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CORRESPONDENCE

Recurrent positive SARS-CoV-2 RNA tests in recovered and discharged patients☆

Test ARN para SARS-CoV-2 positivos recurrentes en pacientes recuperados y dados de alta hospitalaria

Dear Director:

The ongoing severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic remains a global concern that requires a comprehensive approach to reduce rapid transmission, starting from case detection, inpatient care, as well as post-hospital management. Guidelines recommend [Supp. Ref. 1,2] two consecutive negative polymerase chain reaction (PCR) tests from respiratory specimens at a 24 h interval as hospital discharge criteria. However, concerns have risen over recent reports of increasing re-detectable positive (RP) SARS-CoV-2 RNA tests observed among recovered and discharged patients.[1,2]

These reports raise questions about whether recovered patients are at risk of relapse/reinfection, and whether they are capable of infecting others. However, no clear evidence is currently available on this matter. Aiming to summarize the current evidence, a meta-analysis was performed to estimate the prevalence of RP SARS-CoV-2 RNA tests among recovered patients, in addition to the days of RNA-positive conversion since last negative/discharge.

A comprehensive literature search was conducted through an electronic database dated up to May 2020, with search terms such as ''recovered/discharged patients'', ''coronavirus 2019/COVID-19'', ''SARS-CoV-2'', ''positive PCR'' used in combination without language restriction. The inclusion criteria were:

1 Observational studies or case reports that described some RP SARS-CoV-2 RNA tests among recovered/discharged patients.
2 Studies that recorded a time of RNA-positive conversion since last negative/discharge.

Fourteen studies were included in this meta-analysis (Table 1)[1–10] [Sup. Ref. 3–6]. The pooled prevalence of the RP SARS-CoV-2 RNA test among recovered patients was 32.9% (93/450 subjects, 95% CI 20.7–45.1%, Fig. 1)[1,4,5,9,10] [Sup. Ref. 4,5], which was higher than previously reported [Supp. Ref. 7]. The shortest time to RNA-positive conversion since last negative/discharge was 1 day while the longest was 24 days (Table 1).

A plausible explanation for the RP cases is prolonged viral RNA shedding, shown to be detectable in nasopharyngeal swab/stool specimens up to one month after symptom onset [Supp. Ref. 8,9]. Additionally, as demonstrated by Hu et al., viral fragments were mainly detected in the stool of recovered patients, emphasizing that these fragments are unlikely to be a source of infection [Supp. Ref. 10]. However, it is important to note that the current evidence has shown RNA-positive conversion in patients that have previously presented with two consecutive negative PCR tests. This fact implies the strong possibility of relapse or reinfection. And although one animal study has demonstrated a failure of reinfection after SARS-CoV-2 re-challenge in a primate model [Supp. Ref. 11], more studies are required to confirm this result.

In the absence of reinfection, another plausible explanation of the RP occurrence is the high false-negative rate of SARS-CoV-2 RT-PCR [Supp. Ref. 12]. False negativity can be due to low viral loads under the detection threshold, poor specimen quality, inappropriate sampling and handling techniques, and other technical issues [Supp. Ref. 12,13]. In addition to careful assessment of these issues, other options such as alternative molecular detection techniques and sampling of both upper and lower respiratory tracts may be considered to optimize test sensitivity.

Hence, these results emphasize the importance of accurate diagnostics and appropriate post-hospitalization management during the pandemic, since the infectious capacity of RP cases remain unknown. Based on the evidence on time to conversion, 2–3 weeks home quarantine post-discharge is strongly suggested, alongside personal protective measures (rigorous hand hygiene, cough etiquette, and face masks) to reduce the risk of virus transmission. Intensive monitoring and surveillance should also continue post-discharge, through phone consultation or home visits.

Conflicts of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.rceng.2020.06.005.

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Table 1 Characteristic of the included studies.

Study, Year	Country	Study type	N	No. of RP	Sample	Days of RNA-positive conversion since last negative	Days of RNA-positive conversion since discharge	Symptoms
An et al., 2020	China	Observational	262	38	Nasopharyngeal swab/stool	–	~ 14	Asymptomatic
Chen et al., 2020	China	Case report	1	1	Oropharyngeal swab	3	–	Asymptomatic
Lan et al., 2020	China	Case report	5	5	Throat swab	–	5 – 13	Asymptomatic
Ling et al., 2020	China	Observational	66	11	Oropharyngeal swab	~ 10 – 15	–	Asymptomatic
Li et al., 2020	China	Observational	7	3	Respiratory swab	–	5 – 7	?
Lo et al., 2020	Macau	Observational	10	5	Throat swab/stool	1 – 5	–	?
Luo et al., 2020	China	Case report	1	1	Throat swab	24	22	Asymptomatic
Qu et al., 2020	China	Case report	1	1	Sputum	3	3	Asymptomatic
Xiao et al., 2020	China	Observational	70	15	Throat swab/Deep nasal cavity	–	–	?
Xing et al., 2020 [a]	China	Case report (Pediatric)	3	3	Throat swab/stool	6 – 18	?	Asymptomatic
Xing et al., 2020 [b]	China	Case report	2	2	Throat swab	2 – 6	1 – 5	Asymptomatic
Xu et al., 2020	China	Observational (Pediatric)	10	7	Throat swab/stool	1 – 15	6 – 13	Non-specific and mild symptoms
Yuan et al., 2020	China	Observational	25	14	Cloacal/nasal/ oropharyngeal swab	7.32 ± 3.859 [mean $\pm$ SD]	5.32 ± 4.13 [mean $\pm$ SD]	Asymptomatic
Zhang et al., 2020	China	Case report (Pediatric)	3	3	Stool	–	10 – 13	?

RP, re-detectable positive; SD, standard deviation.

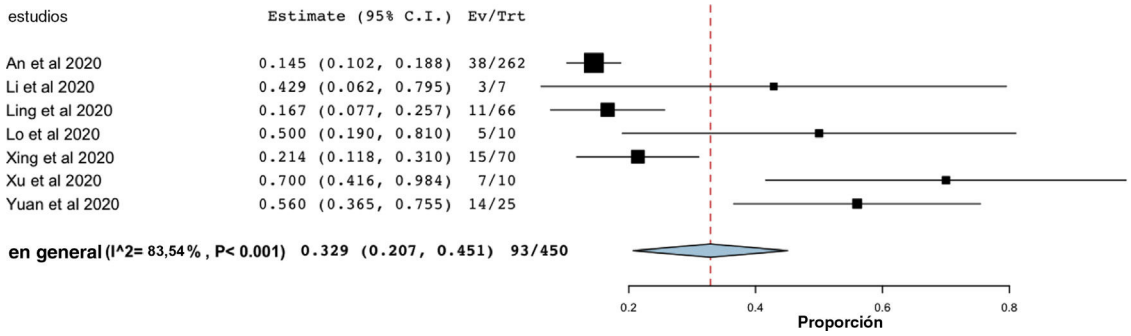

Figure 1 Forest plot of the seven studies estimating the pooled prevalence of re-detectable positive SARS-CoV-2 RNA test among recovered patients.

References

1. An J, Liao X, Xiao T, Qian S, Yuan J, Ye H, et al. Clinical characteristics of the recovered COVID-19 patients with re-detectable positive RNA test. medRxiv. 2020, doi:10.1101/2020.03.26.20044222.
2. Chen D, Xu W, Lei Z, Huang Z, Liu J, Gao Z, et al. Recurrence of positive SARS-CoV-2 RNA in COVID-19: A case report. Int J Infect Dis. 2020;93:297–9, doi:10.1016/j.ijid.2020.03.003.
3. Lan L, Xu D, Ye G, Xia C, Wang S, Li Y, et al. Positive RT-PCR test results in patients recovered from COVID-19. JAMA. 2020, doi:10.1001/jama.2020.2783.
4. 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 (Engl). 2020, doi:10.1097/CM9.0000000000000774.
5. Lo IL, Lio CF, Cheong HH, Lei CI, Cheong TH, Zhong X, et al. Evaluation of SARS-CoV-2 RNA shedding in clinical specimens and clinical characteristics of 10 patients with COVID-19 in Macau. Int J Biol Sci. 2020;16:1698–707, doi:10.7150/ijbs.45357.
6. Qu YM, Kang EM, Cong HY. Positive result of SARS-CoV-2 in sputum from a cured patient with COVID-19. Travel Med Infect Dis. 2020, doi:10.1016/j.tmaid.2020.1016.19.
7. Xing[a] Y, Ni W, Wu Q, Li W, Li G, Tong J, et al. Prolonged presence of SARS-CoV-2 in feces of pediatric patients during the convalescent phase. medRxiv. 2020, doi:10.1101/2020.03.11.20033159.
8. Xing[b] Y, Mo P, Xiao Y, Zhao O, Zhang Y, Wang F. Post-discharge surveillance and positive virus detection in two medical staff recovered from coronavirus disease 2019 (COVID-19), China, January to February 2020. Euro Surveill. 2020, doi:10.2807/1560-7917.ES.2020.25.10.2000191.
9. Xu Y, Li X, Zhu B, Xu Y, Li X, Zhu B, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. Nat Med. 2020, doi:10.1038/s41591-020-0817-4.
10. Yuan J, Kou S, Liang S, Zeng J, Pan Y, Liu L. PCR assays turned positive in 25 discharged COVID-19 patients. Clin Infect Dis. 2020, doi:10.1093/cid/ciaa398.

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Is chronic obstructive pulmonary disease a protective factor in SARS-CoV-2 infection? The importance of bronchodilator treatment☆

¿Es la enfermedad pulmonar obstructiva crónica un factor protector en la infección por SARS-CoV-2? La importancia del tratamiento broncodilatador

Dear Director,

Globally, viruses play an important role in exacerbations of chronic obstructive pulmonary disease (COPD). In a systematic review of infections in patients with COPD that required hospital admission, it was observed that the rhinovirus, respiratory syncytial virus (RSV), and influenza virus were the most prevalent agents, followed by parainfluenza and coronavirus. Coronavirus is the most frequent upper respiratory tract infection and is predominant during the winter months.[1]

In a study conducted in Spain, 26% of patients admitted during the flu season presented with COPD as a comorbidity.[2] Other authors have reported a somewhat lower prevalence of COPD in patients with the flu (17.3%) and an even lower prevalence of COPD in patients with RSV infection (7.6%).[3] There are also studies which have evaluated the presence of COPD as a comorbidity in other coronavirus infections such as SARS, with a rate of 6%,[4] and MERS, with a rate of 13%.[5]

In regard to the current SARS-CoV-2 pandemic, it was initially considered that people with chronic lung diseases could be more prone to presenting with symptoms of the

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