

ABSTRACT

Introduction The effects of COVID-19 infection persist beyond the active phase. Comprehensive description and analysis of the post COVID sequelae in various population groups are critical to minimise the long-term morbidity and mortality associated with COVID-19. This analysis was conducted with an objective to estimate the frequency of post COVID sequelae and subsequently, design a framework for holistic management of post COVID morbidities.

Methods Follow-up data collected as part of a registry-based observational study in 31 hospitals across India since September 2020–October 2022 were used for analysis. All consenting hospitalised patients with COVID-19 are telephonically followed up for up to 1 year post-discharge, using a prestructured form focused on symptom reporting.

Results Dyspnoea, fatigue and mental health issues were reported among 18.6%, 10.5% and 9.3% of the 8042 participants at first follow-up of 30–60 days post-discharge, respectively, which reduced to 11.9%, 6.6% and 9%, respectively, at 1-year follow-up in 2192 participants. Patients who died within 90 days post-discharge were significantly older (adjusted OR: 1.02, 95% CI: 1.01, 1.03), with at least one comorbidity (aOR: 1.76, 95% CI: 1.31, 2.35), and a higher proportion had required intensive care unit admission during the initial hospitalisation due to COVID-19 (aOR: 1.49, 95% CI: 1.08, 2.06) and were discharged at WHO ordinal scale 6–7 (aOR: 49.13 95% CI: 25.43, 94.92). Anti-SARS-CoV-2 vaccination (at least one dose) was protective against such post-discharge mortality (aOR: 0.19, 95% CI: 0.01, 0.03).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Long COVID is seen in a large proportion of patients with COVID-19 with fatigue, dyspnoea, mental health problems, etc as the most common problems.

WHAT THIS STUDY ADDS

⇒ Multiple systems are involved in long COVID, and a large number of patients continue having two or more symptoms of long COVID much beyond the acute phase of COVID-19, which attenuates over 1 year.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Targeted follow-up and developing a holistic multidisciplinary management framework with engagement of care outreach workers as well as teleconsultation could be the way forward in the management of long COVID.
Conclusion Hospitalised patients with COVID-19 experience a variety of long-term sequelae after discharge from hospitals which persists although in reduced proportions until 12 months post-discharge. Developing a holistic management framework with engagement of care outreach workers as well as teleconsultation is a way forward in effective management of post COVID morbidities as well as reducing mortality.

INTRODUCTION

Globally, the COVID-19 pandemic presented unprecedented challenges in the areas of prevention and care, and even today it continues to devastate the economy as well as human lives. COVID-19 complications do not end with recovery from acute infection, but continue to involve multiple systems for periods much longer than the acute phase. Studies have suggested the burden of long COVID to be up to 45% with a range of symptoms including fatigue, dyspnoea, mental health problems, gastrointestinal symptoms, persistent loss of smell and taste, etc. The exact definition and nomenclature for these sequelae are still evolving and are being termed as post COVID condition, long COVID, post COVID syndrome, etc. The WHO defines post COVID condition as ‘an illness that occurs in people who have a history of probable or confirmed SARS-CoV-2 infection; usually three months from the onset of COVID-19, with symptoms and effects that last for at least two months. The symptoms and effects of post COVID condition cannot be explained by an alternative diagnosis.’ The Ministry of Health & Family Welfare, Government of India (MOH&FW, GOI) defines post COVID syndrome as a condition characterised by signs and symptoms that develop during or after an infection consistent with COVID-19 which continue for more than 12 weeks and are not explained by alternative diagnosis. The reasons for long-term sequelae of COVID-19 are incompletely understood and could be multifactorial, including the pre-existing comorbidities, disease severity and therapy received during active disease, grief due to personal losses, mental and psychological effects of the disease, etc. As the population size of COVID-19 survivors is increasing due to the lingering pandemic, post-infection immunity and wide coverage of vaccination, understanding the pattern of post COVID sequelae becomes important with its implication for care and support. In this context, we conducted the present investigation to describe the pattern and estimate the frequency of post COVID sequelae, early post-discharge mortality and the risk factors associated with it. The overall purpose was to help develop a framework for holistic inter-disciplinary management of post COVID-19 sequelae specific to Indian settings.

METHODS

National Clinical Registry for COVID-19 is an ongoing electronic platform developed and maintained by the Indian Council of Medical Research (ICMR) in collaboration with the MOH&FW, GOI; All India Institute of Medical Sciences, New Delhi; and ICMR-National Institute of Medical Statistics (NIMS). This is an observational registry-based study where data from demographic, clinical, laboratory parameters and follow-up details are captured. The structure and protocol of the registry are available in the public domain (https://www.icmr.gov.in/tab1ar1.html). More details about the functioning of the registry are published elsewhere.

Participants

The registry enrolls consecutive patients who are hospitalised and have COVID-19 infection confirmed by real time-PCR or nucleic acid amplification test or rapid antigen test across a network of 42 participating hospitals. No exclusion criteria are applied. In hospitals willing to undertake follow-up, consenting participants are followed up every month after being discharged from the hospital for the first 3 months and then once in every 3 months till one year post-discharge. The follow-up is primarily telephonic, but some patients are followed up physically based on the discretion of the treating physician and the policy of the treating hospital.

Participant retention algorithm and profile

Until October 2022, 8042, 5060, 3912, 5007, 2269 and 2192 participants had been contacted at the six time points in the year after discharge, respectively, as discussed earlier. The number of participants for whom a telephonic contact was attempted, who were reported to have died and who could not be contacted at each follow-up time point is depicted in figure 1. At first to sixth follow-up, 83.4%, 89.8%, 85.7%, 85.5%, 85.5% and 84.8% of the patients were alive, respectively. The reported death was highest at the first follow-up, that is, 4.3% and was reported to be 1.8%, 1.5%, 2.2%, 1.7% and 2.4% at second, third, fourth, fifth and sixth follow-up, respectively.

Data collection

Data are being collected using a prestructured case report form adapted from the WHO questionnaires, and are being entered into an electronic portal, developed and maintained by the ICMR-NIMS, New Delhi. In response to the evolving evidence on post COVID symptoms, the questionnaire is updated as and when need arises.

In the present investigation, we included data from patients in 31 hospitals who have been followed up post-discharge from September 2020 to October 2022. Signs and symptoms have been presented as frequency and proportions, while continuous data are presented as mean (SD) or median (IQR), as appropriate. Data analysis was carried out using STATA V.14 (College Station, Texas, USA). Multivariate logistic regression model was used for identifying factors independently associated with mortality within 90 days of discharge. The frequency of post COVID symptoms was also segregated by the three waves of the pandemic, corresponding to alpha, delta and omicron wave.
Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

A comparison of characteristics at hospital admission for participants who were reported to be symptomatic and asymptomatic at first follow-up (30–60 days post-discharge) is presented in table 1. Over 60% of the participants were males; the proportion of symptomatic and asymptomatic patients at follow-up across gender was not different. The patients reporting symptoms at follow-up were significantly older and a higher proportion among them had at least one comorbidity. The median WHO ordinal scale11 at admission was higher among the symptomatic when compared with asymptomatic.

The patient characteristics such as age, gender and comorbidities at the first follow-up and sixth follow-up were comparable.

Symptoms in patients with COVID-19 post-discharge

The most common symptoms at first follow-up after discharge were dyspnoea, fatigue and mental health issues reported among 18.6%, 10.5% and 9.3% of the patients, respectively. At 1 year, the proportion reporting dyspnoea, fatigue and mental health issues reduced to 11.9%, 6.6% and 9%, respectively. Other common issues reported were weakness of limbs, body ache, joint pain, cough, headache, vomiting, chest pain, fever, and loss of taste or smell which ranged from 1% to 6.7% during first follow-up and 0.1–4.5% at the 1-year follow-up post-discharge. A variety of other symptoms and issues were reported in less than 1% of participants (figure 2). Most of the symptoms gradually decreased during follow-up from a 30-day to 1-year period. Only 10.1% and 6.9% of patients having dyspnoea and mental health issues, respectively, had required intensive care unit (ICU) admission during the original hospital admission. Over 15% of the followed up population reported two or more symptoms at all six follow-ups, while over 2% of population reported six or more symptoms.
more symptoms at the first follow-up. The proportion of patients with number of reported symptoms is available in the online supplemental file.

At the first follow-up at 30–60 days, 4.3% of the participants were reported to have died, while at the second follow-up, another 1.8% had died. Table 2 shows the characteristics of patients who died before the second follow-up after being discharged from the hospital versus those who survived until the second follow-up, which was done between 60 and 90 days of discharge from the hospital.

### Table 1  Baseline characteristics at the time of hospital admission of participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>30–60 days after discharge, n=6705</th>
<th></th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Symptomatic, n=2133</td>
<td>Asymptomatic, n=4572</td>
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<tr>
<td>Male</td>
<td>1335 (62.6)</td>
<td>2847 (62.3)</td>
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</tr>
<tr>
<td>Female</td>
<td>797 (37.3)</td>
<td>1725 (37.7)</td>
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</tr>
<tr>
<td>Transgender</td>
<td>1 (0.1)</td>
<td>–</td>
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<tr>
<td>Age groups (completed years)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>0–19</td>
<td>65 (3.1)</td>
<td>345 (7.6)</td>
<td></td>
</tr>
<tr>
<td>20–39</td>
<td>508 (23.8)</td>
<td>1699 (37.2)</td>
<td></td>
</tr>
<tr>
<td>40–59</td>
<td>843 (39.5)</td>
<td>1436 (31.4)</td>
<td></td>
</tr>
<tr>
<td>60 and above</td>
<td>717 (33.6)</td>
<td>1092 (23.9)</td>
<td></td>
</tr>
<tr>
<td>Patients with at least one comorbidity</td>
<td>1352 (63.4)</td>
<td>1998 (43.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WHO ordinal scale at discharge</td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>0–2</td>
<td>1921 (90.1)</td>
<td>4040 (88.4)</td>
<td></td>
</tr>
<tr>
<td>3–5</td>
<td>193 (9.1)</td>
<td>502 (11)</td>
<td></td>
</tr>
<tr>
<td>6–7</td>
<td>19 (0.9)</td>
<td>30 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Patients requiring ICU stay during hospitalisation</td>
<td>275 (12.9)</td>
<td>487 (10.7)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Values are reported as n (%) unless specified.

*Comparisons are made between the participants who were symptomatic and asymptomatic at first follow-up.

ICU, intensive care unit.

[Table 1: Baseline characteristics at the time of hospital admission of participants]

### Figure 2  Symptom profile of participants post-discharge.
hospital. The mean age of the deceased was 51.6 years (SD ±19.6 years), which was significantly higher than those who survived. Among those who died, a significantly higher proportion were above 60 years of age (44.2% vs 30.7%), had at least one comorbidity (68.2% vs 52.3%) and had required ICU admission during their original hospital stay (29% vs 11.7%) as compared with survivors. A definitive cause of death was available in only 137 patients; majority (88, 64.2%) had died owing to cardiac causes that included heart failure and myocardial infarction. Respiratory failure and sepsis/septic shock caused death among 26 (19%) and 15 (10.9%) participants, respectively. Stroke, pre-existing malignancy, chronic kidney disease and mucormycosis were reported to be a cause of death for three, three, one and one patients, respectively. Forty-seven per cent (204 of 434) of the patients who did not survive until the second follow-up died at home, while the rest (53%; 230 of 434) died at a healthcare facility. The median gap between discharge and death from the hospital was 14 (IQR: 5–29) days.

Comparison of the three waves of the pandemic
The patients were grouped based on the date of admission to the hospital with respect to the three waves of the pandemic, considering first wave from the beginning of the pandemic until 1 February 2021, second wave spanning from 2 February 2021 until 15 December 2021, and the third wave from 16 December 2021 to 20 February 2022. The numbers of patients followed up in the first, second and third wave were 2037 (30.4%), 3636 (54.2%) and 1032 (15.4%), respectively. While dyspnoea, mental health issues and fatigue were highest among patients admitted during the second wave of COVID-19, the post-discharge death before the first follow-up was highest among the patients admitted during the third wave of COVID-19 (figure 3).
Currently, with high infectivity and low mortality of SARS-CoV-2 infection, the number of COVID-19 survivors is going up, and is amenable to further increase as the pandemic lingers on. COVID-19 has been associated with sequelae like fatigue, headache, attention disorder, dyspnoea, hair fall and others. This makes constituting multidisciplinary teams essential for holistic management of patients presenting with COVID-19 sequelae at various treatment centres.

Our study shows that the most common symptoms at first follow-up after discharge were dyspnoea, fatigue and mental health issues. Within the first 60 days after discharge, 4.3% of the patients had died. The post-discharge death is highest during the third wave, though the rest of the common symptoms were more during the second wave of COVID-19.

The most common issues reported by patients with COVID-19 post-discharge in our study were mental health morbidity, dyspnoea and subjective symptoms such as fatigue, weakness of limbs, body ache and joint pains. A pre-COVID-19 multisite study in India has observed depression to be prevalent in 2.68% of the general population, while another study in Australia has observed a prevalence of dyspnoea in the general population as 8.9%. The considerable proportion of survivors reporting mental health issues is of concern. Moreover, subjective symptoms might not be fatal, nevertheless compromises the quality of life of the survivors. The WHO has reported a noticeable surge of 25% in global prevalence of anxiety and stress during the first year of the COVID-19 pandemic. Studies suggest that psychiatric consequences of COVID-19 are widespread, and they persist probably even beyond 6 months. The reasons for the mental health issues could be many including fear of death, loneliness due to isolation, stress of being admitted to the hospital, grief due to personal loss and even monetary loss during the pandemic. The WHO also reported that provision of mental health services was hit hardest by the pandemic. Even during non-pandemic times, mental health services are not readily sought in India, due to multiple factors. In order to cater to these issues, we suggest that psychiatric care in terms of counselling, medication and further functional linkages with peer groups and helplines would be quintessential. The GOI has recently announced the launch of the National Tele-Mental Health Program (NTMHP), which would have linkages with various levels of medical institutions. Subsequently, the National Institute of Mental Health and Neurosciences announced an initiative under the
NTMHP named as ‘Tele-Mental Health Assistance and Nationally Actionable Plan through States’ to provide round-the-clock telemental health services, especially to the underserved.\textsuperscript{21} It could be explored as to how these initiatives could be linked to the COVID-19 clinics. Another common problem faced by the patients post-COVID-19 was dyspnoea which might require specialised care from a pulmonologist, and in order to gradually increase the lung capacity, training would be required from exercise medicine specialists.

Our study revealed that 4.3\% of the participants died before the first follow-up conducted within 60 days post-discharge; nearly 55\% of the deceased had been readmitted to the hospital. A meta-analysis and systematic review conducted by Ramzi reported that about one-tenth of the discharged patients needed hospitalisation after initial discharge, and post-discharge mortality was 7.87\%, most of which occurred within 30 days of discharge.\textsuperscript{22} Another large cohort study from the UK reported that approximately one-third of the patients had to be readmitted after discharge and more than 1 in 10 died after discharge.\textsuperscript{23} High recorded hospital readmission and post-discharge mortality necessitates evaluation of discharge criteria following COVID-19 care and justifies prospective follow-up of these patients. Our analysis showed that the most common causes of death among the patients discharged from hospitals were related to cardiac and respiratory problems, followed by sepsis, malignancy and stroke. Heart disease and cerebrovascular accidents have been observed among large cohorts of post-COVID-19 patients in China, Sweden, the USA and the UK.\textsuperscript{18,23–25} A few researchers have also reported an increase in all-cause mortality among COVID-19 survivors.\textsuperscript{25} Multiple mechanisms including direct viral invasion of cardiomyocytes and subsequent cell death, endothelitis, transcription alteration, complement-mediated coagulopathy and downregulation of ACE2 and dysregulation of the renin–angiotensin–aldosterone system (RAAS) have been hypothesised for such cardiovascular events in the long run.\textsuperscript{23} Putative mechanisms for occurrence of stroke include viral invasion of the central nervous system, neural effects of immune response and any hypercoagulable state and alterations in balance between classic RAAS and ACE2 pathway.\textsuperscript{26–29}

We noted that the frequency of comorbidities was higher among the patients who died, compared with those who survived. Our team showed earlier that the pre-existing comorbidities increased the burden of death among inpatients with COVID-19.\textsuperscript{8} Researchers in Brazil have recorded that the presence of diabetes has been associated with post-discharge mortality.\textsuperscript{30} It was reassuring to observe that only 16\% of patients who died had been vaccinated, as compared with nearly 50\% among those who had survived. It has been observed previously that the mortality among hospitalised patients is lower among the patients vaccinated with at least one dose of the anti-SARS-CoV-2 vaccine.\textsuperscript{8} Paradoxically, post-discharge death was highest among our patient cohort admitted during the third wave of SARS-CoV-2 infection in India which was largely caused by the omicron variant.

Figure 4 Evidence-based framework for holistic management of COVID-19 sequelae. Grass roots-level workers sensitised with the health needs of post-COVID-19 patients. Post COVID OPD at Primary health centre (PHC)/Community health centre (CHC)/district hospitals at specified time and days with multiple virtual linkages. CAD, coronary artery disease; OPD, outpatient department.
Noticeably, this variant is considered as the least severe and least fatal among all the variants of concern.\textsuperscript{31,32} This could have been attributed to better follow-up during after the third wave. Detection of early warning signals towards occurrence of any cardiovascular or cerebrovascular events and early initiation of therapy will be helpful in ameliorating post-discharge morbidity and mortality, especially in COVID-19 survivors above 60 years of age with at least one comorbidity and a history of severe COVID-19 or ICU admission.

India has a well-established public health system, with a wide coverage by grass roots-level healthcare workers including Accredited Social Health Activist (ASHA) workers, anganwadi workers and multipurpose workers. Being from the community, they are often the first point of contact for the community to discuss their health issues and seek guidance. This existing robust workforce needs to be sensitised regarding the health needs of COVID-19 survivors, so that the patients can be channelled to the right place for their health needs. As COVID-19 survivors have been reporting symptoms pertaining to multiple organ systems, it is advisable to have a dedicated outpatient clinic for them managed by physicians trained in the needs and clinical management of post COVID condition/post COVID syndrome.\textsuperscript{6,7} The lowest level of health providers in our country is at the level of subcentre and primary health centre, where specialist care is not available. Leveraging the technological advancements and high internet penetration, the outpatient departments (OPDs) can have a ready virtual communication with the required specialists, at specified times in order to decrease the load at specialist OPDs and also to minimise multiple referrals which could increase the strain on already overburdened healthcare system. Web linkages will also help in minimising the indirect as well as direct out-of-pocket expenditures for the patients which are often a deterrent for health seeking among patients.\textsuperscript{35}

Keeping all the aforementioned considerations into account, we constructed a framework for management of COVID-19 sequelae (figure 4). As per the reported symptoms in the patients being followed up, we suggest mental health services with functional linkage with peer support groups and suicide helplines should be established. To cater to the high population with dyspnoea, pulmonary medicine specialist along with exercise medicine and alternate medicine could be helpful. For prevention and early identification of stroke and coronary artery disease, the medical officers at the grass roots level could be trained, or a web linkage with the respective specialists could be established. Considering the high load of post COVID symptoms among the old, a geriatric medicine specialist is required. A well-functioning laboratory is of utmost importance for diagnosis and treatment at the earliest. Considering the multiplicity of specialties that are required to cater to the diverse range of symptoms, it could be helpful if specialist care is available via telemedicine or using the other modern techniques of web conferencing.

It is important that the grass roots-level care workers are sensitised to link patients with post COVID sequelae with appropriate facility. The clinician/nursing staff available at the subcentre and primary healthcare centres should be provided basic training for managing the general common sequelae of COVID-19, such as fatigue, joint pains, headache, vomiting, diarrhoea, etc, and also to identify the early signs of impending myocardial infarction, heart failure and stroke, which have been well described in the guidelines for management of post COVID sequelae by MOH&FW.\textsuperscript{6,7} Additionally, a seamless referral mechanism (including teleconsultation) would be needed to effectively manage long-term morbidity and reduce post-COVID-19 mortality.

**Strength and limitations**

To the best of our knowledge, this study is the most widely represented Indian study that includes patients from all geographical locations in the country. Additionally, a wide range of symptoms/sequelae could be recorded owing to the exhaustive questionnaire used.

Considerable loss of participants to follow-up is one of the limitations of this study, which could be attributed to multiple factors, including reluctance of patients with COVID-19 to be followed up, overworked hospital staff, specifically during the second wave of COVID-19, frequent staff turnover and SARS-CoV-2 infections among the study staff. While non-participation of post-COVID-19 survivors in the study would lead to overestimation of the proportion of death in those experiencing post COVID sequelae, non-participation of families of those who died post-COVID-19 would lead to underestimation. There might have been an underestimation of the persistent symptoms due to the high lost to follow-up rate. Additionally, only a few patients were followed up physically, most of the follow-up being done telephonically. Hence, we had to depend on the self-reported symptoms for estimating the post COVID sequelae which were not backed by investigations.

Deaths recorded in individuals post-COVID-19 may not necessarily be due to COVID-19, and in-depth exploration of the same was beyond the scope of this investigation. The scope of this study also did not allow comparing morbidity and mortality among post-COVID-19 population with those following other viral infections, chronic diseases or in healthy population as there were no control groups enrolled.

**CONCLUSION**

Hospitalised patients with COVID-19 experience a variety of long-term sequelae after discharge from hospitals which persists although in reduced proportions until 12 months post-discharge. Targeted follow-up and developing a holistic management framework with engagement of care outreach workers as well as teleconsultation appear important in this regard. This could help in

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effective management of post-COVID-19 morbidities as well as reducing mortality.

Author affiliations
1 Clinical Studies & Trials Unit, Indian Council of Medical Research, New Delhi, India
2 Postgraduate Institute of Medical Education and Research, Chandigarh, India
3 Medical College and Hospital Kolkata, Kolkata, India
4 College of Medicine and Sagore Dutta Hospital, Kolkata, India
5 All India Institute of Medical Sciences, Jodhpur, India
6 National Institute of Medical Statistics, New Delhi, India
7 Indian Council of Medical Research, New Delhi, India
8 All India Institute of Medical Sciences, Raipur, India
9 Smt NHL Municipal Medical College, Ahmedabad, India
10 CIMS Hospital, Ahmadabad, India
11 All India Institute of Medical Sciences, Bhubaneswar, India
12 RD Gardi Medical College, Ujjain, India
13 Christian Medical College and Hospital, Ludhiana, India
14 NEIGRIHMS, Shillong, India
15 Dr D Y Patil Medical College Hospital and Research Centre, Pune, India
16 Late BRK Memorial Medical College, Jagdalpur, India
17 SP Medical College, Bikaner, India
18 SMS Medical College and Hospital, Jaipur, India
19 Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, India
20 GSBS Medical Institute and Research Centre, Vadodara, India
21 GMERS Medical College, Himmatnagar, India
22 Department of Health and Family Welfare, Government of Nagaland, Kohima, India
23 Naga Hospital Authority, Kohima, India
24 Mahatma Gandhi Medical College and Hospital, Jaipur, India
25 SOA IMS and SUM Hospital, Bhubaneswar, India
26 All India Institute of Medical Sciences, Bhopal, India
27 Institute of Postgraduate Medical Education and Research, Kolkata, India
28 ESIC Gayatri Hospital, Chhattisgarh, India
29 Gandhi Medical College, Bhopal, India
30 Medanta, The Medicity, Gurgoan, India
31 JN Medical College, Aligarh, India
32 Department of Pharmacology, Institute of Postgraduate Medical Education and Research, Kolkata, India
33 King George Medical University, Lucknow, India
34 Guwahati Institute of Medical Science, Guwahati, India
35 Shri Atal Bihari Vajpayee Medical College and Research Institute, Beneralu, India
36 Kakatiya Medical College, Warangal, India
37 All India Institute of Medical Sciences, New Delhi, India

Contributors AM is the guarantor. Study design, data analysis, data interpretation and manuscript writing team—AK, AB, AM, AT, AM, PB, GRM and DS. Monitoring and conduct of the study—AM, GK, AT, PM and LKS. Patient enrolment, conduct of study, clinical care and data collection—AB, AT, SM, PB, RM, SS, VS, HD, DS, SG, PG, MD, SC, DK, MKG, ADG, TDB, PKK, AYS, JFR, AP, NS, SB, MKP, PRM, AP, AS, MJ, KK, VN, SP, SKS, BRK, ND, BG, JG, SB, AA, HKA, DJ, ADS, PN, MP, MA, NK, CNH, NK, RV, LP, JPS, RJK, AK, YR, KR, HMP, AMS, AD, SN, KS, NS, SF, AG, HD, VBS, SA, KYML, PKM, SM, MVVR and BB. Postgraduate Institute of Medical Education and Research, Chandigarh: AB, RM, SS, VS, Medical College Kolkata: AT, HD, DS, SG; College of Medicine and Sagore Dutta Hospital, Kolkata: SM, PG, MD, SC; All India Institute of Medical Sciences, Jodhpur: PB, DK, MKG, ADG; All India Institute of Medical Sciences, Raipur: TDB, PKK, AYS, MNL; Municipal Medical College: JFR, KR, HMP, NMS, CIMS Hospital, Ahmadabad: AP, NS; All India Institute of Medical Sciences, Bhubaneshwar: SB, MKP, PRM; RD Gardi Medical College, Ujain: AP AS; CMC Ludhiana: MJ, AS; North Eastern India Gandhi Regional Institute of Health and Medical Sciences, Shillong: VN, SP; Dr DY Patil Medical College, Pune: SNS, BRK, Late BRK Memorial Medical College, Jagdalpur: ND; SP Medical College, Bikaner: BG, JG; SMS Medical College and Hospital: SB, AA; Pandit Bhagwat Dayal Sharma Postgraduate Institute of Medical Sciences: HKA, DJ; GSBS Medical Institute and Research Centre Vadodara: ADS, PN; GMERS Medical College, Himmatnagar: MP, MA; Department of Health and Family Welfare, Nagaland: NK, Naga Hospital Authority, Nagaland: CNH; Mahatma Gandhi Medical College, Jaipur: NS, RV, IMS and SUM Hospital, Bhubaneshwar: LP, JPS; All India Institute of Medical Sciences, Bhopal: RJ, AK; Institute of Postgraduate Medical Education and Research: YR, SG, AH; ESI Hospital, Raipur: AM, Gandhi Medical College, Bhopal: SD, NS, Medanta, Gurugram: SK, Jawaharlal Nehru Medical College: MS, NF; King George’s Medical University: HD; Guwahati Institute of Medical Sciences: VBS, SA; Shri Atal Bihari Vajpayee Medical College and Research Institution Bhubaneshwar: KYML; Kakatiya Medical College, Warangal: PKM; Indian Council of Medical Research: GK, AM, AT, LKS, SP; ICMR-National Institute of Medical Statistics: GRM, DS, PRM, MVVR; All India Institute of Medical Sciences, Delhi: BB.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study involves human participants. The National Clinical Registry for COVID-19 has been approved by the Central Ethics Committee for Human Research at ICMR (CECHR); ref number: NCDR/BEU/ICMR-CECHR/75(2020) as well as Institutional Ethics Committee of all the participating institutes. Written informed consent or audio-visual consent was taken from all patients who are being followed up after discharge from the hospital.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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ORCID iDs
Aparna Mukherjee http://orcid.org/0000-0001-7298-5097
Samiran Panda http://orcid.org/0000-0002-5077-6275

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