Original Article

Silent Hypoxia in Coronavirus disease-2019: Is it more dangerous? -A retrospective cohort study

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ABSTRACT

Background: Hypoxia in patients with COVID-19 is one of the strongest predictors of mortality. Silent hypoxia is characterised by the presence of hypoxia without dyspnoea. Silent hypoxia has been shown to affect the outcome in previous studies. **Methods:** This was a retrospective study of a cohort of patients with SARS-CoV-2 infection who were hypoxic at presentation. Clinical, laboratory and treatment parameters in patients with silent hypoxia and dyspnoeic hypoxia were compared. Multivariate logistic regression models were fitted to identify the factors predicting mortality. **Results:** Among 2080 patients with COVID-19 admitted to our hospital, 811 patients were hypoxic with SpO_2 <94% at the time of presentation. Among them, 174 (21.45%) did not have dyspnoea since the onset of COVID-19 symptoms. Further, 5.2% of patients were completely asymptomatic for COVID-19 and were found to be hypoxic only on pulse oximetry. The case fatality rate in patients with silent hypoxia was 45.4% as compared to 40.03% in dyspnoeic hypoxic patients ($P = 0.202$). The odds ratio of death was 1.1 (95% CI: 0.41–2.97) in the patients with silent hypoxia after adjusting for baseline characteristics, laboratory parameters, treatment and in-hospital complications, which did not reach statistical significance ($P = 0.851$). **Conclusion:** Silent hypoxia may be the only presenting feature of COVID-19. As the case fatality rate is comparable between silent and dyspnoeic hypoxia, it should be recognised early and treated as aggressively. Because home isolation is recommended in patients with COVID-19, it is essential to use pulse oximetry in the home setting to identify these patients.

KEY WORDS: Asymptomatic hypoxia, case fatality rate, COVID-19, coronavirus disease, happy hypoxia, hypoxemia hypoxia, SARS-CoV-2, silent hypoxia

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INTRODUCTION

Coronavirus disease (COVID-19) has been a mystery to the scientific world right from the discovery of the first case of COVID-19 pneumonia to its spread, presentation and treatment. A baffling aspect of its presentation is hypoxia, which might even be otherwise incompatible with life, but without dyspnoea, which is expected to occur to compensate for such a degree of hypoxia. This phenomenon is called silent hypoxia or happy hypoxia.[1] Because hypoxia in COVID-19 is an independent factor in predicting increased risk of intensive care unit requirement and in-hospital mortality, the presence of silent hypoxia as a presenting symptom in patients can be very treacherous as it might delay the diagnosis and subsequent initiation of treatment, giving the patient a false sense of well-being.[2] In the study of a cohort of 2080 patients at our centre, the presence of hypoxia (SpO_2<94%) was associated with 12 times higher odds of death.[3]

The incidence of silent hypoxia in COVID-19 has been reported to be 32%–65% in various studies.[4–6] The reports on patients with silent hypoxia are conflicting, with some studies reporting poorer outcomes while others reporting better outcomes.[7] In the pandemic setting, patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are advised to isolate at home due to the non-availability of hospital beds and seek hospitalisation when red flags such as breathlessness and tachypnoea occur.[8] In patients with community-acquired pneumonia, risk prediction tools such as CURB-65 and pneumonia severity index are used to decide if the patients need admission or can be managed on an outpatient basis. These scores rely on tachypnoea to assess respiratory function and do not recommend home pulse oximetry. Silent hypoxia can be devastating if not recognised early by patients and caregivers as they can be completely asymptomatic or present with only fever and upper respiratory symptoms without significant respiratory distress but may show severe hypoxia on pulse oximetry or blood gas analysis.

Physiologically, hypoxia causes stimulation of peripheral chemoreceptors present in the carotid body which signals the medulla oblongata to increase the minute ventilation and hence causes dyspnoea.[9] Various theories have been put forward in attempts to explain the cause of silent hypoxia based on this phenomenon. Angiotensin-converting enzyme-2 receptors, which act as a receptor for entry of the SARS-CoV-2 virus into host cells, are also present in the carotid body. Thus, these receptors are implicated in causing a decrease in sensitivity of the carotid body to hypoxia, leading to normal ventilation even in face of life-threatening hypoxia.[10] In addition, SARS-CoV-2 infection leads to cytokine storm and neovascular proliferation in the lungs, which causes right to left shunting of blood and subsequently hypoxia. Hypoxia causes an increase in ventilation, which leads to hypocapnia as carbon dioxide is more diffusible than oxygen. The resulting hypocapnia prevents any further increase in minute ventilation, causing hypocapnic hypoxia without dyspnoea.[11] Some theories suggest the spread of the virus from the oral cavity via a neural route through facial, glossopharyngeal and vagus nerve to nucleus tractus solitarius or from nasal cavity via the cribriform plate and ethmoidal sinus directly into the brain. Such spread might lead to inflammation and impaired signal processing of hypoxia at the higher centres, leading to normal breathing despite severe hypoxia.[12,13] Other theories, ranging from gut dysbiosis and formation of free radicals to impaired autonomic regulation, have also been proposed.[14–16]

Though the physiological mechanism of silent hypoxia is not very clear, it can potentially escalate to severe acute respiratory distress syndrome (ARDS), cardiorespiratory collapse and even death, as described in previous studies. We compare the clinical, laboratory and treatment parameters and evaluate the outcomes of patients with dyspnoeic and silent hypoxia in COVID-19 in a cohort of patients admitted to our hospital.

METHODS

Study design

This was a retrospective cohort study conducted in the National Cancer Institute (Jhajjar), All India Institute of Medical Sciences, New Delhi, which is a tertiary care institute in India. The study was approved by the ethics committee of the institution.

Patients

We enrolled all consecutive patients who were admitted with SARS-CoV-2 infection at our institute who had hypoxia (SpO_2<94%) while breathing room air or needed oxygen support to maintain saturation >94%) at the time of presentation to the hospital. The demographic, clinical and laboratory parameters of the patients were collected from the case records and the electronic hospital management system of the hospital. All the patients included in our study were diagnosed with SARS-CoV-2 infection by detecting viral RNA in respiratory samples by reverse transcription-polymerase chain reaction, nucleic acid amplification tests or rapid antigen tests.

Case definitions

Dyspnoea is a subjective experience of breathing discomfort that the patient was asked to report at the time of admission. Hypoxia was defined as oxygen saturation (SpO_2) <94% on room air and severe hypoxia as SpO_2<90% on room air.[17,18] Patients who were on oxygen supplementation to maintain a saturation above 94% were considered hypoxic regardless of oxygen saturation. The case definitions used in this study were based on the criteria described in the paper on the clinical features and outcomes of the entire cohort of patients who were treated at our institute during the period from April to June 2021.[3]

Statistical analysis

The data were summarised using means and standard deviations for normal data and as medians and interquartile ranges (p25–p75) for non-parametric data, and means were compared using the *t* test and medians using the Wilcoxon rank-sum test. The categorical data were summarised as proportions and compared using the Chi2 test or Fisher's exact as appropriate. All statistical tests were performed with the use of a two-sided type I error rate of 5%. Missing data were not imputed; the summary parameters were calculated with the available data, and the denominators (n) for each parameter were mentioned.

Univariate analysis was done to compare the various parameters between those who were discharged and those who died. Multivariate logistic regression analysis was done using models developed by including those that were found to be significant on univariate analysis as well as parameters of clinical relevance. We also included those parameters that we thought would influence the outcomes based on available scientific literature. Sensitivity analysis was done by dropping such parameters and by comparing the various models obtained by dropping them. All analysis was performed using STATA-Version 13.0 software.

RESULTS

Among 2080 COVID-19 patients admitted to our hospital from April to June 2021, 811 patients were presented with hypoxia. Among them, 637 patients (78.55%) had dyspnoea (dyspnoeic hypoxia group), and 174 patients (21.45%) had no dyspnoea (silent hypoxia group). The demographic and baseline characteristics among patients with dyspnoeic and silent hypoxia are compared in Table 1.

Out of the patients with silent hypoxia, 41% were males and 59% were females, and this was statistically significant. It was found that nine completely asymptomatic patients were hypoxic at the time of presentation to the screening area. This translates to 5.2% of cases presenting who were completely asymptomatic and had hypoxia found only on pulse oximetry. Among the patients with silent hypoxia, 65% presented in the first week of symptoms when viremia plays a role in the pathogenesis as compared to 30% who presented in the second week during the inflammatory phase. This was in contrast to the patients with dyspnoeic hypoxia, in whom presentation in the inflammatory phase of the illness was higher (275 (45.2%) ($P < 0.001$).

It is important to note that almost half of the patients with dyspnoea as a symptom along with hypoxia were brought to the hospital on oxygen. However, only 35% (60) of patients without dyspnoea had their hypoxia diagnosed before reaching the hospital and been started on oxygen before the presentation by the paramedical workers during transportation ($P < 0.001$). The rest of the demographic and clinical parameters were comparable between the patients with silent as well as dyspnoeic hypoxia. The laboratory parameters of these two groups are compared in Table 2. More patients with dyspnoeic hypoxia had leucocytosis (48.9%) as compared to silent hypoxia (33.6%) ($P = 0.003$). The rest of the laboratory parameters were comparable between the two groups. Table 3 compares the various treatments received by both groups. The high-frequency nasal cannula was used for oxygen delivery in 16% of patients with dyspnoeic hypoxia, while 9.5% were in the silent hypoxia group. High-dose methylprednisolone therapy was also given to a higher proportion of patients with dyspnoeic hypoxia as compared to silent hypoxia. Apart from these, no significant differences were seen between other treatment modalities such as antiviral drugs or tocilizumab between the groups. Multivariable logistic regression models [Table 4] were fitted to calculate the odds of death with silent hypoxia as the explanatory variable and other clinical, laboratory and treatment parameters as covariates. We found that though these models showed a higher odds of death among patients with silent hypoxia, none of them were statistically significant.

DISCUSSION

Though few case reports have described the perplexing entity of silent hypoxia, there are a handful of cohort studies that have described the demographic, clinical and laboratory findings in such patients.[10,19,20] Brouqui *et al*.,[4] in their retrospective study, analysed data from 3rd March 27th to April, 2020 by using dyspnoea status, oxygen saturation, blood gas analysis and low-dose computed tomography scan reports. They defined hypoxia as SpO2≤95%. They reported the incidence of silent hypoxia to be 14.2% based on oxygen saturation with pulse oximetry and 26.1% based on blood gas analysis. They reported these patients to be strongly associated with poor outcomes, the suggested cause being most patients belonging to the elderly age group and chronic diseases.

Another retrospective cohort study by Okuhama *et al*.[5] reported the incidence of silent hypoxia to be 3%, and the authors defined hypoxia to be SpO2<94%. They reported that the patients with silent hypoxia might also have a poor prognosis but not associated with old age or chronic diseases and suggested that some other mechanisms might be involved in this respect. This cohort did not have a comparison arm and was a descriptive study of eight patients who presented with silent hypoxia among a total of 270 patients with COVID-19. None of these patients died; however, the authors did not compare these patients with silent hypoxia with those with dyspnoeic hypoxia, nor did they present the incidence of silent hypoxia among patients with hypoxia.

Busana *et al*.[7] reported a cohort of 213 patients with hypoxia defined as PaO2/FiO2 <300 as assessed by a blood gas analysis (partial pressure of oxygen/fraction

Table 1: Demographic and baseline characteristics among patients with dyspnoeic and silent hypoxia

	n (col%)			*P*
	Total	**Dyspnoeic hypoxia**	**non-dyspnoeic (silent) hypoxia**	
Age (*n*=811)				
<18 years	207 (25.52%)	164 (25.75%)	43 (24.71%)	0.366
45-60 years	341 (42.05%)	274 (43.01%)	67 (38.51%)	
>60 years	263 (32.43%)	199 (31.24%)	64 (36.78%)	
Sex (*n*=811)				
Female	269 (33.17%)	198 (31.08%)	71 (40.8%)	0.016
Male	542 (66.83%)	439 (68.92%)	103 (59.2%)	
Primary Condition (*n*=811)				
Non-COVID	20 (2.47%)	12 (1.88%)	8 (4.6%)	0.041
COVID	791 (97.53%)	625 (98.12%)	166 (95.4%)	
Vaccination (*n*=791)				
No	604 (76.36%)	472 (76.01%)	132 (77.65%)	0.656
Yes	187 (23.64%)	149 (23.99%)	38 (22.35%)	
Comorbidities (*n*=810)				
0	364 (44.94%)	297 (46.7%)	67 (38.51%)	0.129
1	264 (32.59%)	198 (31.13%)	66 (37.93%)	
2 or more	182 (22.47%)	141 (22.17%)	41 (23.56%)	
Hypertension (*n*=810)				
Yes	238 (29.38%)	188 (29.56%)	50 (28.74%)	0.833
Diabetes (*n*=810)				
Yes	223 (27.53%)	176 (27.67%)	47 (27.01%)	0.863
Symptomatic (*n*=810)				
No	9 (1.11%)	0 (0%)	9 (5.2%)	<0.001
Yes	801 (98.89%)	637 (100%)	164 (94.8%)	
Symptom to admission weeks (*n*=774)				
1	431 (55.68%)	323 (53.13%)	108 (65.06%)	<0.001
2	324 (41.86%)	275 (45.23%)	49 (29.52%)	
3	10 (1.29%)	10 (1.64%)	0 (0%)	
Asymptomatic	9 (1.16%)	0 (0%)	9 (5.42%)	
Presenting Symptoms (*n*=811)				
Fever				
Yes	649 (80.02%)	521 (81.79%)	128 (73.56%)	0.016
Dry Cough				
Yes	447 (55.12%)	344 (54%)	103 (59.2%)	0.222
Cough with Expectoration				
Yes	103 (12.7%)	77 (12.09%)	26 (14.94%)	0.316
Rhinitis				
Yes	11 (1.36%)	8 (1.26%)	3 (1.72%)	0.71
Sore throat				
Yes	115 (14.18%)	90 (14.13%)	25 (14.37%)	0.936
Fatigue				
Yes	103 (12.7%)	78 (12.24%)	25 (14.37%)	0.456
Myalgia				
Yes	115 (14.18%)	83 (13.03%)	32 (18.39%)	0.072
Chest pain				
Yes	55 (6.78%)	42 (6.59%)	13 (7.47%)	0.683
Gastrointestinal				
Yes	58 (7.15%)	38 (5.97%)	20 (11.49%)	0.012
Drowsiness				
Yes	7 (0.86%)	4 (0.63%)	3 (1.72%)	0.173
Loss of smell				
Yes	49 (6.04%)	37 (5.81%)	12 (6.9%)	0
Loss of taste				
Yes	45 (5.55%)	37 (5.81%)	8 (4.6%)	0.536
Oxygen status at Presentation (n=811)				
Room Air	432 (53.27%)	318 (49.92%)	114 (65.52%)	<0.001
On Oxygen	379 (46.73%)	319 (50.08%)	60 (34.48%)	

of inspired oxygen < 300). They classified the patients into a dyspnoeic hypoxia group and silent hypoxia group and found that the mortality in the dyspnoeic group (29.7%) was higher than that in the silent hypoxia group (17.6%), though these figures did not attain statistical significance ($P = 0.083$).

Grimshaw *et al*.[6] reported a cohort of 470 patients with hypoxia defined as SpO_2<80% and found that 5% of them had no breathlessness. In this study, the authors observed that the patients with silent hypoxia presented earlier to the hospital due to new-onset headaches and the mortality was higher in patients with dyspnoeic hypoxia (43.2%)

Table 2: Laboratory parameters of patients with dyspnoeic and silent hypoxia

Parameter	Dyspnoeic Hypoxia		Non-Dyspnoeic (Silent) Hypoxia		*P*
	Available observations (N)	*n* (col%)	Available observations (N)	*n* (col%)	
Anaemia (Hb <11)	520	87 (16.73%)	140	26 (18.57%)	0.608
Leukocyte Count	520		140		
Normal		252 (48.46%)		85 (60.71%)	0.003
Leukopenia (<4000/mm^3)		14 (2.69%)		8 (5.71%)	
Leucocytosis (>11000/mm^3)		254 (48.85%)		47 (33.57%)	
Thrombocytopenia (<1.5 lakh/mm^3)	522	66 (12.64%)	140	21 (15%)	0.464
Hyperferritinaemia (>322 ng/mL)	192	159 (82.81%)	40	30 (75%)	0.247
D-dimer >500 ng/mL	432	178 (41.2%)	115	47 (40.87%)	0.948
IL-6 >4.4 pg/mL	328	267 (81.4%)	68	58 (85.29%)	0.446
CRP >0.5 mg/dL	485	474 (97.73%)	133	128 (96.24%)	0.337
Creatinine >1 mg/dL	528	124 (23.48%)	146	44 (30.14%)	0.1

*WBC- White blood cell, LDH- Lactate dehydrogenase, SGPT- Serum glutamic pyruvic transaminase,. ALT-Alanine aminotransferase, SGOT-Serum glutamic oxaloacetic transaminase, AST- Aspartate. Aminotransferase, A: G - Albumin: Globulin, Hb- Haemoglobin, IL-6 - Interleukin-6

Table 3: Treatment parameters of patients with dyspnoeic and silent hypoxia

	Dyspnoeic hypoxia			Non-dyspnoeic (silent) hypoxia		
	Available for	Available observations (N)	n (col %)	Available observations (N)	*n* (col %)	*P*
HFNC	792	624	100 (16.03%)	168	16 (9.52%)	0.034
NIV	806	633	179 (28.28%)	173	36 (20.81%)	0.049
IMV	810	637	170 (26.69%)	173	41 (23.7%)	0.427
Either NIV or IMV	811	637	228 (35.79%)	174	52 (29.89%)	0.146
Steroids	809	635	583 (91.81%)	174	157 (90.23%)	0.508
Methylprednisolone Pulse	762	612	128 (20.92%)	150	13 (8.67%)	0.001
Anticoagulants	793	632	557 (88.13%)	161	128 (79.5%)	0.004
Inhaled Steroids	767	616	194 (31.49%)	151	29 (19.21%)	0.003
Ivermectin	762	613	100 (16.31%)	149	27 (18.12%)	0.595
Doxycycline	763	613	140 (22.84%)	150	35 (23.33%)	0.897
Minocycline	763	613	18 (2.94%)	150	7 (4.67%)	0.286
Azithromycin	762	612	107 (17.48%)	150	28 (18.67%)	0.734
Ceftriaxone	763	613	174 (28.38%)	150	35 (23.33%)	0
Levofloxacin	765	615	161 (26.18%)	150	16 (10.67%)	0
Tocilizumab	770	619	23 (3.72%)	151	8 (5.3%)	0.375
Remdesivir	770	616	232 (37.66%)	154	57 (37.01%)	0.882
Zinc	729	584	163 (27.91%)	145	37 (25.52%)	0.563
In-Hospital complications						
Hyperglycaemia	704	566	221 (39.05%)	138	49 (35.51%)	0.443
Renal Dysfunction	741	584	166 (28.42%)	157	51 (32.48%)	0.321
Hypotension	797	628	55 (8.76%)	169	20 (11.83%)	0.224
Hospital Acquired Infection	47	39	26 (66.67%)	8	6 (75%)	0.645
Critical illness	811	637	232 (36.42%)	174	56 (32.18%)	0.301
Final Outcome	811					
Discharges			382 (59.97%)		95 (54.6%)	0.202
Deaths			255 (40.03%)		79 (45.4%)	

*HFNC- High-flow nasal cannula, NIV- Non-invasive ventilation, IMV- Invasive mechanical ventilation

as compared to those with silent hypoxia (30.4%). The overall mortality in this cohort was also higher than the reported mortality in other studies probably due to the definition of hypoxia to be a much lower oxygen saturation of <80%.

We defined hypoxia to be SpO_2 < 94% as per the BTS guidelines for oxygen use.[18] Our study was done during the period from April to June 2021 during the 'second wave' of the pandemic in India. We found the incidence of silent hypoxia to be 21.45%. Our study did not find any statistically significant difference in outcome between the silent and dyspnoeic hypoxic groups. Also, the age and comorbid disease status were not significantly different in our patients, suggesting that silent hypoxia was a presentation that was equally spread among all ages and comorbidities in the population.

We found leucocytosis to be significantly more in patients with dyspnoeic hypoxia. Because leucocytosis points towards a hyperinflammatory state, further research is required to know if dyspnoeic hypoxia has different pathophysiology as compared to patients with silent hypoxia.[21] The presence of leucocytosis could have led to these patients being identified as having a cytokine storm and thus could have led the clinicians to significantly greater use of methylprednisolone pulse therapy, inhaled corticosteroids, antibiotics and also respiratory support such as non-invasive ventilation (NIV) and high-flow nasal cannula (HFNC) in the dyspnoeic hypoxic group.

Table 4: Odds of death among those with happy hypoxia compared to those without happy hypoxia

	Odds Ratio (95% CI)	*P*
Model 1: Univariate	1.25 (0.89-1.75)	0.202
Model 2: Adjusted for age, gender, comorbidities, vaccination	1.14 (0.8-1.64)	0.474
Model 3: Model 2 plus symptoms	1.24 (0.81-1.89)	0.323
Model 4: Model 3 plus baseline lab parameters	1.22 (0.68-2.19)	0.504
Model 5: Model 4 plus treatment parameters	1.06 (0.43-2.61)	0.894
Model 6: Model 5 plus in-hospital complications	1.1 (0.41-2.97)	0.851

A more aggressive approach in treatment was adopted in the dyspnoeic hypoxic group in terms of using high-dose methylprednisolone pulse, but the usage of anti-interleukin therapy such as tocilizumab or antivirals were comparable between the groups. In patients with baseline hypoxia, in both groups, which later deteriorated and progressed to death, inflammatory markers such as d-dimer were elevated in more than 40% of patients, while IL-6 levels were elevated in more than 80% of patients. This reinforces the fact that it has a strong correlation with disease severity and is a reliable prognostic marker for in-hospital mortality in patients with COVID-19.[22] However, these inflammatory markers did not differ between the patients with silent and dyspnoeic hypoxia in our cohort.

In a comparative study of vaccinated and unvaccinated individuals from our cohort, we found that vaccination significantly reduced the odds of developing hypoxia and death.[23] However, the presentation of silent hypoxia was not significantly different in the groups receiving the vaccination against COVID-19 and non-vaccinated groups. Further research on the pathogenesis of post-vaccination breakthrough infections is needed. In our cohort, 21.45% of patients with hypoxia did not have breathlessness and were found to be hypoxic only on pulse oximetry. As it is well known that the presence of hypoxia is the strongest predictor of death, this finding emphasises the fact that in addition to clinical examination, pulse oximetry should be an integral part of disease assessment at the primary care level and mere presence or absence of dyspnoea should not be used to triage patients. As pulse oximetry is an easy-to-use non-invasive method to watch for silent hypoxia at home, COVID-19 patients undergoing home isolation should be suggested to undergo such monitoring regularly for early diagnosis and seeking treatment before it is too late.[24] The general public should also be educated that silent hypoxia is also a presenting feature of COVID-19, and they should look for an increase in respiratory rate without any discomfort to the patient so that presence of such features does not go unrecognised. As observed in this cohort, more patients who had dyspnoeic hypoxia were started on oxygen by the paramedical personnel as compared to those with silent hypoxia. This data suggests that the presence of dyspnoea is easily triaged, and silent hypoxia might be missed by the public as well as paramedics. As silent hypoxia is similar to dyspnoeic hypoxia in terms of outcomes, it is imperative to do pulse oximetry in every patient diagnosed with SARS-CoV-2 infection. The major limitation of the present study is its retrospective nature. Some parameters were missing in the collected data; we excluded those parameters from our study analysis. We retrospectively obtained pulse oximetry and breathlessness data that is subject to bias. Our findings, however, may be useful for understanding more about silent hypoxia.

CONCLUSION

Silent hypoxia is a significant problem in COVID-19. Hypoxia if untreated can be fatal and with huge numbers of patients during each 'wave', patients with dyspnoeic hypoxia are more likely to visit the hospital and get triaged into severe illness categories and thus receive quick and appropriate care. On the contrary, patients with silent hypoxia are likely to just get tested due to other symptoms only to be found to be hypoxic later or be completely unaware of the disease and found only on pulse oximetry or blood gas analysis. However, once the patient lands in the hospital, both dyspnoeic and silent hypoxia have a similar clinical course, and silent hypoxia does not seem to alter the natural history among hospitalised patients with COVID-19. As silent hypoxia and dyspnoeic hypoxia have similar outcomes, it is of paramount importance to do pulse oximetry in every patient diagnosed with SARS-CoV-2 infection.

Availability of data and material

The data will be available upon reasonable request to the corresponding author.

Prior publication

The article has been hosted on the preprint server MedRxiv (MEDRXIV/2021/262668)

Ethics Approval

Approved by Institutional Ethics Committee of AIIMS, New Delhi

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Conflicts of interest

There are no conflicts of interest.

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