

World Journal of *Clinical Cases*

World J Clin Cases 2021 January 6; 9(1): 1-290



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Editorial Board Member of *World Journal of Clinical Cases*, Dr. Antonio Corvino is a PhD in the Motor Science and Wellness Department of University of Naples "Parthenope". After obtaining his MD degree from the School of Medicine, Second University of Naples (2008), he completed a residency in Radiology at the University of Naples Federico II (2014). Following post-graduate training at the Catholic University of Rome, yielding a second level Master's degree in "Internal Ultrasound Diagnostic and Echo-Guided Therapies" (2015), he served on the directive board of Young Directive of Italian Society of Ultrasound in Medicine and Biology (2016-2018). His ongoing research interests involve ultrasound and ultrasound contrast media in abdominal and non-abdominal applications, mainly in gastrointestinal, hepatic, vascular, and musculoskeletal imaging. (L-Editor: Filipodia)

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The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2020 Edition of Journal Citation Reports® cites the 2019 impact factor (IF) for *WJCC* as 1.013; IF without journal self cites: 0.991; Ranking: 120 among 165 journals in medicine, general and internal; and Quartile category: Q3.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yan-Xia Xing; Production Department Director: Yun-Xiaojian Wu; Editorial Office Director: Jin-Lai Wang.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Sandro Vento, Bao-gan Peng

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

January 6, 2021

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<https://www.wjgnet.com/bpg/gerinfo/204>

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<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Necessary problems in re-emergence of COVID-19

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Author contributions: Ren LZ and Liu S conceived the idea for the manuscript; Chen S and Zhang LY wrote the manuscript; Zhang LY and Ouyang HS reviewed the literature.

Conflict-of-interest statement: The authors declare no conflict of interest involved.

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Manuscript source: Invited manuscript

Specialty type: Medicine, research and experimental

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Abstract

The ongoing pandemic of coronavirus disease 2019 poses a great threat to human beings. Although numerous patients have recovered, re-positive cases have been reported in several countries. Till now, we still know very little about the disease and its pathogen severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Therefore, more attention should be paid to the following aspects, such as post-discharge surveillance, asymptomatic infection, re-evaluation of influenza-like symptoms, and dynamic monitoring of genomic mutation of SARS-CoV-2.

Key Words: COVID-19; SARS-CoV-2; Re-positive; Follow-up; Asymptomatic infection

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Core Tip: To date, the re-emergence of coronavirus disease 2019 has been reported in several countries or cities. Therefore, more attention should be paid to the following aspects, such as post-discharge surveillance, asymptomatic infection, re-evaluation of influenza-like symptoms, and dynamic monitoring of genomic mutation of severe acute respiratory syndrome coronavirus 2.

Citation: Chen S, Ren LZ, Ouyang HS, Liu S, Zhang LY. Necessary problems in re-emergence of COVID-19. *World J Clin Cases* 2021; 9(1): 1-7

URL: <https://www.wjgnet.com/2307-8960/full/v9/i1/1.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v9.i1.1>

Country/Territory of origin: China**Peer-review report's scientific quality classification**Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0**Received:** October 14, 2020**Peer-review started:** October 14, 2020**First decision:** November 3, 2020**Revised:** November 5, 2020**Accepted:** November 21, 2020**Article in press:** November 21, 2020**Published online:** January 6, 2021**P-Reviewer:** Słomka A, Warabi Y**S-Editor:** Fan JR**L-Editor:** Wang TQ**P-Editor:** Xing YX

INTRODUCTION

The ongoing pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) results in more than 46840783 confirmed cases and 1204028 deaths in more than 210 countries, areas, or territories by November 3, 2020 (<https://www.who.int/>). Cheerfully, numerous patients have recovered and been discharged from the hospital after careful treatment by medical staff with candidate chemical medicine and traditional Chinese medicines^[1]. However, several studies showed that positive results of SARS-CoV-2 were detected in many recovered patients^[2-6]. The total re-positive rate is 7.7%-19.8% or even higher^[2,3]. Furthermore, 52% and 30% of re-positive patients had IgG and IgM antibodies against SARS-CoV-2, respectively, while 35% of them exhibit one or more COVID-19-related symptoms^[6]. To date, the re-emergence of the disease has also been reported in several countries or cities. Therefore, more attention should be paid to the following aspects.

POST-DISCHARGE SURVEILLANCE IS NECESSARY FOR RECOVERED PATIENTS

The occurrence of reinfection or re-positivity in the recovered patient may be caused by the following reasons. First, the detection method used to evaluate the disease has a poor sensitivity or low sensitivity to clinical samples, resulting in false-negative error. Currently, although many detection methods were reported and used for diagnosis of the SARS-CoV-2 infection, different methods have different sensitivities and specificities, with different degrees of error rates^[7]. A case recently reported in China showed that the results of the first seven tests were negative, but the eighth test confirmed it as a COVID-19 case. These results suggest that more sensitive and specific diagnostic methods are still needed to be developed for COVID-19 detection.

Second, the sampling method, samples, and sampling time may affect the diagnosis. As reported, SARS-CoV-2 was found in many organs, such as the lungs, lymph nodes, spleen, liver, heart, kidneys, semen, brain, and blood, suggesting that the virus can infect and replicate in almost all human organs. However, the amount of virus in different tissues is different. A case report showed that the rectal swabs of six discharged patients were positive and the throat swabs of one discharged patient were positive, but the throat swabs of all seven discharged patients were negative^[8]. They also found that the time from discharge to positive RT-PCR after recovery is 7-11 d^[8]. Moreover, it was reported that SARS-CoV-2 is more mysterious and infectious than other viruses. Thus, the virus may escape from the host's immune system and hide in somewhere of the body that cannot be detected by currently used diagnostic methods. Besides, prolonged but intermittent viral shedding from the recovered patient may also affect the levels of virus in the samples^[9]. Therefore, samples of different tissues, especially samples from the lower respiratory tract, should be selected simultaneously for diagnosis.

The third possible cause may be the discontinuation of antiviral drugs as reported by Wu and colleagues^[9]. To date, no effective antiviral medicines have been obtained worldwide. Although several drugs, including chemical drugs, traditional Chinese medicine, and other drugs, have antiviral effects^[1], these drugs cannot eliminate the virus in the body, but can only inhibit the replication of the virus to a certain extent, leading to asymptomatic infection in re-positive patients. Thus, the surviving virus can still replicate in large quantities after drug withdrawal, resulting in positive results of nucleic acid tests or even worse. In addition, Wong *et al.*^[3] found that the re-positive risk of women is about one third higher than that of men, the re-positive risk of symptomatic patients is at least twice that of asymptomatic patients, and the re-positive risk of patients taking lopinavir/ritonavir is more than 50% higher than that of patients not taking lopinavir^[3]. Moreover, recent results showed that lopinavir/ritonavir is not effective in the treatment of COVID-19^[10,11]. These results suggest that the reasons for the recovered patients testing positive again may be varied and the probability of re-positive rate may be relatively high.

Importantly, as reported previously, lipid metabolism was changed^[12] and peripheral memory B cell response was undetectable^[13] in the recovered SARS-CoV patient in long-term follow-up studies, suggesting that SARS-CoV may cause some clinical sequela in the recovered patients. Since SARS-CoV-2 and SARS-CoV belong to the same family (*Coronavirus* family), and SARS-CoV-2 is more infectious than the latter, whether the SARS-CoV-2 will bring some adverse prognosis to the recovered patients still needs further long-term follow-up study.

Therefore, it is necessary to conduct a long-term follow-up study for recovered patients. Notably, it is necessary to re-evaluate the current standards for patients to be discharged from the hospital or to stop quarantine and continue treatment.

ASYMPTOMATIC INFECTION PLAYS A CRUCIAL ROLE IN RE-EMERGENCE OF THE DISEASE

Asymptomatic infection, also known as inapparent or subclinical infection, is widely found in viral infectious diseases and protozoa-related diseases, such as Ebola virus, human immunodeficiency virus, and *Babesia*. It refers to an infection that has no clinical symptoms but is positive by nucleic acid detection. However, when the conditions are suitable, the virus may replicate in large numbers and eventually spread among individuals. As reported by several studies^[1,14,15], a high proportion (43%-50%) of asymptomatic infections were found in the respiratory tract and saliva samples of quarantined people, which may pose an increasing threat to human health, with the continuous increase of the traveling population worldwide.

It was reported that a patient with asymptomatic infection of SARS-CoV-2 must have a medical history of contact with the confirmed patient, or he/she has been to the epidemic area where the epidemic is occurring. Therefore, asymptomatic infection of COVID-19 may occur for several possible reasons. First, the incubation period of the SARS-CoV-2 is 1 to 14 d or even as long as 24 d in some cases^[16,17]. At the initial stage of infection, the amount of virus is relatively small, and thus no clinical symptoms occur. Second, because the infected person is in good physical condition, the immune system of the infected person effectively inhibits the viral infection process. Third, the virus infection is mild, which is not enough to stimulate an effective immune response in the human body. Moreover, other reasons, such as living environment conditions and basic diseases, will also affect the virus infection and the disease process.

It is worth noting that at present we still know very little about COVID-19 and SARS-CoV-2. However, despite asymptomatic infection, the virus may replicate in the human body and shed from the infected person, thus leading to transmission at the community level^[15]. Huang *et al.*^[18] reported that SARS-CoV-2 can spread asymptotically and rapidly during the incubation period^[18], which was further confirmed by the World Health Organization on July 9, 2020. Chang and colleagues reported that half of the patients with COVID-19 were viral positive even after the resolution of their symptoms up to 8 d^[19], which may be one of the reasons why some recovered patients return to positive. These results indicate that the virus is infectious in the asymptomatic stage and in some cases in convalescent patients, which may become a potential source of SARS-CoV-2 infection or the main driving force of the current pandemic.

Therefore, monitoring asymptomatic infection among the population, especially recent travelers, is undoubtedly an urgent task for controlling the COVID-19. Clinically, nucleic acid detection methods are sensitive but prone to false negatives, while antibody detection methods are slightly less sensitive but more accurate. Thus, we suggest combining the two methods to detect asymptomatic infection of COVID-19.

RE-EVALUATION OF SAMPLES FROM THE PATIENT WITH INFLUENZA-LIKE SYMPTOMS IS BETTER FOR TRACKING THE ORIGIN OF THE VIRUS

Because the symptoms of COVID-19 are similar to those of influenza and other respiratory infections, COVID-19 patients may likely be treated as ordinary influenza patients, resulting in a missed diagnosis. Kong and colleagues re-analyzed 640 throat swabs collected from patients in Wuhan with influenza-like-illness and found that 9 of the 640 throat swabs were positive for SARS-CoV-2 RNA by quantitative PCR^[20]. Lu *et al.*^[21] estimated that as of May 16, 2020, the actual cases of COVID-19 may be 5 to 10 times more than the reported cases, and the total estimated number of cases in the United States is between 6 million and 12.2 million^[21]. Thus, monitoring influenza-like diseases and re-evaluating the samples from patients with influenza-like symptoms may provide a broader understanding of COVID-19, which may be helpful to trace the source and transmission route of SARS-CoV-2.

Moreover, although the symptoms of influenza and COVID-19 are similar, there are several clinical differences between COVID-19 and influenza or other respiratory

infections. It was reported that anosmia, dysgeusia, diarrhea, frontal headache, and bilateral cracklings sounds were statistically more common in COVID-19, while sputum production, dyspnea, sore throat, conjunctival hyperemia, tearing, vomiting, and rhonchi sounds were more frequent with influenza infection^[22]. Besides, COVID-19 patients may become critically ill in the second week post-infection (about day 10), while influenza patients get worse at the end of the first week post-infection (about day 7)^[22]. Symptom monitoring as well as pathogen identification can provide a more timely choice for first-line screening and public health interventions on the diseases as well as seasonal influenza^[23,24]. Therefore, it is an urgent need to develop methods to distinguish COVID-19 cases from other upper respiratory tract and/or influenza-like diseases.

DYNAMIC MONITORING OF GENOMIC MUTATION OF SARS-COV-2 ISOLATE IS IMPORTANT

SARS-CoV-2 belongs to the *Coronavirus* family, *Betacoronavirus* genus, and *Sarbecovirus* subgenus, containing a linear single positive-stranded RNA genome of about 30 kb^[25]. Recent reports showed that mutations occur in the population due to RNA editing in the transcriptome of SARS-CoV-2 or nucleotide substitutions in the viral genome^[26-32]. A synonymous mutation of D614G was located in the B cell epitope of viral S1 domain, by which SARS-CoV-2 can be divided into two subtypes, SARS-CoV-2a and SARS-CoV-2b^[33]. Moreover, SARS-CoV-2b strains exhibit severely reduced antigenicity compared with that of SARS-CoV-2a^[33]. The D614G mutation in the viral spike protein reduces S1 shedding and increases the infectivity of SARS-CoV-2^[25,30]. Pachetti and colleagues found eight mutation hot spots of SARS-CoV-2 at positions 1397, 2891, 14408, 17746, 17857, 18060, 23403, and 28881, including a novel mutation of RNA-dependent RNA polymerase (RdRp) at position 14408^[32], which may affect the recognition of antiviral drugs and RdRp, and the binding of RdRp and template RNA. These results indicate that the mutation may substantially affect the viral transmission, pathogenicity, and drug-resistance phenotypes as well as antigenicity and immunogenicity of vaccines.

Furthermore, numerous pieces of evidence show that SARS-CoV-2 infection has occurred in humans for a long time or even years ago. A recent report showed the spike protein receptor binding domain (RBD) may have a high affinity for human cell targets at least since 2013^[34]. Besides, the vaccine is the best way to prevent and control virus infection, however, although several candidate vaccines have been applied in clinical trials, the efficacy and safety of these vaccines still need further evaluation. Notably, it was reported that the majority of the analyzed population is seronegative to SARS-CoV-2 infection, as low seroprevalence was observed in COVID-19 hotspots, with 5%-10% in Spain, 10.8% in Swiss, 7.3% in Sweden, and 3.8% in Wuhan, China^[35,36], suggesting that the natural herd immunity in the population is not suitable for SARS-CoV-2 infection and effective vaccine against the disease is urgently needed. Therefore, the study of virus mutation can provide a basis for virus traceability, and is also beneficial to the design and development of an efficient and safe vaccine.

CONCLUSION

In conclusion, the COVID-19 epidemic has brought great harm to human beings. However, little is known about the disease and SARS-CoV-2 virus. In particular, recent reports show that the epidemic has risen for the second wave in Europe, and re-infection of the virus occurs in some countries^[37-39]. SARS-CoV-2 D614G variant exhibits enhanced binding, replication, and transmission activities *in vitro* and *in vivo*^[40,41]. Therefore, more stringent strategies are needed to control the spread of the virus, such as post-discharge surveillance of recovered patients, monitoring asymptomatic infections, re-evaluating samples of a patient with influenza-like symptoms, and dynamically monitoring genomic mutation of SARS-CoV-2 isolates.

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