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Original Research Article

Duration of viral clearance and factors associated with viral clearance among COVID-19 patients admitted in a tertiary care center in north Kerala

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ABSTRACT

Background: COVID-19 pandemic has afflicted the global health scenario for nearly two years. There are limited studies regarding potential predictors of viral clearance in COVID-19 patients. These predictors can aid in identifying patients with prolonged viral shedding and initiate further research for interpreting host immune response to COVID-19. Viral clearance data in treated patients may shed light on the relationship between the host immune system and SARS-CoV-2. Objective of this study was to estimate viral clearance and study the factors associated with viral clearance in COVID-19 patients.
Methods: A descriptive study was conducted among 588 COVID-19 patients admitted during the 6-month study period. Data was collected from case records and analyzed using SPSS version 21. Results expressed as mean, standard deviation, frequencies, and percentages. Pearson Chi square test used to find association between viral clearance and associated factors.
Results: Among the 588 COVID-19 patients, majority (54%) were females. 21-30 years age-group had the maximum proportion (29.2%) of cases. Most common comorbidity reported was diabetes mellitus. The mean duration of viral clearance (VC) was 8.16±2.1 days. Delayed viral clearance was present in 21% of the study population. There was statistically significant association between male gender and delayed viral clearance. ICU admission and delayed VC also had significant association, with 95% of those admitted in ICU having delayed VC. Male gender could be a confounding variable for association between ICU admission and delayed viral clearance.
Conclusions: One fifth of the study population had delayed viral clearance. Delayed viral clearance is associated with male gender and ICU admission.

Keywords: COVID-19, RTPCR conversion time, Viral clearance

INTRODUCTION

The Corona Virus disease-2019 or COVID-19 is a pandemic of zoonotic origin which has spread rapidly over the world from its place of origin in the city of Wuhan in the Hubei province of China. A total of 261,435,768 confirmed cases of COVID-19, including 5,207,634 deaths, reported to WHO, as of 30 November 2021.[1]

India reported 34,587,822 confirmed cases of COVID-19 with 468,980 deaths as on 30 November 2021.[2] Clusters of pneumonia cases were reported from China since late December, leading to WHO declaring a public health emergency of international concern (PHEIC) on 30th January 2020, in the second meeting of the International Health Regulations (2005) Emergency Committee. COVID-19 was declared a pandemic by WHO on 11th March 2020, thereby prompting stringent action internationally.[1]

SARS CoV-2 (severe acute respiratory virus-2) belongs to the beta coronavirus family of RNA viruses. It is of zoonotic origin, phylogenetic analysis of genome led to the conclusion that bats are the reservoir of infection; but intermediate host is yet to be identified.[3] The infection spreads primarily through droplets transmission and fomite spread. The symptoms are non-specific, ranging from asymptomatic cases to mild flu-like symptoms to severe acute respiratory symptoms and death.[4]

Although detailed studies are needed to elucidate the global epidemiology of COVID-19, a wide spectrum of clinical severity is evident, with most patients able to mount a sufficient and appropriate immune response, ultimately leading to viral clearance and case resolution.[4]

SARS-CoV-2 enters alveolar epithelial cells by binding to angiotensin converting enzyme 2 (ACE2) through surface spike (S) protein mediation. Direct viral infection of pulmonary macrophages and dendritic cells causes expression of several proinflammatory cytokines and chemokines. Dendritic cells phagocytose virus in the lungs, migrate to secondary lymphoid organs, and activate antigen-specific T cells, which travel to the lungs and destroy virally infected alveolar cells.[5]

In addition to cytokine release and immune cell recruitment, another potential mechanism that could contribute to successful viral clearance is antibody neutralization. Current literature suggests seroconversion in COVID-19 patients occurs ~7-14 days post symptom onset.[6]

Early in the pandemic, WHO and CDC recommended test-based clearance with at least two negative RT-PCR tests for patients with COVID-19. This can lead to prolonged isolation, as some patients have positive RT-PCR assays for weeks, even though not at the risk of transmitting the infection.[7-9]

The persistence and clearance of viral RNA from swab specimens of patients with COVID-19 remain unclear; hence the need for this study to understand the dynamics of viral clearance and factors associated with viral clearance in COVID-19 patients. Viral clearance data in treated patients may shed light on the relationship between the host immune system and SARS-CoV-2.[10]

There are limited studies regarding potential predictors of viral clearance in COVID-19 patients. These predictors can aid in identifying patients with prolonged viral shedding and initiate further research for interpreting host immune response to COVID-19.

Objectives

To estimate the duration of viral clearance among COVID-19 cases admitted in a tertiary care center in north Kerala. To study the factors associated with viral clearance among COVID-19 cases admitted in a tertiary care center of North Kerala.

METHODS

Design, setting and study population

This was a record based descriptive study in a tertiary care center in north Kerala. All COVID-19 cases admitted from 01 March 2020 to 31 August 2020; the first 6 months of the COVID pandemic were taken as the study population. All patients who were discharged/ referred/died without a repeat RTPCR were excluded from the study.

Data collection and analysis

Data was collected using a proforma from case records and regional PEID Cell database with permission from Regional PEID cell coordinator. Data was entered in MS Excel sheets and analyzed using SPSS Software version 21.

Operational Definitions

COVID-19 case: A person with laboratory confirmation of COVID-19 infection, through RT-PCR, irrespective of clinical signs and symptoms.

Viral clearance: Was considered to have occurred on the first negative RT-PCR results in a COVID-19 case, while asymptomatic.

Duration to viral clearance: Was calculated from day of collection of first positive swab to the day of collection of negative RT-PCR result.

An arbitrary value of 14 days was taken as average duration for viral clearance; and patients who took longer for viral clearance was classified as having delayed viral clearance.

Ethical consideration

Approval was obtained from Institutional Ethical Committee prior to beginning of the data collection. All data was maintained in strict confidentiality.

RESULTS

Demographic profile

A total of 588 cases were included in the study, of which 46% (272) were males and 54% (316) were females. The 21-30 years age group had the highest proportion of cases, 29.2% (172). The mean age of the study population was 38.75±17.45 years, with a minimum age of 20 days and a maximum age of 95 years.

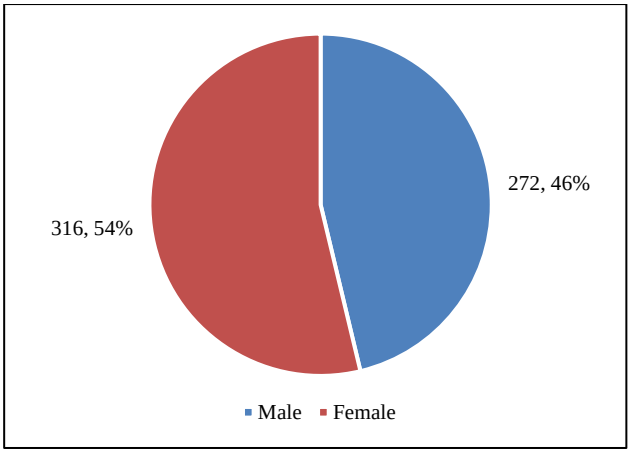

Figure 1: Sex distribution of the study population.

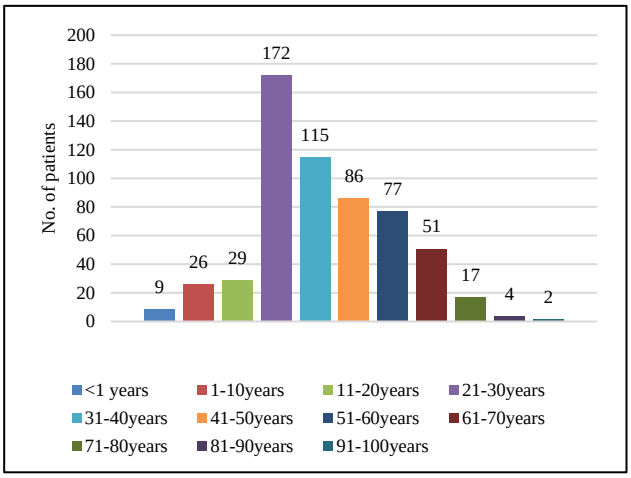

Figure 2: Age group wise distribution of COVID-19 cases.

Co-morbidities

Out of the cases studied, 64% (378) had no comorbidity, while 36% had one or more comorbidity. The most common comorbidity was diabetes mellitus 11.9%, followed by hypertension in 9.7%, reactive airway disease (COPD/bronchial asthma) in 5.3%, coronary artery disease in 2.2%, chronic kidney disease in 1.9% and carcinoma in 0.7%. About 7.7% of the population was pregnant.

Intensive care unit (ICU) admission was necessary for 20.2% (119) of the patients, 65.5% (78) of which were men. There was statistically significant association between male gender and ICU admission ($p<0.05$, Pearson Chi square test).

Viral clearance

The mean duration of viral clearance (VC) was 8.16±2.1 days, ranging from 2-26 days. Delayed viral clearance was seen in 21% (122) of the study population. Age was not significantly associated with delayed viral clearance.

Table 1: Gender versus VC time of COVID 19 cases.

Gender	VC time		Total	P value (Pearson χ^2 test)
	≤14 days	>14 days		
Male	192 (32%)	80 (13.6%)	272 (46.2%)	0.0001
Female	274 (46.5%)	42 (7.2%)	316 (53.7%)	
Total	466 (79%)	122 (21%)	588	

Of the 122 cases with delayed viral clearance, majority; 65.5% (80) were males, with statistically significant association between male gender and delayed viral clearance.

ICU admission and delayed VC had significant association, with 95% of those admitted in ICU having delayed VC ($p<0.05$, Pearson chi square test).

Table 2: ICU admission versus VC time of COVID-19 cases.

ICU admission	VC time		Total	P value (Pearson χ^2 test)
	≤14 days	>14 days		
Yes	464 (78.9%)	5 (0.85%)	469	0.0003
No	2 (0.34%)	117 (19.8%)	119	
Total	466 (79%)	122 (21%)	588	

Comorbidities and viral clearance

Delayed viral clearance observed in higher percentage of those with comorbidity, but the association was not statistically significant for any of the comorbidity studied. In contrast, delayed viral clearance time seen in only 25% of the pregnant COVID-19 cases.

Table 3: Distribution of co-morbidities versus viral clearance.

Comorbidity	VC≤14 days	VC> 14 days
Diabetes mellitus	43% (31)	57% (39)
Hypertension	48% (27)	52% (30)
Coronary artery disease	38% (5)	62% (8)
Chronic kidney disease	37% (4)	63% (7)
Reactive airway disease (COPD/BA)	46% (14)	54% (17)
Carcinoma	25% (1)	75% (3)
Pregnancy	75% (34)	25% (11)

DISCUSSION

In this study, higher proportion of the COVID-19 cases were females (54%) compared to males (46%). This is in discord with studies by Huang et al, Abate et al, Mohan et al and Aggarval et al, all of which had higher proportion of cases among males.[11-14] Since the guideline for hospital isolation of COVID-19 cases mandated hospital admission for all pregnant cases, a higher number of asymptomatic pregnant patients were admitted in this tertiary care institute. This could be one of the possible reasons for the variation from previously reported studies. Male gender was significantly associated with ICU admission, suggesting that the disease was severe in males compared to females.

The mean age of the study population was 38.75±17.45 years, similar to that observed in studies by Yuan et al and Mohan et al.[13,20] Nearly one-third of the cases belonged to the 21-30 year age group, as the case load during the initial months (March 2020 to August 2020) consisted primarily of expats in the working age group and their contacts.

Out of the cases studied, 36% had one or more comorbidity. This is comparable to the prevalence of comorbidity among other studies on COVID-19 cases by Huang et al, Mohan et al, Aggarwal et al and Kayina et al, ranging from 15.9% to 68.8%.[11,13-15]

The most common comorbidity identified from this study was diabetes mellitus in 11.9%, followed by hypertension in 9.7%. In studies by Huang et al, Mohan et al and Aggarwal et al, diabetes mellitus emerged as the most common comorbidity, while studies by Kayina et al, Wei et al had hypertension as the most common comorbidity.[11,13-15,17]

Intensive care unit (ICU) admission was necessary for 20.2% (119) of the patients, 65.5% (78) of which were men. There was statistically significant association between male gender and ICU admission ($p<0.05$, Pearson Chi square test). This can be compared to a study by Grasselli et al on "Risk factors associated with mortality among patients with COVID-19 in intensive care units" in Lombardy, Italy; of the 3988 patients included in the study, 3188 (79.9%) were men. Independent risk factors associated with ICU admission and mortality included older age and male sex.[16]

Also, a systematic review and meta-analysis done by Abate et al on the sex difference in coronavirus disease found the prevalence of symptomatic COVID-19 to be higher in men than in women. The high prevalence of smoking and alcohol consumption was a contributing factor to the high prevalence of COVID-19 among men. There is increasing evidence that COVID-19 produces more severe symptoms and higher mortality among men than among women.[12]

The mean duration of viral clearance (VC) was 8.16±2.1 days in this study. A similar pattern of viral clearance was seen in a study by Yun et al, where the median time from the onset of symptoms to first negative RT-PCR results for oropharyngeal swabs in convalescent patients was 9.5 (6.0-11.0) days.[18]

Whereas, in a study conducted by Wang et al among 18 COVID-19 patients in Wuhan; the median time of real-time PCR conversion was 19.5 days (range 17-24 days) and in a study by Wei et al among 397 COVID-19 cases, the median time from symptoms onset to SARS-CoV-2 nucleic acid negative conversion was 23.5 (15.8, 32.3) days, both showing longer duration for viral clearance than our study.[17,21] Both these studies were conducted in the early phases (March-April 2020) of the COVID-19 pandemic in the epicenter of the pandemic: Wuhan. This could be attributed to the viral genetic variation as the pandemic evolved.

Delayed viral clearance was seen in 21% (122) of the study population; which is comparable to a study by Wei et where, in 17.9% (56/312) of patients, RT-PCR was still positive at 14 days, and a study by Ikegami et al, where 11.8% of individuals tested positive for SARS-CoV-2 by NP swab PCR greater than 14 days after the resolution of symptoms of active disease.[17,22]

In this study, of the 122 cases with delayed viral clearance, 65.5% (80) were males, with statistically significant association between male gender and delayed viral clearance. Similar finding was seen in a study by Xu et al; where prolonged SARS-CoV-2 RNA shedding was significantly associated with male sex.[23] Also, in a study by Shi et al male sex was an independent factor associated with a prolonged duration of SARS-CoV-2 shedding.[24]

ICU admission and delayed VC had significant association in this study, with 95% of those admitted in ICU having delayed VC ($p<0.05$, Pearson chi square test). The study by Xu et al had found significant association between delayed viral clearance and intensive care treatment.[23] Similarly, in a review of literature by Fontana et al among 77 studies on SARS-CoV-2, the pooled median duration of viral RNA shedding from respiratory sources was prolonged among severely ill patients.[27]

Male gender could be a confounding variable for association between ICU admission and delayed viral clearance, as majority (65.5%) of patients admitted in ICU were males.

Delayed viral clearance was observed in higher percentage of those with comorbidity, but the association was not statistically significant for any of the comorbidity studied. Concomitant hypertension was found to be an independent risk factor by a study by Xu et al in Wuhan, China.[23]

There are some limitations of the study. Data could be analysed only for the first 6 months of the pandemic as the testing protocols were revised to not require a repeat PCR for discharge from hospital. Viral clearance could not be calculated for expired patients or those who did not have a repeat PCR test. Also, as the data was collected from case records, completeness of data in terms of comorbidities could not be ensured.

CONCLUSION

The mean duration of viral clearance (VC) was 8.16±2.1 days. Delayed viral clearance seen in 21% of the study population. There was statistically significant association between male gender and delayed viral clearance. ICU admission and delayed VC also had significant association, with 95% of those admitted in ICU having delayed VC ($p<0.05$, Pearson chi square test). Male gender could be a confounding variable for association between ICU admission and delayed viral clearance. Delayed viral clearance was observed in higher percentage of those with comorbidity, but the association was not statistically significant for any of the comorbidity studied.

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REFERENCES

1. WHO Coronavirus (COVID-19) Dashboard. Available from: https://covid19.who.int. Accessed on 1 December 2021.
2. Ministry of Health and Family Welfare COVID-19. New Delhi. Available from: https://www.mohfw.gov.in. Accessed on 1 December 2021.
3. Rabaan AA, Al-Ahmed SH, Haque S, Sah R, Tiwari R, Malik YS, et al. SARS-CoV-2, SARS-CoV, and MERS-COV: a comparative overview. Infez Med. 2020;28(2):174-84.
4. Bohn MK, Hall A, Sepiashvili L, Jung B, Steele S, Adeli K. Pathophysiology of COVID-19: mechanisms underlying disease severity and progression. Physiology. 2020;35(5):288-301.
5. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
6. Bohn MK, Lippi G, Horvath A, Sethi S, Koch D, Ferrari M, et al. Molecular, serological, and biochemical diagnosis and monitoring of COVID-19: IFCC taskforce evaluation of the latest evidence. Clin Chem Lab Med. 2020;58(7):1037-52.
7. Saurabh S, Kumar R, Gupta MK, Bhardwaj P, Nag VL, Garg MK, et al. Prolonged persistence of SARS-CoV-2 in the upper respiratory tract of asymptomatic infected individuals. QJM Mon J Assoc Phys. 2020;113(8):556-60.
8. Park SY, Yun SG, Shin JW, Lee BY, Son HJ, Lee S, et al. Persistent severe acute respiratory syndrome coronavirus 2 detection after resolution of coronavirus disease 2019-associated symptoms/ signs. Korean J Intern Med. 2020;35(4):793-6.
9. Deng W, Guang TW, Yang M, Li JR, Jiang DP, Li CY, et al. Positive results for patients with COVID-19 discharged form hospital in Chongqing, China. BMC Infect Dis. 2020;20(1):429.
10. Farina N, Ramirez GA, De Lorenzo R, Di Filippo L, Conte C, Ciceri F, et al. COVID-19: Pharmacology and kinetics of viral clearance. Pharmacol Res. 2020;161:105114.
11. Huang X, Wei F, Hu L, Wen L, Chen K. Epidemiology and clinical characteristics of COVID-19. Arch Iran Med. 2020;23(4):268-71
12. Abate BB, Kassie AM, Kassaw MW, Aragie TG, Masresha SA. Sex difference in coronavirus disease (COVID-19): a systematic review and meta-analysis. BMJ open. 2020;10(10):e040129.
13. Mohan A, Tiwari P, Bhatnagar S, Patel A, Maurya A, Dar L, et al. Clinico-demographic profile and hospital outcomes of COVID-19 patients admitted at a tertiary care centre in north India. Indian J Med Res. 2020;152(1 and 2):61-9.
14. Aggarwal A, Shrivastava A, Kumar A, Ali A. clinical and epidemiological features of SARS-CoV-2 patients in SARI ward of a tertiary care centre in New Delhi. J Assoc Physicians India. 2020;68(7):19-26.
15. Kayina CA, Haritha D, Soni L, Behera S, Nair PR, Gouri M, et al. Epidemiological and clinical characteristics and early outcome of COVID-19 patients in a tertiary care teaching hospital in India: a preliminary analysis. Indian J Med Res. 2020;152(1 and 2):100–4.
16. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. JAMA Intern Med. 2020;180(10):1345-55.
17. Wei CJ, Hu XX, Ye GM, Yang JM, Cheng ZS, Wang XH. Time and risk factors of viral clearance in COVID-19 patients. Chin Med J. 2021;134(17):2131-3.
18. Ling Y, Xu SB, Lin YX, Tian D, Zhu ZQ, Dai FH, et al. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. Chin Med J. 2020;133(9):1039-43.
19. Wang K, Zhang X, Sun J, Ye J, Wang F, Hua J, et al. Differences of severe acute respiratory syndrome coronavirus 2 shedding duration in sputum and nasopharyngeal swab specimens among adult inpatients with coronavirus disease 2019. Chest. 2020;158(5):1876-84.
20. Yuan J, Zou R, Zeng L, Kou S, Lan J, Li X, et al. The correlation between viral clearance and biochemical outcomes of 94 COVID-19 infected

discharged patients. Inflamm Res. 2020;69(6):599-606.
21. Wang L, Gao YH, Lou LL, Zhang GJ. The clinical dynamics of 18 cases of COVID-19 outside of Wuhan, China. Eur Respir J. 2020;55(4):2000398.
22. Ikegami S, Benirschke R, Flanagan T, Tanna N, Klein T, Elue R, et al. Persistence of SARS-CoV-2 nasopharyngeal swab PCR positivity in COVID-19 convalescent plasma donors. Transfusion. 2020;60(12):2962-8.
23. Xu K, Chen Y, Yuan J, Yi P, Ding C, Wu W, et al. Factors associated with prolonged viral rna shedding in patients with coronavirus disease 2019 (COVID-19). Clin Infect Dis. 2020;71(15):799-806.
24. Shi D, Wu W, Wang Q, Xu K, Xie J, Wu J, et al. Clinical characteristics and factors associated with long-term viral excretion in patients with severe acute respiratory syndrome coronavirus 2 infection: a single-center 28-day study. J Infect Dis. 2020;222(6):910-8.
25. Rhee C, Kanjilal S, Baker M, Klompas M. Duration of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infectivity: when is it safe to discontinue isolation? Clin Infect Dis. 2021;72(8):1467-74.
26. Lu J, Peng J, Xiong Q, Liu Z, Lin H, Tan X, et al. Clinical, immunological and virological characterization of COVID-19 patients that test re-positive for SARS-CoV-2 by RT-PCR. EBioMedicine. 2020 Sep 1;59:102960.
27. Fontana LM, Villamagna AH, Sikka MK, McGregor JC. Understanding viral shedding of severe acute respiratory coronavirus virus 2 (SARS-CoV-2): Review of current literature. Infect Control Hosp Epidemiol. 2021;42(6):659-68.

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