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 \( \text{SpO}_2 < 94\% \) 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
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.[11] 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 ($\text{SpO}_2 < 94\%$) was associated with 12 times higher odds of death.[9]

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 case 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 cribiform 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 ($\text{SpO}_2 < 94\%$) 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 ($\text{SpO}_2$) < 94% on room air and severe hypoxia as $\text{SpO}_2 < 90\%$ 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.[16,19,20] 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
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.\textsuperscript{[6]} reported a cohort of 470 patients with hypoxia defined as $\text{SpO}_2 < 80\%$ 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 1: Demographic and baseline characteristics among patients with dyspnoeic and silent hypoxia

| Characteristic                     | Total | Dyspnoeic hypoxia | Non-dyspnoeic (silent) hypoxia | $P$  |
|------------------------------------|-------|-------------------|--------------------------------|------|
| 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|
| No                                 | 572 (70.62%) | 424 (68.44%)     | 148 (71.26%)                   |      |
| **Diabetes (n=810)**               |       |                   |                                |      |
| Yes                                | 223 (27.53%) | 176 (27.67%)     | 47 (27.01%)                    | 0.863|
| No                                 | 588 (72.47%) | 435 (67.33%)     | 153 (72.99%)                   |      |
| **Symptomatic (n=810)**            |       |                   |                                |      |
| Yes                                | 801 (98.89%) | 637 (100%)       | 164 (94.8%)                    | <0.001|
| No                                 | 9 (1.11%) | 0 (0%)            | 9 (5.2%)                       |      |
| **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                              | 649 (80.02%) | 521 (81.79%)     | 128 (73.56%)                   | 0.016|
| Dry Cough                          | 447 (55.12%) | 344 (54%)        | 103 (59.2%)                    | 0.222|
| Cough with Expectoration           | 103 (12.7%) | 77 (12.09%)      | 26 (14.94%)                    | 0.316|
| Rhinitis                           | 11 (1.36%) | 8 (1.26%)         | 3 (1.72%)                      | 0.71 |
| Sore throat                        | 115 (14.18%) | 90 (14.13%)      | 25 (14.37%)                    | 0.936|
| Fatigue                            | 103 (12.7%) | 78 (12.24%)      | 25 (14.37%)                    | 0.456|
| Myalgia                            | 115 (14.18%) | 83 (13.03%)      | 32 (18.39%)                    | 0.072|
| Chest pain                         | 55 (6.78%) | 42 (6.59%)        | 13 (7.47%)                     | 0.683|
| Gastrointestinal                   | 58 (7.15%) | 38 (5.97%)        | 20 (11.49%)                    | 0.012|
| Drowsiness                         | 7 (0.86%) | 4 (0.63%)         | 3 (1.72%)                      | 0.173|
| Loss of smell                      | 49 (6.04%) | 37 (5.81%)        | 12 (6.9%)                      | 0    |
| Loss of taste                      | 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%)                    |      |
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. The presence of leucocytosis could have led to these patients being identified as having a cytokine storm presentation that was equally spread among all ages and comorbidities in the population.

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 SpO2 < 94% as per the BTS guidelines for oxygen use. 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
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.

**CONCLUSION**

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.\(^\text{[12]}\) 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.\(^\text{[23]}\) 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.\(^\text{[16]}\) The general public should also be educated about silent hypoxia. As 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.

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

| Model          | 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 |

**REFERENCES**

1. Bickler PE, Feiner JR, Lipnick MS, McKleroy W. “Silent” presentation of hypoxemia and cardiorespiratory compensation in COVID-19. Anesthesiology 2021;134:262–9.
2. Xie J, Covassin N, Fan Z, Singh P, Gao W, Li G, et al. Association between hypoxemia and mortality in patients with COVID-19. Mayo Clin Proc 2020;95:1138–47.
3. Elavarasi A, Raju Sagiraju HK, Garg RK, Ratre B, Sirohiya P, Gupta N, et al. Clinical features, demography, and predictors of outcomes of SARS-CoV-2 infection at a tertiary care hospital in India: A cohort study. Lung India [Internet] 2022;39:16-26.
4. Brouqui P, Amrane S, Million M, Cortaredona S, Parola P, Lagier JC, et al. Asymptomatic hypoxia in COVID-19 is associated with poor outcome.
5. Okuhama A, Ishikane M, Hotta M, Sato L, Akiyama Y, Morioka S, et al. Clinical and radiological findings of silent hypoxia among COVID-19 patients. Int J Infect Dis 2021;102:233–8.

6. García-Grimshaw M, Flores-Silva FD, Chiquete E, Cantú-Brito C, Michel-Chávez A, Vigueras-Hernández AP, et al. Characteristics and predictors for silent hypoxemia in a cohort of hospitalized COVID-19 patients. Auton Neurosci 2021;235:102855.

7. Busana M, Gasperetti A, Giosa L, Forleo GB, Schiavone M, Mitacchione G, et al. Prevalence and outcome of silent hypoxemia in COVID-19. Minerva Anestesiol 2021;87:325-33.

8. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Interim guidance. Pediatr Med Rodz 2020;16:9–26.

9. Moosavi SH, Golestanian E, Binks AP, Lansing RW, Brown R, Banzett RB. Hypoxic and hypercapnic drives to breathe generate equivalent levels of air hunger in humans. J Appl Physiol (1985) 2003;94:141–54.

10. Tobin MJ, Laghi F, Jubran A. Why covid-19 silent hypoxemia is baffling to physicians. Am J Respir Crit Care Med 2020;202:1598–9.

11. Jounieaux V, Rodenstein DO, Mahjoub Y. On happy hypoxia and on sadly ignored “Acute vascular distress syndrome” in patients with covid-19. Am J Respir Crit Care Med 2020;202:1598–9.

12. U R A, Verma K. Happy hypoxemia in COVID-19: A neural hypothesis. ACS Chem Neurosci 2020;11:1865–7.

13. Nouri-Vaskeh M, Sharifi A, Khalili N, Zand R, Sharifi A. Dysneic and non-dysneic (silent) hypoxemia in COVID-19: Possible neurological mechanism. Clin Neurol Neurosurg 2020;198:106217.

14. Gopal AB, Chakraborty S, Padhan PK, Barik A, Dixit P, Chakraborty D, et al. Silent hypoxia in COVID-19: A gut microbiota connection. Curr Opin Physiol 2021;23:100456.

15. Baker J, Incognito AV, Wilson RJ, Raj SR. Syncope and silent hypoxemia in COVID-19: Implications for the autonomic field. Auton Neurosci 2021;235:102842.

16. Machado-Curbelo C. Silent or “Happy” hypoxemia: An urgent dilemma for COVID-19 patient care. MEDICC Rev 2020;22:85–6.

17. Guidelines on Clinical Management of COVID – 19 | AIIMS Covid Information Portal [Internet]. [cited 2022 Mar 24]. Available from: https://covid.aiims.edu/guidelines-on-clinical-management-of-covid-19/.

18. O’Driscoll BR, Howard LS, Eatis J, Mak V. British Thoracic Society Guideline for oxygen use in adults in healthcare and emergency settings. BMJ Open Respir Res 2017;4:e000170.

19. Lari A, Alherz M, Nouri A, Botras L, Taqi S. Caution against precaution: A case report on silent hypoxia in COVID-19. Ann Med Surg (Lond) 2020;60:301–3.

20. Chandra A, Chakraborty U, Pal J, Karmakar P. Silent hypoxia: A frequently overlooked clinical entity in patients with COVID-19. BMJ Case Rep 2020;13:e237207.

21. Wang J, Jiang M, Chen X, Montaner LJ. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: Review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts. J Leukoc Biol 2020;108:17–41.

22. Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: A case control study. J Intensive Care 2020;8:49.

23. Sagiraju HKR, Elavarasi A, Gupta N, Garg RK, Paul SS, Vig S, et al. The effectiveness of SARS-CoV-2 vaccination in preventing severe illness and death – real-world data from a cohort of patients hospitalized with COVID-19. medRxiv 2021;2021.08.26.21262705. doi.org/10.1101/2021.08.26.21262705.

24. Jouffroy R, Jost D, Prunet B. Prehospital pulse oximetry: A red flag for early detection of silent hypoxemia in COVID-19 patients. Crit Care 2020;24:313.