

To study duration of viral clearance in COVID 19 patients: A Prospective study from Bangalore, India



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ABSTRACT

Background: COVID-19 infection, which first reported as a cluster of pneumonia from Wuhan, China, in December 2019, has rapidly emerged as a global pandemic. During the early course of the pandemic. The duration of infectious virus replication is an important factor for clinicians. There is a significant correlation between the duration of SARS-CoV-2 virus clearance and the prognosis of COVID-19. **Aims and Objective:** To study Duration of viral clearance in COVID 19 patients, admitted in an Indian setting. **Materials and Methods:** The prospective single-center study considered adults patients of both the gender, diagnosed with COVID-19 infection by RT-PCR technique. Necessary demographic and clinical data were collected and selected subjects were followed-up until discharge or death. Based on the number of days required for viral clearance, the subjects were classified as: group 1: \leq 14 days, group 2: 15-28 days, and group 3: $>$ 28 days. **Results:** The study included 536 patients it was found that mean duration required for viral clearance was around 8.98 ± 3.54 . Mean ages noted for group 1, 2 and 3 (based on viral clearance) were 37.57 ± 13.65 years, 37.12 ± 13.73 years and 49.50 ± 23.56 years respectively. There was a significant difference between mean age of group 1 and 2, as well as group 1 and 3. Moreover, the distribution of patients across different age group was found to be statistically significant ($P < 0.05$). Significant difference was noted between three groups with respect to the comorbidity status ($P < 0.0001$). The COVID-related symptoms dyspnea and cough were more prominent in group 3 ($P < 0.05$). TLC which is statistically significant ($p < 0.05$), lower the TLC more the duration of viral clearance and more the duration of hospital stay. **Conclusion:** The mean days of viral clearance noted in COVID subjects is around 8.98 ± 3.54 days. There was a significant difference between mean age of group 1 and 2, as well as group 1 and 3. However, there is no statistically significant correlation between duration of hospital stay and inflammatory markers except TLC which is statistically significant ($p < 0.05$), lower the TLC more the duration of viral clearance and more the duration of hospital stay.

Keywords: COVID-19; Viral clearance; Inflammatory markers; Total leucocyte count

INTRODUCTION

COVID-19 infection, which first reported as a cluster of pneumonia from Wuhan, China, in December 2019, has rapidly emerged as a global pandemic.¹ During the early course of the pandemic, Italy had the highest infection burden and India remained much less affected with

corresponding mortality rates of 14.24% and 3.03%.² The total cases in India has now crossed 29 million mark and officially confirmed deaths being 382785, according to the Health Ministry data published on June 16, 2021.

The incubation period of SARS-CoV-2 ranges from 1 to 14 days, with a mean of 5 to 6 days. The first studies

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indicated that the viral load persisted up to 8 days after the onset of symptoms in mild cases and peaked in day 11 in more severe cases.^{3,4} The duration of infectious virus replication is an important factor for clinicians. There is a significant correlation between the duration of SARS-CoV-2 virus clearance and the prognosis of COVID-19. A longer duration of viral clearance in adult patients with COVID-19 increases the risk of death.⁵ However, upon the resolution of clinical symptoms the clearance of SARS-CoV-2 from respiratory samples remains unclear, making the establishment of patient discharge and the ending isolation criteria difficult. COVID-19 patients may be discharged based on clinical resolution of symptoms, and evidence for viral RNA clearance from the upper respiratory tract. Understanding the SARS-CoV-2 viral clearance profile is crucial to establish a retesting plan on discharge and ending isolation of patients. We aimed to evaluate the number of days that a patient needed to achieve undetectable levels of SARS-CoV-2 in upper respiratory tract specimens (nasopharyngeal swab and/or an oropharyngeal swab).

MATERIALS AND METHODS

The prospective study was carried out between March and May 2020 at a Bengaluru-based hospital setting. Approval and clearance were obtained from the Institutional ethics committee. The study included patients aged ≥ 18 years of both the gender, diagnosed with COVID-19 infection by RT-PCR technique. The study excluded patients < 18 years and those not willing to provide signed informed consent prior to the study. Case record form with follow-up chart was used to record the demographic data, and duration and clinical features of the disease.

Case record form with follow-up chart was used to record the demographic data, and duration and clinical features of the disease. Patients' data like clinical symptoms and incidence of co-morbidities like hypertension, diabetes, and metabolic disorders like renal, cardiac and respiratory disorders were collected. Biochemical reports were collected (CBC, LDH, CRP, Ferritin and D-Dimer). Based on the number of days required for viral clearance, the subjects were classified as: group 1: ≤ 14 days, group 2: 15-28 days, and group 3: > 28 days.

Statistical analysis

Carried out using software R version 3.6. Continuous variables were expressed as means, and standard deviation and categorical variables were presented as counts and percentages. Patients were grouped as survival and succumbed to death. Different parameters were compared between the groups using t-test for continuous and chi-square test for categorical data. The optimal cut points were estimated for significant

continuous variables using receiver operating curve (ROC) analysis. Multiple regression analysis was carried out and odds ratio with confidence interval (CI) were estimated to determine the effect of significant factors on outcome death and survival. For evaluating the mean days of viral clearance, many mild and moderate cases were not considered due to the implementation of the revised third discharge policy. P value < 0.05 was considered as statistically significant.

RESULTS

Out of 536 patients who had viral clearance information, 449 (83.77%), 121 (22.58%) and 6 (1.12%) patients were categorized into group 1, 2 and 3 respectively. The overall mean viral clearance time for 536 patients was found to be 8.98 ± 3.54 days.

Comparison of different variables across the different groups is shown (Table 1). Mean ages noted for group 1, 2 and 3 were 37.57 ± 13.65 years, 37.12 ± 13.73 years and 49.50 ± 23.56 years respectively. There was a significant difference between mean age of group 1 and 2, as well as group 1 and 3. Moreover, the distribution of patients across different age group was found to be statistically significant ($P < 0.05$). The maximum number of patients belonged to the age group of 30-39 years and least number of patients in ≥ 70 years.

Significant difference was noted between three groups with respect to the comorbidity status ($P < 0.0001$). In the group 3, around 33% of the subjects had diabetes as opposed to only around 5% in group 1, and 2.50% of the subjects belonging to the group 3 and other ICU facilities when compared to the other two groups ($P < 0.0016$) (Table 2).

No Significant difference was noted between three groups with respect to the inflammatory markers Except TLC which is statistically significant ($p < 0.05$) lower the TLC

Table 1: Age distribution of the study participants

Variable	Group 1 (n= 449)	Group 2 (n= 121)	Group 3 (n= 6)	P value
Age (years)	37.57 ± 13.65^a	37.12 ± 13.73^b	49.50 ± 23.56^b	< 0.001
Age Group				< 0.00001
<30 years, n (%)	160(35.63)	42(34.71)	0(0)	
30-40 years, n (%)	118(26.28)	32(26.45)	3(50.00)	
40-50 years, n (%)	78(17.37)	22(18.18)	1(16.67)	
50-60 years, n (%)	53(11.80)	14(11.57)	0(0)	
60-70 years, n (%)	33(7.35)	10(8.26)	1(16.67)	
≥ 70 years, n (%)	7(1.56)	1(0.83)	1(16.67)	

Group 1 = ≤ 14 days, Group 2 = 14-28 days and Group 3 = ≥ 28 days; statistically significant if $P < 0.05$; different superscript across the row differ significantly ($P < 0.05$ for t-test)

Table 2: Correlation of Comorbidities

Variable	Group 1 (n= 449)	Group 2 (n= 121)	Group 3 (n= 6)	P value
Comorbidities				
None	310(69.04)	74(61.16)	3(50.00)	< 0.00001
Diabetes only	25(5.57)	6(4.96)	2(33.33)	
Hypertension only	21(4.68)	4(3.13)	0 (0)	
Diabetes or Hypertension with other complications	38(8.46)	16(13.22)	0(0)	
Chronic Kidney disease	0(0)	0(0)	0(0)	
Other	55(12.25)	62(51.20)	1(16.67)	
ICU requirement	25(5.57)	17(14.05)	3(50.00)	< 0.00001
Asymptomatic, n (%)	316(70.38)	81(66.94)	3(50.00)	0.4469

Group 1= \leq 14 days, Group 2 =14-28 days and Group 3= \geq 28 days; statistically significant if P< 0.05; different superscript across the row differ significantly (P<0.05 for t-test)

more the duration of viral clearance and more the duration of hospital stay (Table 3).

In all the three groups categorized based on viral clearance, more than half of the subjects were asymptomatic (>50%). The COVID-related symptoms dyspnea and cough were more prominent in group 3 (P<0.05) and the other symptoms like fever, myalgia, sore throat and headache were not significantly differed between the groups (P>0.05). The corresponding number of subjects who succumbed to death in group 1, 2 and 3 were 42(9.35%), 0(0%) and 1(17.63%) respectively (P 0.0187).

DISCUSSION

The present study found that viral clearance time for 536 patients was found to be 8.98 \pm 3.54 day as the mean time for final viral clearance in subjects. Carmo et al., observed the persistence of viral RNA for more than 2 weeks, which may not be linked to disease severity, but with a weaker immune response.⁶ Samrah et al., found median viral shedding duration of 13 days. Patients having symptoms or/and the presence of abnormal radiological findings were associated with delayed viral clearance. Symptomatic COVID-19 patients may still have respiratory viral shedding for up to 20 days after clinical cure.⁷

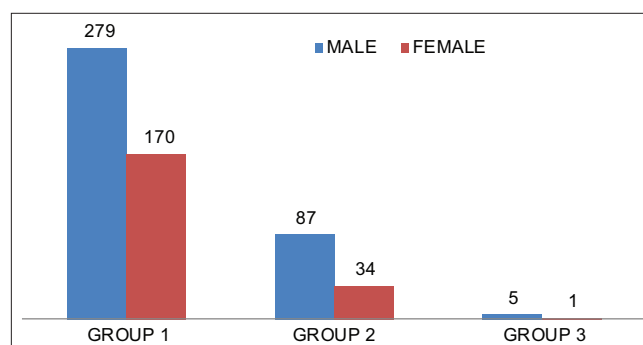
Age distribution

Mean ages noted for group1, 2 and 3 were 37.57 \pm 13.65 years, 37.12 \pm 13.73 years and 49.50 \pm 23.56 years respectively. There was a significant difference between mean age of group 1 and 2, as well as group 1 and 3. Moreover, the distribution of patients across different age group was found to be statistically significant (P<0.05). Hirai et al.,

Table 3: Correlation of Inflammatory markers

Laboratory parameters	Group 1 (n= 449)	Group 2 (n= 121)	Group 3 (n= 6)	P value
Hemoglobin	13.26 \pm 2.33	13.17 \pm 2.15	13.13 \pm 1.15	0.9223
Total Leucocyte count	8126 \pm 2740.56 ^a	7516 \pm 2621.08 ^b	5717 \pm 2316.39 ^x	0.0114
Neutrophil	61.52 \pm 11.29	59.85 \pm 12.91	58.00 \pm 7.62	0.3007
Lymphocytes	28.75 \pm 10.08	29.37 \pm 10.90	30.83 \pm 6.68	0.7539
Neutrophils lymphocytes ratio	2.64 \pm 1.80	2.73 \pm 2.50	2.02 \pm 0.83	0.6603
LDH	245.80 \pm 105.33	243.5 \pm 96.17	281.30 \pm 39.83	0.6802
D-dimer	0.75 \pm 0.63	1.65 \pm 8.89	0.73 \pm 0.29	0.1015
C-Reactive Protein	13.28 \pm 35.16	16.13 \pm 44.25	32.07 \pm 45.04	0.3753
Ferritin	212.60 \pm 301.19	222.35 \pm 316.87	312.8 \pm 206.67	0.6987

Group 1= \leq 14 days, Group 2 =14-28 days and Group 3= \geq 28 days; statistically significant if P< 0.05; different superscript across the row differ significantly (P<0.05 for t-test)

**Figure 1: Sex distribution among groups**

observed that the younger patients who recovered from COVID-19 took less time to clear SARS-CoV-2 compared to the elderly patients; thus, a classification of the isolation periods based on age could be considered.⁸ Male 62.14% in Group1, 71.9% in Group 2, 83.3% in Group3, Female 37.8% in Group 1, 28.10% in Group 2, 16.67% in Group 3 respectively (Figure 1).

Comorbidities

Significant difference was noted between three groups with respect to the comorbidity status (P<0.0001). In the group 3, around 33% of the subjects had diabetes as opposed to only around 5% in group 1, and 2.50% of the subjects belonging to the group 3. Shu et al., reported in their study that delayed admission and underlying comorbidities may effectively predict SARS-CoV-2 RNA clearance.⁹ Abraham et al., showed in their study that those participants without comorbidities recovered more quickly

than those with at least one comorbidity.¹⁰ Trump et al., in their study reported hypertension as one of the factors which causes delay of viral clearance and exacerbates airway hyperinflammation in patients with COVID-19.¹¹

Correlation with Inflammatory markers

In the current study, the total leukocyte count (TLC) was found to be statistically significant with respect to the viral clearance, lower the TLC more the duration of viral clearance and more the duration of hospital stay ($p < 0.05$), whereas there was no statistically significant correlation between CRP, D-Dimer, Ferritin levels with viral clearance. In a study conducted by Xue et al., reported those patients with history of hypertension, an elevated IL-6 level, and an elevated percentage of NK cells were predisposed to higher risk with prolonged viral clearance.¹²

CONCLUSION

The present study has underscored maximum of around 8.98 ± 3.54 days as mean days of viral clearance required in most of the COVID positive patients. There was a significant difference between mean age of group 1 and 2, as well as group 1 and 3.

There is no statistically significant correlation between duration of hospital stay and inflammatory markers except TLC which is statistically significant ($p < 0.05$), lower the TLC more the duration of viral clearance and more the duration of hospital stay.

Limitations of the study

Single centered study and small sample size.

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Author's Contribution:

SR - Concept and design of the study; Interpreted the results; reviewed the literature and manuscript preparation and revision of the manuscript; AHR - Statistically analysed and interpreted, preparation of manuscript; SY - Concept, coordination, review of literature and manuscript preparation.

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