The need for improved discharge criteria for hospitalised patients with COVID-19 – implications for patients in long term care facilities

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Abstract: In the COVID-19 pandemic, patients who are older and residents of long term care facilities (LTCF) are at greatest risk of worse clinical outcomes. We reviewed discharge criteria for hospitalised COVID-19 patients from ten countries with the highest incidence of COVID-19 cases as of 26th July 2020. Five countries (Brazil, Mexico, Peru, Chile and Iran) had no discharge criteria; the remaining five (United States of America, India, Russia, South Africa and the United Kingdom) had discharge guidelines with large inter-country variability. India and Russia recommend discharge for a clinically recovered patient with two negative reverse transcription polymerase chain reaction (RT-PCR) tests 24 hours apart; the USA offers either a symptom based strategy – clinical recovery and ten days after symptom onset, or the same test-based strategy. The UK suggests that patients can be discharged when patients have clinically recovered; South Africa recommends discharge 14 days after symptom onset if clinically stable.

We recommend a unified, simpler discharge criteria, based on current studies which suggest that most SARS-CoV-2 loses its infectivity by 10 days post-symptom onset. In asymptomatic cases, this can be taken as 10 days after the first positive PCR result. Additional days of isolation beyond this should be left to the discretion of individual clinician. This represents a practical compromise between unnecessarily prolonged admissions and returning highly infectious patients back to their care facilities, and is of particular importance in older patients discharged to LTCFs, residents of which may be at greatest risk of transmission and worse clinical outcomes.

Key words: COVID-19, SARS-CoV-2, discharge, infectivity, long term care facilities, older people.

Keypoints:

- There is large heterogeneity of existing discharge criteria for hospitalised COVID-19 patients from different countries.
- There is no evidence for the use of RT-PCR in patients with confirmed COVID-19 as a marker of infectivity in late disease
- Further research is required to establish how infectiveness can be measured accurately and in a cost effective way.

- Development of evidence-based discharge guidance for patients hospitalised with COVID-19 is an urgent research priority.
- Current evidence suggests that most patients are non-infective 10 days post symptom onset or after first positive PCR result

COVID-19 is a global pandemic. Older patients are at risk of hospitalisation and severe disease.[1] Globally, a high proportion of long term care facilities (LTCF) have reported COVID-19 outbreaks, with high rates of morbidity and mortality in residents.[2,3] In the UK, according to the latest report from the Care Quality Commission, as of 5th June 2020, 11,614 nursing home residents died of COVID-19, contributing to a quarter of all COVID-19 related deaths.[4] In some European countries, the proportion of COVID-19 cases in LTCFs who have died has exceeded 60% of all reported deaths, underlining the severe impact of COVID-19 on this frail population.[2,5]

The transmission dynamics of COVID-19, combined with low availability of testing in some countries have fuelled a rapid spread within and between facilities..[3] Residents of LTCF who display symptoms of COVID-19 are commonly hospitalised. However, it is currently not clear when a patient with COVID-19, can be discharged after sufficient clinical improvement in hospital. Where they continue to be infectious following recovery, this may lead to increased transmission within LTCFs. On the other hand, a prolonged inpatient stay may put them at risk of nosocomial infections, and occupying a hospital bed unnecessarily, with potential downstream impacts on patient flow and hospital capacity.

We therefore reviewed the discharge criteria for inpatients with COVID-19 in the 10 countries with the highest incidence of COVID-19, as of 26th July 2020(Table 1). We studied publicly available guidance from the US Centers for Disease Control and Prevention (CDC), the European Centre for

Disease Prevention and Control (ECDC), Public Health England (PHE) and the Ministries of Health in Russia, South Africa and India, on management of hospitalised COVID-19 patients.

The 10 countries with the incidence of COVID-19 were, from highest to lowest: US, Brazil, India, Russia, South Africa, Mexico, Peru, Chile, United Kingdom and Iran (Table 1). The median incidence of COVID-19 cases was 409,618 cases (interquartile range: 343,592-1,385685). We did not find any discharge criteria for half of all countries (Brazil, Mexico, Peru, Chile and Iran). Russia and India followed the criteria suggested by the European Centre for Disease Prevention and Control (ECDC) – that clinically recovered patients with suspected or confirmed COVID-19 should have at least two negative reverse-transcriptase polymerase chain reaction (RT-PCR) tests from respiratory specimens taken 24 hours apart , both being collected at least seven days after the first positive RT-PCR test.

The USA is the only country to provide guidance on the management of both symptomatic and asymptomatic patients with COVID-19. It offers two strategies for symptomatic patients with COVID-19: either the patient has had 3 days without fever, improvement in respiratory symptoms and at least 10 days since onset of symptoms; or two negative RT-PCR tests from respiratory specimens 24 hours apart (with no required interval post-symptom onset). For asymptomatic patients with COVID-19, the CDC recommends patients should remain in transmission-based precautions until either 10 days have passed since the date of their first positive test or two negative RT-PCR tests from respiratory specimens taken 24 hours apart (with no required interval post-symptom onset).

The UK and South Africa do not use RT-PCR tests to guide all discharges. The UK suggests that the majority of patients can be discharged when they are clinically well, apart from LTCF residents who should be tested 48 hours prior to discharge. These guidelines do not state what actions have to be taken in the situation of testing positive or negative. South Africa recommends that patients can be discharged 14 days after there are clinically stable (not requiring oxygen) or 14 days after onset of symptoms.

Hence, current discharge criteria are highly heterogeneous among countries, with no clear consensus, and have significant limitations. First, viral RNA from the upper respiratory tract does not seem to correlate with culturable, and therefore infectious, virus in late stage disease. Wölfel et al. isolated virus samples from the upper respiratory tract in nine symptomatic patients (young to middle-aged professionals) with mild symptoms of COVID-19.[6] Culturable virus remained detectable up to 8 days post-symptom onset, but was no longer detectable by day 10. However, viral RNA remained detectable by PCR up to at least day 20.

Arons et al. performed universal PCR testing and viral culture at two time points seven days apart in a nursing home outbreak of COVID-19 in the USA, involving 76 residents (aged 70-90 years old) of whom 48 were SARS-CoV-2 positive.[7] Of these 48 cases, 17 showed typical symptoms (fever, cough, dyspnoea), 4 showed atypical symptoms (chills, malaise, confusion, nasal congestion or rhinorrhoea, myalgia, headache, dizziness, nausea, diarrhoea), 24 were pre-symptomatic and 3 remained asymptomatic at the time of testing. Surprisingly, despite the wide spectrum of clinical illness and the age of these patients, the authors found that the viral loads were similar in each group and did not change significantly with the number of days post-symptom onset. In addition, viable virus was detectable by culture from 6 days before symptom onset up to 9 days after, indicating these patients were only infectious during this period, despite PCR positivity being detectable up to 13 days post-illness onset.

Bullard et al. tested 90 samples obtained from patients aged 30-59 years (median 45 years) using SARS-CoV-2 PCR and virus culture in a Vero cell-line. They found that 26 (28.9%) of these samples were culture positive, but no virus could be grown beyond day 8 post-symptom onset, despite PCR positivity persisting for up to 21 days. Culture positive samples exhibited higher viral loads (corresponding to lower Ct values of 16-18) compared with culture negative samples (Ct values 22-33).[8]

Second, it appears that transmission of SARS-CoV-2 appears to occur predominantly in the presymptomatic phase and less than five days after symptom onset. Cheng and colleagues show a detailed contact tracing response to cases in Taiwan. They found no secondary transmission from contact exposures after the fifth day of symptom onset, suggesting a relatively short infectious period. [9] He and colleagues reported temporal patterns of viral shedding in 94 patients with laboratory confirmed COVID-19 and modelled COVID-19 infectivity profiles from a separate sample of 77 infector-infectee transmission pairs. They found that the highest viral load in throat swabs were at the time of symptom onset.[10] A recent study of COVID-19 in the quarantined Italian town of Vo found that 42% of COVID-19 cases were asymptomatic infections. The lack of effective guidelines on safe discharge of patients with nosocomial acquisition of COVID-19 who are asymptomatic or presymptomatic could potentially lead to outbreaks in LTCFs.[11]

Third, no guideline has an approach tailored to discharge to LTCFs, where frail, vulnerable and ultimately the highest risk residents require daily assistance with all activities of daily living. Potentially related to this are some findings of live SARS-CoV-2 in the faeces of some patients from China [12,13], earlier on in the pandemic (Feb 2020). However, five months on from these reports, there have not been any reports of major COVID-19 outbreaks related to this route of transmission.

Therefore, the use of PCR-based discharge criteria alone may be unhelpfulin determining infectivity and the timing of patient discharge. Although SARS-CoV-2 viral culture offers an indication of virus infectivity, it may take 3-6 days to observe a cytopathic effect, is labour-intensive and requires high level laboratory (Category 3/Biosafety Level 3) facilities. Furthermore, most diagnostic laboratories in the UK have stopped offering viral culture as a service and the skill sets/infrastructure needed to deliver it no longer exist.

Whilst PCR-based testing on inactivated viral extracts is safer and quicker, and can be semi- or fully automated, PCR results do not necessarily give a reliable indication of infectivity. Although Bullard

and colleagues found a strong and non-overlapping correlation between Ct values and growth of SARS-CoV-2 in cell culture, Ct values are not interchangeable between assays, and can be impacted by the assay's gene target(s), nucleic acid extraction system and PCR amplification chemistry. Furthermore, Ct values do not necessarily correlate to the presence/absence of symptoms, or specific symptom patterns, and may not change over time in some patients.

Based on the above, we recommend simpler discharge criteria, which states that the hospitalised patient is non-infective 10 days after symptom onset, or date of first PCR positive result. This is in line with the most recent WHO guidance on the 'criteria for releasing COVID-19 patients from isolation' [14]:

"Symptomatic patients: 10 days after symptom onset, plus at least 3 additional days without symptoms (including without fever and without respiratory symptoms); Asymptomatic cases: 10 days after positive test for SARS-CoV-2"

Thus, if initially symptomatic patients are already asymptomatic by day 10, post-symptom onset, the criteria are the same. Incidentally, the UK has recently extended their recommended self-isolation period to ten days, for those in the community who have tested positive for SARS-CoV-2 or have Covid-19 symptoms.[15]

We believe this approach to be simple, the most evidence based, and applicable to all countries – for the moment. However, as the COVID-19 pandemic continues to evolve, any new evidence will be reviewed and incorporated as required, to update this guidance.

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Table 1: National guidance regarding discharge of hospitalized COVID-19 patients from the 10 countries with the highest incidence of COVID-19 as of 26 July 2020.

Countries	Number infected	Discharge guiadance: source	Is Negative NP swab considered as a discharge criterion?	Two negative swabs 24 hours apart prior to discharge	Resolution of clinical symptoms	Number of days since symptom onset before patient can be discharged	Additional comments
US	4,181,268	CDC USA[1]	Yes	Yes	Yes	10	Two different strategies; one symptom based, another test based
Brazil	2,394,513	None found	N/A	N/A	N/A	N/A	N/A
India	1,385,685	Ministry of Health and Family Welfare, Government of India[2]	Yes (only for severe cases)	Yes (only for severe cases)	Yes	10	Guidelines were changed from earlier guidelines which required all

							categories of patients to test negative on two consecutive RT PCR tests conducted at a 24 hour interval before they could be discharged (based on interim guidance from WHO which said that monitoring of a confirmed patient could stop if two negative tests are recorded more than 24 hours apart.)[3]
Russia	811,073	Ministry of Health of Russia [4]	Yes	Yes	Yes	Non-specified	N/A
South Africa	434,200	Republic of South Africa[5]	No	N/A	Yes	14	De-isolate 14 days after clinically stable (not requiring oxygen) or 14 days

							after onset of symptoms (if did not require oxygen)
Mexico	385,036	None found	None found	N/A	N/A	N?A	N/A
Peru	375,961	None found	None found	N/A	N/A	N/A	N/A
Chile	343,592	None found	None found	N/A	N/A	N/A	N/A
United Kingdom	300,275	Public Health England (PHE)[6]		No. All patients discharged to a LTCF should be tested 48 hours prior to discharge, and result related to receiving organizatio n.	No	N/A	Patients can and should be discharged before resolution of symptoms, provided they are deemed fit for discharge. According to DHSC adult social care plan[7], for LTCF residents: " Where a test result is still awaited, the patient will be discharged and pending the result, isolated in

							the same way as a COVID-positive patient will be"
Iran	291,172	None found	None found	N/A	N/A	N/A	N/A

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