Letter to the Editor

CT suggests discharged Covid-19 patients who were retested RT-PCR positive again for SARS-CoV-2 more likely had false negative RT-PCR tests before discharging

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According to the Covid-19 discharging guideline in China, the patients ready for discharging should meet the following criteria: (I) body temperature is normal for more than 3 days; (II) obvious alleviation of respiratory symptoms; (III) remarkable absorption of lung lesions on chest imaging; (IV) two consecutive (with a 24-hour interval) negative RT-PCR tests for SARS-CoV-2 (1). In February this year it caused a lot of media coverage when four discharged Covid-19 patients were RT-PCR retested positive (RP) again for SARS-CoV-2 during their follow-up (FU) (2). However, since RT-PCR testing for SARS-CoV-2 is known to have certain range of false negative rate (3), simple logic would suggest these patients had false negative RT-PCR testing before discharging. The accuracy and predictive value of RT-PCR SARS-CoV-2 tests have not been systematically evaluated, while it is known that the sensitivity of RT-PCR testing depends on a number of factors including the precise RT-PCR assay, the type of specimen obtained, the quality of the specimen, and duration of illness at the time of testing (3). Simplistic statistic would suggest that, if RT-PCR false negative rate is 40%, then even if it is tested twice, a false negative rate of 16% would remain.

Recently Li *et al.* (4) reported a study carried out in a Chengdu hospital (Sichuan, China) designated for Covid-19 patient care. During January 17 to March 20, 2020, with the 85 patients who were treated, discharged, and had post-discharge FU. Fifteen RP patients (15/85, 17.6%) were re-admitted due to RP result. All these cases had CT imaging both right before discharging and when 're-tested RT-PCR positive'. The CT findings suggested there was no lesion progression during the interval between discharging and readmission, actually most cases showed further lung lesion resolvement (4). Li *et al.* concluded that '*in our opinion, quarantining at home after discharge is still necessary, and a bi-monthly follow-up is recommended. The specific CT manifestation that we observed, that is, the transformation from reticulation to GGO, might be a sign of the existence of the virus and the patient is not fully recovered; therefore, we should give great attention for these circumstances*'. However, transformation from reticulation to ground-glass opacity (GGO), without increase in extent, is likely to suggest lesion resolvement in their cases. Similar finding has been illustrated in a recent study by Du *et al.* (5). GGO indicates a partial filling of air spaces in the lungs by exudate or transudate, as well as interstitial thickening or partial collapse of lung alveoli. Lu *et al.* (6) reported the 12th and 24th month FU CT of an avian influenza subtype A H5N1 virus pneumonia case demonstrated ground-grass shadows, apparent reticular pattern, irregular linear opacities, and interlobular septal thickening and intra-lobular lines. Wong *et al.* (7) reported that in their severe acute respiratory syndrome (SARS) patients the areas with persistent ground-glass opacification after 6 months represented fibrosis. An analysis of Li

et al.'s results still suggests their patients had RT-PCR false negative testing before the discharging. It is expected these patients would return to true negative soon, and unlikely they would remain infectious; though continuous quarantine for a further period will be a safer measure.

Much have been published on this RP topic. In the report from Shenzhen, China, An *et al.* (8) and Yuan *et al.* (9) reported their RP rate was 14.5% (38/262), similar to Li *et al.*'s rate of 17.6% (4). An *et al.* (8) and Yuan *et al.* (9) further noted that the RP patients were more likely to be younger, had mild and moderate conditions, displayed fewer symptoms during the initial disease course. At this time of hospital re-admission, 8 RP patients (32%) had mild cough, and otherwise the patients showed no obvious clinical symptoms or disease progression indicated by normal or improving CT imaging and inflammatory cytokine levels. CT scan showed 12 patients had improvement of lung lesions compared with images before discharging, while other patients showed no worsening than previous results. The RT-PCR results turned to negative within an average of 2.73 days of hospital stay after re-admission. All 21 close contacts of RP patients were tested negative for SARS-CoV-2, and no suspicious clinical symptoms were noted (8,9).

Other publications reported very similar findings. Xiao *et al.* (10) reported a study of 70 Covid-19 patients with 15 (21.4%) patients had RP, and most of RP patients had relief in symptoms or imaging features. Tang *et al.* (11) reported among 209 discharged patients, 9 (4.3%) re-tested positive in throat swabs only, 13 patients (6.2%) re-tested positive in anal swabs only, and 22 (10.5%) re-tested positive in either. No infection was discovered among close contacts of these RP patients. They suggested the risk of RP testing gradually vanishes over time. Zheng *et al.* (12) reported 3 RP patients (3/20, 15%), with 1 tested positive by fecal RNA, while 2 tested positive by both salivary and fecal RNA tests at 1 week of FU. During the FU, all three cases had improved with no increase in their temperature, and improvement in WBC and lymphocyte counts, as well as their CT scans. There was no difference in symptoms between those who remained negative and those who were positive; all cases experienced steady improvement. Moreover, at the week-2 FU, all 20 patients tested negative for SARS-CoV-2, irrespective of sampling route. Zhang *et al.* (13) reported seven RP patients, they were asymptomatic and chest CT images showed no change from the last scan before discharging. Patients' RT-PCR re-testing results turned negative again in several days. Xing *et al.* (14) reported two RP cases (3.23%) among 62 Covid-19 patients, with none of the two cases experienced discomfort and chest CT showed no deterioration. Lan *et al.* (2) reported four RP patients with Covid-19 had positive RT-PCR test results 5 to 13 days after discharging, no family members of these patients were infected. The reports above show an average RP rate of 15%, which, following simplistic statistics, suggests a false negative rate of slightly below 40% for a single test ($0.386 \times 0.386 = 0.15$). This is in line with the false negative rate of RT-PCR in a number of reports from China (3).

A few case reports noted similar findings. Dou *et al.* (15) described two RP cases with their lung lesions further resolved during the interval of initial discharging and positive RT-PCR re-testing. Li *et al.* (16) reported a RP case, who was asymptomatic at re-admission and his chest CT scans showed improvement of original lesions with a few ground-glass opacities. Luo (17) also reported a RP case showing CT finding improvement during the interval of initial discharging and positive RT-PCR re-testing.

Of note, Li *et al.* (18) reported a case whom, based on CT finding of scattered patches and GGO on both lungs, the authors described as '*provides evidence for us to judge the reoccurrence of COVID-19*'. However, at least based on the images they provided in their article, I personally could not find evidence of 'reoccurrence'. Their reading is more likely to be an over-interpretation. They also noted this patient's condition was 'stable'.

There are many additional evidences to show that these RP patients unlikely had 'reinfection'. Most of the RP patients had another a period of self-isolation (at least 2 weeks) after initial discharging, it is quite unlikely that the RP patients contacted other infectious Covid-19 patients during the period of self-isolation. Virus-specific IgG play important roles in virus neutralization and prevention against further infection. SARS-CoV-2 is very similar to the virus SARS-CoV which caused SARS outbreak in 2002. It has been shown that IgG antibodies against SARS-CoV can persist for at least 12 years (19). In a study of rhesus macaques infected with SARS-CoV-2, the animals did not develop reinfection following recovery and re-challenge (20).

Concerning whether RP patients with positive RT-PCR are able to transmit the infection to other people with close contact, as noted above there is till now no evidence that any reported RP patients infected others including their family members. Note the detection of viral RNA does not necessarily indicate the presence of infectious virus. There may be a threshold of viral RNA level below which infectivity is unlikely. Viral RNA levels from upper

respiratory specimens appear to be higher soon after symptom onset compared with later in the illness. Patients might be more infectious in the earlier stage of infection (21). In the study of nine patients with mild Covid-19, infectious virus was not detected from respiratory specimens when the viral RNA level was $<10^6$ copies/mL (22). Additionally, infectious virus was isolated from naso/oropharyngeal and sputum specimens during the first 8 days of illness, but not after this interval, despite continued high viral RNA levels at these sites (22). According to the United States Centers for Disease Control and Prevention, when patients continue to have detectable SARS-CoV-2 RNA in upper respiratory samples following clinical recovery, by 3 days after recovery, the RNA concentrations are generally at or below the levels at which replication-competent virus can be reliably isolated (3,23). Moreover, Hu *et al.* (24) studied 12 RP patients in Guangzhou (RP rate: 10%, 12/120), they reported that that detectable viral genome in RP patients might only mean the presence of viral fragments and would not form an infection origin. They also noted that more anal samples were positive than throat samples.

As noted above, anal samples are more likely to show RP than throat samples (11,12,24). A few studies showed more rectal swab positives were found in a later stage of infection as compared with oral swab positives, suggesting viral shedding through oral-fecal route (25-27). Person-to-person spread of SARS-CoV-2 occur mainly via respiratory droplets, resembling the spread of influenza. Although it would be difficult to confirm, fecal-oral transmission has not been clinically described, does not appear to be a significant factor in the spread of infection (3).

In conclusion, many articles reported positive RT-PCR test for SARS-CoV-2 in Covid-19 patients following clinical improvement and negative results of two consecutive tests. These positive re-tests usually occur shortly after the negative tests, are not associated with worsening symptoms, may not represent infectious virus, and unlikely reflect reinfection. For these patients, unless there is a clinical symptom worsening, FU CT may not be necessary (28,29).

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Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/qims-2020-19). YXJW serves as an unpaid Editor-in-Chief of *Quantitative Imaging in Medicine and Surgery*.

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