COVID-19 relapse: a diagnostic predicament for clinicians

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Abstract

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The ongoing outbreak of COVID-19 that began in Wuhan, China, has constituted a Public Health Emergency of International Concern, with cases confirmed in more than 200 countries. Currently, infected individuals are the primary source of infection and multiple cases of relapse are also reported following the recovery. It is highly concerning about the nature of relapse which may be caused due to reactivation or reinfection. While the present testing scenario of using different molecular techniques has several loop holes that can report false results and hamper the process of effectively preventing the transmission of the virus. Various recommendations need modifications as to effectively stop the horizontal transmission of the virus and look deeply into the links with relapse cases to prevent a second wave during a pandemic.

Etiological agent for the ongoing pandemic of COVID-19 is a novel coronavirus, better known as SARS-CoV-2. Principal symptom of COVID-19 includes Acute Respiratory Distress Syndrome (ARDS) which is similar the symptoms of Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV-1) and Middle East Respiratory Syndrome (MERS) infection. However,SARS-CoV-2 pneumonia recovery rate is comparatively higher and mortality rate is comparatively lower than the other two. According to World Health Organization (WHO) guidelines the infected patient should be discharged from hospital after the containment period of 14 days along with two consecutive negative RT-PCR results of swab sample at least 24 hours apart (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-theyhappen).During January 28 to March 13,COVID-19 relapse cases have been documented in Shangqui, Henan province[**1**] and later in Korea [https://www.reuters.com/article/us-health-coronavirus-southkorea/south-korea-reports-more-recovered-coronavirus-patients-testing-positive-again-idUSKCN21V0JQ]. Pathogenesis of these relapse cases needs further exploration as they hold important links towards the development of a second wave of the pandemic. Here in this article, we propose the following hypotheses on how COVID-19 relapse can play a significant role in disease burden and further horizontal transmission, based on available evidence.

Antibody response of SARS-CoV-2 infected individuals is mounted between 10 to 14 days depending on the magnitude of the disease severity. Therefore, infected individuals with low antibody titre should be

followed up properly for evidence of reinfection [**2**]. Additionally, antibody testing for SARS-CoV-2 may give rise to false positive tests as it is unable to distinguish between live virus and dead virus. This particular limitation of antibody testing method should be carefully considered before declaration about reinfection or relapse. Furthermore, improper sampling procedure, different source of swab samples, specificity/sensitivity of nucleic acid test kit can lead to the false negative RT-PCR results implying the persistence of infection rather than recurrence or relapse [**3**].

Distinct viral clades of SARS-CoV-2 (A2a, B1) result in variation of virulence [**4**].Considering this fact, there is a possibility that duration between primary infection and relapse may vary across different clades. Furthermore, there is a possibility that the nature of protective neutralizing antibodies (NAbs) may vary for different strains as well. Hence it can be hypothesized that NAbs of primary infection may be unable to protect re-infection by other strains. It also remains to be seen whether in case of relapse low amount of existing NAbs increase during the second course of infection.

Viral latency or incubation period might be considered as a significant variable in relation to relapse. Reports have suggested disparity of viral latency period and a range of up to a maximum of 24 days is also reported [**5**] It might be considered that high latency period of the virus due to simmering viral replication can result in late reactivation of the virus and manifestation of the symptoms. Hence, there is a possibility that the asymptomatic individual might become symptomatic on late reactivation of the virus as virus detection varies from person to person. Therefore, should we consider the symptomatic case as a first occurrence for the virus or late reactivation /relapse from the virus which had been transmitted very early into that person and gone unreported for many days? This can also result in asymptomatic carriers without being detected even through testing given the low viral loads; yet the virus present in them in a latent state.

Another undermined factor might be the viral shedding which may cause transmission from an apparently recovered individual or asymptomatic individual to a healthy individual [**6**]. The Viral shedding may begin 2-3 days before the appearance of symptoms with viral loads decreased monotonically after onset of symptoms[**7**] The virus has been detected in patients at a median of 20 days up to 37 days [**8**]. The viral transmission not only comes through droplet or aerosol route but also through the faeco-oral route [**9**]. The participation of tears and conjunctival secretions in viral shedding has also been speculated [**10**]. All these non classical routes of virus shedding might go unrecognized during discharge of patients who are tested negative only through nasopharynageal swab RT-PCR. Probable loads of viral titer still present in various non-classical transmission routes of the recovered patients even after many days are not only able to spread the infection but also may cause a relapse of the same.

In conclusion, the ongoing public health emergency should look after protocols regarding both molecular testing and antibody testing to contain the pandemic. The infected individuals should strictly be discharged only after two proper consecutive RT-PCR negative results of swab samples from various sources so that it can be helpful to reduce clinically recovered individuals with apparently hidden viral source. Even after that the convalescent patients should be monitored by the health system during the post-discharge domiciliary quarantine period of 14 days and on completion of this period they should be tested again. This will avoid increment in numbers of asymptomatic individuals with reactivation or relapse. Besides, the antibody testing should not be authorised during the time of discharge as its variation of sensitivity/specificity has potential enough to suppress the actual scenario. That said, there remain a few unanswered questions at this point in time - "Does the virus really clear out from the system after the primary infection?" ; "Is it safe to assume that the dead fragments of virus residing inside the body cannot infect someone after the first course of infection ?" ; "He/She is completely cured of the diseases for rest of the life never to test positive again ?"

Reference-

Minlin Jiang, Ya Li, Mingli Han Recurrent PCR positivity after hospital discharge of people with coronavirus disease 2019 (COVID-19) *Journal of Infection*https://www.journalofinfection.com/article/S01634453(20)30152-3/pdf

Paul Kellam, Wendy Barcla The dynamics of humoral immune responses following SARS-CoV-2 infection and the potential for reinfection *JOURNAL of general VIROLOGY* https://doi.org/10.1099/jgv.0.001439

Xie C, Lu J, Wu D, Zhang L, Zhao H, Rao B, et al. False negative rate of COVID-19 is eliminated by using nasal swab test. Travel Medicine and Infectious Disease 2020. https://doi.org/10.1016/j.tmaid.2020.101668.

Adam Brufsky Distinct Viral Clades of SARS-CoV-2: Implications for Modeling of Viral Spread *JOURNAL of medical VIROLOGY* https://doi.org/10.1002/jmv.25902

W. Wang, J. Tang, F. WeiUpdated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, ChinaJ Med Virol, 92 (2020), pp. 441-447

Tapiwa Ganyani, Cecile Kremer, Dongxuan Chen, Andrea Torneri, Christel Faes, Jacco Wallinga, Niel HensmedRxiv 2020.03.05.20031815; doi: https://doi.org/10.1101/2020.03.05.20031815

He, X., Lau, E.H.Y., Wu, P. *et al.* Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med* 26, 672–675 (2020). https://doi.org/10.1038/s41591-020-0869-5

Zhou, F. et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 395, 1054–1062 (2020)

Hindson, J. COVID-19: faecal–oral transmission?. *Nat Rev Gastroenterol Hepatol* 17, 259 (2020). https://doi.org/10.1038/s41575-020-0295-7

Jianhua Xia MM Jianping Tong MD Mengyun Liu MM Ye Shen MD Dongyu Guo MD Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection *JOURNAL of medical VIROLOGY* https://doi.org/10.1002/jmv.25725