive till the 6th week. In the 7th week, there was a substantial reduction in viral positivity among the patients and till the 9th week, the viral positivity reached the minimum level (i.e., only 1 patient remained positive).

The median duration of viral positivity in the patients was calculated to be 45 days (Interquartile range, 42-48 days).

Correlation of demographic and clinical variables with viral persistence till the 6th week

Out of the total 51 patients included in the study, SARS-CoV-2 viral persistence was observed in 38 (74.5%) patients till the 6th week whereas the virus became not detectable in 13 (25.5%) patients at the 6th week. Table 1 depicts the demographic and clinical variables in total patients (n = 51) as well as in the 38 patients with viral persistence till the 6th week and 13 patients who were tested negative for the virus at the 6th week, separately.

Of the total 51 patients included in the study, 34 (66.67%) patients presented with clinical features of SARI at the time of admission. Among the 38 patients with viral persistence till the 6th week, the proportion of patients presenting with SARI was found to be 78.95% (30 patients) whereas, among 13 patients who tested negative in repeat molecular testing at the 6th week, 30.76% (4 patients) presented with SARI at the time of admission. The clinical presentation of SARI at admission was found to be significantly higher (Fisher's exact test; $p = 0.0046$) among patients with SARS-CoV-2 persistence till the 6th week than among

Table 1. Clinical and demographic variables associated with SARS-CoV-2 positivity beyond the fifth week of the laboratory confirmation of COVID-19.

Variables	No. of cases (%)	Patients with SARS-CoV-2 persistence after 6th week	Patients tested negative for SARS-CoV-2 at 6th week	*p* value
Age				
≤ 18 years	02 (3.92)	0	02	
19-60 years	39 (76.47)	30	09	0.12
> 60 years	10 (19.61)	08	02	
Gender				
Male	31 (60.78)	24	07	1
Female	20 (39.22)	14	06	
COVID-19 Vaccination				
Vaccinated with at least one dose	07 (14)	05	02	1
Not vaccinated	43 (86)	32	11	
Initial presentation				
SARI *	**34 (66.67)**	**30**	**04**	**0.0046**
Non-SARI	**17 (33.33)**	**08**	09	
Type of care				
ICU	18 (35.29)	14	04	0.752
Non-ICU	33 (64.71)	24	09	
Chronic lung disease				
Present	15 (29.41)	14	01	0.2363
Absent	36 (70.59)	24	12	
Chronic renal disease				
Present	03 (5.88)	03	0	0.5612
Absent	48 (94.12)	35	13	
Chronic liver disease				
Present	02 (3.92)	01	01	0.4486
Absent	49 (96.08)	37	12	
Heart disease				
Present	09 (17.65)	08	01	0.4169
Absent	42 (82.35)	30	12	
Hypertension				
Present	14 (27.45)	12	02	0.4723
Absent	37 (72.55)	26	11	
Diabetes				
Present	07 (13.73)	07	0	0.1695
Absent	44 (86.27)	31	13	
Immune suppression				
Present	0	0	0	1
Absent	51 (100)	38	13	
Malignancy				
Present	02 (3.92)	02	0	1
Absent	49 (96.08)	36	13	

* SARI: Severe Acute Respiratory Infection.

patients who were tested negative for SARS-CoV-2 at the 6th week. Further analysis also showed that patients presenting with SARI had 8.43 times (95% CI, 2.0546 to 34.6503, *p*-value 0.0031) higher odds of having SARS-CoV-2 persistence in respiratory specimens till the 6th week (30 out of 34 patients with SARI had viral persistence till the 6th week) than a patient not presenting with SARI (8 out of 17 patients without SARI also had viral persistence till the 6th week).

None of the other variables like age, gender; COVID-19 vaccination status; type of care needed; or underlying conditions (chronic lung, liver, heart, kidney disease, hypertension, diabetes, malignancy, and immune suppression) were found to be associated with viral persistence till the 6th week (Table 1).

Discussion

Although SARS-CoV-2 predominantly involves the respiratory system and presents with a respiratory viral illness, it also causes an array of clinical manifestations in the major organ systems of the body [11]. Inside the respiratory system too, there exists a wide clinical spectrum of COVID-19. Clinical management of the patients also differs based on the disease severity viz. mild, moderate, severe disease [12]. The World Health Organization (WHO) strongly recommends close inpatient monitoring of all moderate to severe COVID-19 patients in the healthcare facility [12]. Patients with severe disease especially those with underlying comorbidities are prone to fatal complications, namely ARDS, pulmonary edema, embolism, and heart failure, necessitating prolonged hospitalization. The institution of invasive mechanical ventilation further complicates the clinical course with adverse ventilator-associated events further extending the duration of hospital stay [13]. We conducted the present study targeting such moderate and severe patients who had persistent symptoms and estimated the usual time through which SARS-CoV-2 RNA viral RNA could be detected with repeat molecular testing in such patients.

In the present study, the SARS-CoV-2 RNA could be detected with repeat molecular testing at the 5th week of initial laboratory confirmation in all 51 patients included in the study. In the 6th week, 38 (74.5%) patients tested positive for SARS-CoV-2 RNA with repeat testing and the rest of the (13; 25.5%) turned out to be negative for viral RNA. Thereafter a substantial decrease in viral RNA positivity was noticed among the patients with only 6 patients (11.76%) remaining positive for viral RNA in the repeat testing in the 7th week. In the 9th week, the viral positivity reached the minimum level (i.e., only one patient remained positive for SARS-CoV-2 in the repeat molecular testing). Overall, the median duration for viral positivity after initial laboratory confirmation of COVID-19 was found to be 45 days (Interquartile range, 42-48 days). These findings suggested that our patients had prolonged viral positivity and repeat testing only after 6 weeks of initial laboratory confirmation could be advised before transferring the patients from the dedicated COVID-19 treatment center to other centers for long-term in-patient care.

The presence of viral nucleic acid as late as 143 days in the nasopharyngeal specimen was reported previously [14]. Carmo *et al.* in their study reported that the mean duration of admitted patients (n = 36) remained positive for SARS-CoV-2 viral RNA was 35.38 ± 8.0 days [15]. In another study, Shu *et al.* reported that a relatively early viral clearance occurred in their patients with a median duration of 16 days [5]. It was noteworthy to mention that the latter study included mild and asymptomatic patients whereas the patients included in our study had moderate to severe COVID-19 with continuing symptoms even after 28 days of inpatient care. The persistence of SARS-CoV-2 was presumed to be one of the several causes of long COVID-19 disease [14]. RNA viruses including coronaviruses were long known to be capable of persisting in the host and resulting in chronic disease [16]. However, the exact mechanism behind the protection of these RNA viruses and their escape from the innate or adaptive immune responses were not clearly understood to date [16]. The persistence of SARS-CoV-2 was attributed to immune suppression in patients [14]. Steroids were widely used all over the world to treat severe COVID-19 cases and these drugs had the potential to cause immune suppression at higher doses. During the second wave of the pandemic, glucocorticoids were frequently used in the treatment of the patients in our study center [17]. The use of glucocorticoids could lead the prolonged SARS-CoV-2 persistence in our patients. Moreover, there was also a possibility of an enhanced immune escape mechanism by the virus itself leading to persistence in the host. The present study was conducted during the ongoing second wave of the COVID-19 pandemic in India and the delta variant (B.1.617.2) of SARS-CoV-2 was mostly attributed as the cause of the second wave [18]. It was evident from the neutralization assays that the B.1.617.2 variant had increased potential for escape from neutralizing antibodies compared to earlier variants of SARS-CoV-2 [19]. This might also be the reason behind the long persistence of the virus in our

patients infected during the second wave of the COVID-19 pandemic in India.

We also investigated some demographic and clinical parameters which might be associated with the persistence of the SARS-CoV-2 RNA. Our study found no significant association between the persistence of SARS-CoV-2 positivity till the 6th week with underlying comorbid conditions or demographic variables in the patients. This finding could be supported by the study by Joukar*et al.* who stated that no significant associations were found between clinical and demographic characteristics of patients and duration of SARS-CoV-2 RNA persistence [20]. On the contrary, Shu *et al.* reported that prolonged SARS-CoV-2 RNA positivity was significantly associated and underlying comorbid conditions (p = 0.029) [5]. Furthermore, we also observed that the initial presentation of SARI at the time of admission was significantly associated with the persistent viral positivity till the 6th week (p = 0.0046). During the second wave of COVID-19 in India, hospitals were overrun and COVID-19 patients struggled to get hospital admission with many patients presenting late with symptoms of advanced disease suggestive of SARI. Delayed admission was also reported previously to be associated with prolonged SARS-CoV-2 RNA positivity (p < 0.001) [5]. This finding indirectly supported our observation of the significant association of the SARI at presentation (possibly resulting from delay in admission) and persistent viral positivity in our study.

Detecting viral positivity with repeat molecular testing in the admitted patients with persistent symptoms indirectly indicated the infectiousness in our patients and the need for isolation in dedicated COVID-19 treatment centers [4]. However, the detection of SARS-CoV-2 RNA in repeat testing and its relationship with the infectiousness of the patient remained a contentious topic and needs to be investigated further. Some researchers argued that persistent positivity in repeat molecular testing only represented the inert RNA without the virus [14]. On the contrary, we considered this assumption unlikely because RNA becomes rapidly degraded in the body. Zahn *et al.* in their study reported that infectious and replication-competent SARS-CoV-2 viruses could be isolated in cell lines for up to 37 days from the clinical throat swabs of the mild COVID-19 patients who were persistently tested positive for SARS-CoV-2 virus with repeat rRT-PCR based testing [21]. This finding supported our argument for repeat molecular testing to predict the infectiousness in COVID-19 patients. We further make strong recommendations for SARS-CoV-2 viral dynamics studies supported with viral culture including moderate and severe COVID-19 patients especially those with continuing symptoms and requiring long-term inpatient care.

The study had a few limitations. Firstly, the included patients belonged to a single dedicated COVID-19 treatment center. The inclusion of more patients from multiple treatment facilities could generalize the study findings to a wider target population. Secondly, the results of the study were based on the findings from one repeat molecular test per week for each patient. Although two separate clinical specimens from two different sites (i.e., oropharyngeal and nasopharyngeal swab specimens) were collected by trained personnel for repeat molecular testing each week, a false negative result could occur due to the presence of PCR inhibitors in the clinical specimens. Finally, the present study retrospectively collected data for a limited period and could not analyze many variables for hypothesis testing owing to the problems in data retrieval. Follow-up data of the patients beyond the study period (e.g., outcome of the patients, recurrence of viral positivity after tested negative, etc.) could not be analyzed and included in the study. Future longitudinal studies may address this problem and analyze the variables in the hypothesis testing more comprehensively. Despite these limitations, the study exclusively focused on moderate and severe COVID-19 patients based on the definite categorization of patients. To the best of our knowledge, no previous study with a similar and larger sample size to date exclusively investigated the persistence of SARS-CoV-2 viral RNA focusing on the moderate and severely COVID-19 patients with continuing symptoms.

To summarize, the SARS-CoV-2 virus could be detected with rRT PCR based molecular testing in nasopharyngeal and oropharyngeal swab specimens of moderate and severe COVID-19 patients for a long period (median 45 days) after initial laboratory confirmation of COVID-19. It may be advisable to conduct the repeat testing after six weeks of the first laboratory confirmation in these patients if warranted for transferring out to non-COVID-19 treatment centers. Patients who presented with clinical features of SARI during admission were more likely to have SARS-CoV-2 viral persistence till 6 weeks from the first laboratory confirmation of the disease.

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Authors' contributions

UBS and AD conceptualized the study. All the authors were involved in the study methodology. Data were compiled by AD and SK. AD did the data analysis. AD and AJV prepared the initial draft. Revision of the draft was done by SS, KB, and LW. Final editing was done by RC and UBS. All the authors read and approved the study.

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