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REVIEW

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Patient follow-up after discharge after COVID-19 pneumonia: Considerations for infectious control

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Abstract

Coronavirus disease 2019 (COVID-19) represents a significant global medical issue, with a growing number of cumulative confirmed cases. However, a large number of patients with COVID-19 have overcome the disease, meeting hospital discharge criteria, and are gradually returning to work and social life. Nonetheless, COVID-19 may cause further downstream issues in these patients, such as due to possible reactivation of the virus, long-term pulmonary defects, and posttraumatic stress disorder. In this study, we, therefore, queried relevant literature concerning severe acute respiratory syndrome, Middle East respiratory syndrome, and COVID-19 for reference to come to a consensus on follow-up strategies. We found that strategies, such as the implementation of polymerase chain reaction testing, imaging surveillance, and psychological assessments, starting at the time of discharge, were necessary for long-term follow-up. If close care is given to every aspect of coronavirus management, we expect that the pandemic outbreak will soon be overcome.

KEYWORDS

coronavirus disease 2019, discharge, follow-up, Middle East respiratory syndrome, severe acute respiratory syndrome

1 | INTRODUCTION

At the end of 2019, a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) emerged in Wuhan, China, and caused the outbreak of coronavirus disease 2019 (COVID-19).[1,2] Since the index patient was hospitalized on 12 December 2019, SARS-CoV-2 has rapidly spread around the globe. As of 6 May 2020, 3 588 773 cases have been confirmed worldwide, and 247 503 patients have died.[4] Molecular analysis indicates that SARS-CoV-2 most likely originated from bats after passage in intermediate hosts, which highlights the high zoonotic potential of coronaviruses.[5] Similar to the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome coronavirus (MERS), COVID-19 has so far been treated with a variety of therapeutic strategies, such as antiviral therapies, glucocorticoids, pulmonary supportive therapy, traditional Chinese medicine, and immunotherapy.[6-13] Notably, when patients advance into acute respiratory distress syndrome, glucocorticoid therapy has been shown to exert a significant curative effect due to repression of the cytokine storm.[12,14]

Currently, the WHO reports a COVID-19 mortality rate of 4.4%, compared with 9.6% for SARS and 34.4% for MERS, which indicates that this new viral disease is not as fatal as initially anticipated.[4,15] However, even after symptoms have been alleviated in patients after treatment, relapse of COVID-19 still represents a considerable risk.[16] As mentioned above, corticosteroid therapy might be an option to manage severe pneumonia, however, tapering off the corticosteroid dose could lead to recurrence.[17] Similarly, even when patients reached apparent recovery, viral load occasionally remains at high levels, meaning that these patients could still act as virus carriers.[18]

Thus, a clear definition of discharge criteria and follow-up strategies is critical for the global management of this pandemic. We searched the literature in Pubmed, Web of Science, and the

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Cochrane Library, and summarize the findings concerning the standard of discharge and follow-up of SARS, MERS, and COVID-19 for the consideration of clinicians in this report.

2 | DISCHARGE CRITERIA FOR PANDEMIC COVID-19

At present, in China, there are 73 159 cumulative cured, with only 4735 confirmed hospitalized cases (Table 1).[19]

2.1 | Coronavirus disease 2019

We found the following discharge criteria for COVID-19: the blood oxygen saturation of the patient should have returned to normal levels without a need for oxygen support, normal body temperature for more than 3 days, negative polymerase chain reaction (PCR) tests on two consecutive occasions with a sampling interval of at least a day, and a chest computed tomography (CT) showing that the lesion is essentially absorbed, or only a few fibrous stripes can be observed.[20] Some researchers recommended that the body temperature should be at normal levels for more than a week before discharge.[16] The assessments before discharge were the following: CT lesions, which were mainly ground-glass opacities (GGOs), should have decreased in size and consolidations, if present, and should have decreased in density. The viral load in stool and urine should be tested using real-time reverse transcription-PCR (rRT-PCR) if possible.[21-24] We found the following clinical feature descriptions for discharge: leukocytes and lymphocytes were increased in routine blood analysis, indicating recovery and restoration of immune function, the ear temperature was below 37.5℃, blood oxygen saturation was higher than 93% without supplementary oxygen, and the general health was discussed and evaluated by a multidisciplinary team of experts in hospital.[6,25]

2.2 | Severe acute respiratory syndrome

For SARS, a viral disease derived from *Paguma larvata* and originated from Guangdong, China, the discharge criteria were determined as an afebrile condition for 4 consecutive days, improvement of previously abnormal blood analysis, radiographic improvement, and a period of at least 21 days following the onset of illness, though it has been shown that the SARS coronavirus may still be detectable in the stool of recovered patients for up to 3 weeks.[12] Moreover, some clinicians

TABLE 1 Discharge criteria for coronavirus disease

Items	Details of discharge criteria	Reference
RT-PCR	The interval of two consecutive negative real-time RT-PCR results from upper respiratory tract samples should be 24 to 96 h or longer.	6,16,18,23-25,29-31
Imaging manifestations	Improvements in lesion absorption observed by chest radiography or chest CT scan, including the following items: **(1)** Reduction of GGO size; **(2)** decrease of consolidation density; **(3)** only fibrous stripes left.	6,12,16,18,21,22,24-28
Clinical features	**(1)** Essentially normal body temperature (ear temperature under 37.5℃) for 3-7 d or longer. **(2)** Normal blood oxygen saturation (>93%) without supplementary oxygen. **(3)** Normal laboratory tests: **i)** white cell counts, **i)** platelet counts, **i)** creatinine phosphokinase, **i)** lactate dehydrogenase, **a)** liver function tests,[a] **a)** C reactive protein. **(4)** Improvement of clinical symptoms.	6,12,16,18,24-29,31
For patients tapering corticosteroid	Corticosteroids completely discontinued for more than 1 wk, with above conditions met.	16

Abbreviations: CT, computed tomography; GGO, ground-glass opacities; RT-PCR, reverse transcription-polymerase chain reaction.
[a]Liver function tests include prothrombin time/international normalized ratio, activated partial thromboplastin time, albumin, bilirubin (direct and indirect), aspartate transaminase or serum glutamic-oxaloacetic transaminase, and alanine transaminase or serum glutamic pyruvic transaminase.

suggested that chest consolidation should have reduced by 25% for discharge, the patient should not require supplementary oxygen. Clinicians advised discharged patients to stay home for 1 week with a facemask, and as coronavirus might be shed in feces, emphasized toilet hygiene.[26] Guidelines from the World Health Organization indicated that an afebrile condition for 48 hours (or, more conservatively, 72 hours in Singapore) might be a sufficient discharge criterion.[27,28] No consecutive PCR testing was mentioned.

2.3 | Middle East respiratory syndrome coronavirus

MERS, originating in the Middle East and transmitted from camels, was more severe than COVID-19 and SARS, predominantly due to the induction of life-threatening injuries such as renal failure and septic shock.[13] The discharge criteria for patients with MERS were not precisely clear, which might be due to flexible policies in different hospitals. Testing for viral shedding was recommended to assist decision-making when readily available, and repeat testing should be carried out 24 and 48 hours after the resolution of symptoms. If two repeated PCR tests were negative, discontinuation of isolation and droplet precautions of MERS might be considered after discussion with an infectious disease physician.[29] Another study recommended that the interval between the two consecutive negative PCR tests should be more than 48 hours.[30] As for the guidelines in China, studies have suggested that the PCR testing interval should be between 2 to 4 days, with essentially normal body temperature and improved clinical symptoms.[31]

3 | THE POTENTIAL EVENTS AFTER DISCHARGE

Discharge should not be considered as the final point of overcoming coronavirus, and the disease should not be taken lightly even after discharge, not only by patients as well as close contacts but also clinicians, radiologists, and psychologists (Table 2).

TABLE 2 Potential events after discharge

Items	Postdischarge abnormalities	Reference
Laboratory test	(1) Proportion of positive PCR in discharged patients: 3.2%-9.1%. (2) Positive results of PCR in lower respiratory tract >2 wk. (3) Positive results of PCR in stool or urine >4 wk.	18,32,33,39
Relapse of clinical features	Manifestations: (1) Fever; (2) cough; (3) sore throat; (4) fatigue; (5) palpitation; (6) shortness of breath; (7) dyspnea; (8) osteonecrosis; (9) renal injury; (10) hepatic injury. Blood analysis: (1) Progressive lymphopenia; (2) progressive neutrophilia.	32,41,43,44
Residual radiological manifestations	(1) GGO; (2) consolidation; (3) fibrous stripes.	18,42,43
Mental health	(1) Depressive symptoms; (2) anxiety symptoms; (3) stress; (4) posttraumatic stress disorder.	45-49

Abbreviations: GGO, ground-glass opacities; PCR, polymerase chain reaction.

3.1 | Positive laboratory test

Previous studies have demonstrated that asymptomatic and mildly symptomatic case patients can test PCR-positive greater than 2 weeks from lower respiratory tract specimens.[18] Approximately, 3.2% to 9.1% of patients discharged from the hospital might experience reactivation of SARS-CoV-2—however, without specific clinical characteristics to distinguish it.[32,33] Patients with previously negative rRT-PCR have been occasionally shown to test positive again 4 to 17 days after discharge, potentially due to factors such as sex, older age, glucocorticoid therapy, high-baseline SARS-CoV-2 load, variable genotypes, or related to reinfection or secondary bacterial or viral infection.[16,32,33]

These findings suggest that at least a proportion of recovered patients may still be viral carriers.[18] Hepatitis C virus is exceptionally susceptible to mutation, and the immune protection of the human body cannot keep up with the rate of mutation, meaning that after mutation, the original immunity cannot stave off the mutated virus, and reinfection will occur.[34] Interestingly, this does not seem to be the case for SARS-CoV-2. Genomes of 104 strains SARS-CoV-2 isolated from different locations subjected to whole-gene sequencing showed a 99.9% homology, with no evidence for SARS-CoV-2 mutation.[16] Furthermore, the diagnosis rate of rRT-PCR has been shown to be about approximately 50% to 97% (72 ± 15 [mean ± SD]),[35-38] which indicates that there could be a large number of discharged patients shedding the virus from stool or urine for longer than 4 weeks (29-36 days).[39,40]

3.2 | Reactivated clinical features and residual radiological manifestations

Clinical features, such as fever, cough, a sore throat, fatigue, progressive lymphopenia, or neutrophilia, may recur in the immediate future of discharged patients.[32] Fifty-six percent (56.3%) of discharged patients were shown to still present palpitation, shortness of breath, or dyspnea after physical activity due to the incomplete absorption of the pulmonary opacities. Corticosteroids were applied again for the alleviation of symptoms.[41] However, given the acceptance of remaining fibrous stripes, GGO, or consolidation in the lung, for which absorption could take a broad spectrum of time (see Section 2), these manifestations were not surprising.[18,42,43]

Another outcome of COVID-19 that cannot be overlooked is the osteonecrosis. The prevalence of osteonecrosis in patients using corticosteroids was 9.9%, with a total dosage of greater than 1900 mg hydrocortisone, greater than 2000 mg methylprednisolone, greater than 13 340 mg hydrocortisone-equivalent corticosteroid therapy, and more than 18 days on corticosteroid therapy representing significant risk factors for the subsequent development of osteonecrosis.[43] Moreover, the impairment of liver and kidney function required a longer time to recover.[44]

3.3 | Mental health

During the initial phase of the COVID-19 outbreak in China, 53.8% of respondents rated the psychological impact of the outbreak as moderate or severe; 16.5% reported moderate to severe depressive symptoms; 28.8% reported moderate to severe anxiety symptoms; and 8.1% reported moderate to severe stress levels.[45] Identically, most SARS survivors had favorable physical recovery from their illness, but some patients and their caregivers reported a significant reduction in mental health 1 year later.[46] Early strategies that aim to prevent and treat traumatization, as well as the psychological burden of an epidemic in medical staff and the general public are vitally necessary.

One significant mental health concern is posttraumatic stress disorder (PTSD). Inferred from an Impact of Event Scale score of N26, the occurrence was 41.7%.[47] In another study in Hong Kong, among 131 survivors, 4% at 1 month and 5% at 3 months post-discharge experienced symptoms corresponding to PTSD.[48] Hong et al[49] had reported that of the 68 subjects who finished at least two follow-up interviews, 44.1% developed PTSD throughout the period of the study.

4 | THE FOLLOW-UP STRATEGIES

As overcoming the coronavirus pandemic will likely take considerable further global efforts, there will also be a need to emphasize pneumonia follow-up management to prevent potential factors that could reignite viral transmission after discharge (Table 3).

4.1 | Isolation and nucleic acid test after discharged

For discharged patients as well as their close contacts, further 14 days of quarantine at home are required.[50] Simultaneously, to prevent cross-infection at home, centralized isolations are recommended.[16] Nevertheless, there is a MERS case report showing that a nurse, although kept isolated at home, consistently tested PCR-positive for more than 5 weeks after the first sampling.[51] This finding should be taken into consideration to update the isolation strategy for some extreme cases.

Several studies have shown an interesting phenomenon, with patients kept under surveillance and quarantined at home after discharge testing positive again from consecutive throat swabs during the follow-up period.[33,52] As the viral load and titer gradually diminish during the convalescent period, patients should remain quarantined and be observed for at least 2 weeks after discharge and should be tested for viral nucleic acid again after 2 weeks of isolation.[30,40,51] Another recommendation suggests that discharged patients should have a throat swab test for SARS-CoV-2 every day or every other day, for at least five times.[25] Sustained viral shedding supports a strategy of isolation of infected but discharged patients, which should be the basis of optimal future antiviral interventions.[24]

4.2 | Radiology and pulmonary function in surveillance

Residual lesions were common in chest radiology of coronavirus pneumonia. The host's immune response to coronavirus infection leads to lymphocyte proliferation and macrophage infiltration into alveolar septa and interstitial compartments.[53,54] A significantly greater number of intensive care unit admission days, older age, higher chest radiographic scores, chest radiographic deterioration patterns, and peak lactate dehydrogenase levels were observed in patients with lung fibrosis.[55] Complete resolution in the chest CT could be observed only at 4 weeks or longer after the onset of symptoms.[22,56] The radiological manifestation should be tracked until the complete resolution of pulmonary lesions in chest radiographs or CT scanning.[57-60]

In the rehabilitation period, fibrotic changes in the lungs did not resolve in some patients. These patients complained of a restriction of physical activity from general weakness or shortness of breath due to their decreased pulmonary function, resulting in a lower quality of life.[53,54] A SARS study demonstrated that 25.5% of patients had pulmonary diffusion abnormalities, with the diffusive capacity of the lung for carbon monoxide being less than 80%.[61] Another study illustrated that 1 year after recovery from SARS, persistent impairment of pulmonary function was found in about one-third of patients, and the health status of SARS survivors was significantly worse compared to the healthy population ($P < .001$) based on the St. George Respiratory Questionnaire.[62]

TABLE 3 Follow-up strategies of coronavirus disease

Items	Strategies	Reference
Isolation	**(1)** Quarantine at home for a 14-d period after discharge. **(2)** Centralized isolation or isolation in a hotel is recommended.	16,50
PCR	PCR should be carried out again after 2-wk quarantine.	16,30,40,51
Radiology	**(1)** CT or CXR follow-up until complete absorption of pulmonary lesions. **(2)** Patients using corticosteroids should receive an MRI 3-6 mo after discharge.	57-60,63
Pulmonary function	When visiting the out-patient department, patients should receive pulmonary function tests, including: **(1)** FVC; **(2)** FEV1; **(3)** FEV1/FVC; **(4)** DLCO; **(5)** SGRQ.	61,62
Mental health and quality of life	Self-assessment tools: **(1)** The Self-Reporting Questionnaire 20 items; **(2)** The Patient Health Questionnaire-9; **(3)** The Generalized Anxiety Disorder 7 scale; **(4)** The Pittsburgh Sleep Quality Index Scale; **(5)** The Symptom Checklist-90-R; **(6)** The Impact of Event Scale -R, the Hospital Anxiety and Depression Scale; **(7)** The Self-rating Anxiety Scale; **(8)** The Self-rating Depression Scale; **(9)** The Karnofsky Performance Status Scale. Other-assessment tools: **(1)** The Hamilton Depression Rating Scale; **(2)** The Hamilton Anxiety Rating Scale; **(3)** The Positive and Negative Syndrome Scale.	25,44,47,48,64,66,67
Key time points of follow-up	Remote follow-up (time after discharge): **(1)** First 3 d; **(2)** 2 wk; **(3)** 3 mo; **(4)** 6 mo. Out-patient follow-up (time after discharge): **(1)** 1 wk; **(2)** 2 wk; **(3)** 1 mo.	25,68

Abbreviations: CT, computed tomography; CXR, chest radiography; DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; SGRQ, St. George Respiratory Questionnaire.

Magnetic resonance imaging (MRI) for osteonecrosis also has a critical role in follow-up strategies. Individuals who have a risk of avascular necrosis of the femoral head should receive MRI examinations 3 to 6 months after discharge.[63]

4.3 | Mental health and quality of life

On the basis of survey results,[44] a considerable number of SARS patients still experienced psychological issues after discharge from the

hospital. All patients should be dynamically monitored during admission and before discharge, including the extent of personal mental stress, mood, sleep, stress, and other mental state effects.[25] Moreover, self-assessment tools and assessments by others, including a variety of assessment scales, could be utilized to evaluate the psychological outcomes of patients (Table 3).[25,44,47,48,64]

Likewise, the ability to return to normal activity and work without special care requirements are other items to be considered for evaluation during recovery. Pulmonary function defects commonly lead to a limitation of activities, yet a substantial number of patients experienced a reduced exercise capacity which could not be accounted for by an impairment of pulmonary function.[65] As for the severe COVID-19 MERS, 84.6% of survivors could return to normal status, whereas the rest were unable to [66,67] based on the assessment of the Karnofsky Performance Status scale.

4.4 | Remote and out-patient follow-up

Telephone follow-up should be carried out at 3 days, 2 weeks, 3 months, and 6 months after discharge, with out-patient follow-ups at 1 week, 2 weeks, and 1 month after discharge.[25,68]

5 | DISCUSSION AND CONCLUSION

It should be noted that patients could be regarded as misdiagnosed and would not need to be followed up if two negative serological test results are received at two consecutive follow-ups.[63] Owing to the relative success of COVID-19 containment in China, there are now 81 171 discharged cases under follow-up status.[19] For a comprehensive follow-up process, clinicians were able to imitate and adopt a variety of management policies based on the epidemic history of coronaviruses, comprising SARS and MERS. Notably, SARS uses the same entry receptor (angiotensin-converting enzyme 2) as COVID-19, and the pathogenesis, treatment, and the follow-up strategies for COVID-19 could, therefore, be relatively easily deducted.[69] As viral shedding can potentially be sustained for several weeks, hand hygiene and mask-wearing are critical precautionary measures.[70] During the follow-up period, constant hand wiping using a wet towel soaked in water containing 1.00% soap powder, 0.05% active chlorine, or 0.25% active chlorine from sodium hypochlorite and N95 masks, medical masks, and homemade masks made of four-layer kitchen paper and one-layer cloth may supply considerable disease prevention.[71]

By abiding by the follow-up process presented in this review, we expect that management of this outbreak will be achieved soon. Nonetheless, the potency of this outbreak should not be underestimated—COVID-19 remains a significant pandemic, and being discharged from the hospital should not be considered the endpoint of monitoring and precautionary measures. From the time of discharge to long-term follow-up, every aspect of coronavirus management should be readily scrutinized.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

JZ and KW participated in the study design; ZZ performed data collection and analysis; and ZY drafted the manuscript. All authors provided critical review of the manuscript and approved the final draft for publication.

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