Note

Clinical and radiological findings of silent hypoxia among COVID-19 patients

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ABSTRACT

The aim of this study was to describe the clinical and radiological findings of COVID-19 patients with "silent hypoxia," who had no dyspnea on admission even though their oximetry saturation was less than 94%. This retrospective cohort study included all COVID-19 patients (n = 270) at a large tertiary care hospital between January 31 and August 31, 2020. Clinical and radiological characteristics of patients who met our criteria of "silent hypoxia", which included those who reported no dyspnea even though oximetry saturation was <94%, were extracted. Eight patients (3.0%) met the criteria for "silent hypoxia." The median age was 61 years (interquartile range [IQR]: 48.8–72.3), and five (62.5%) were men. All patients had consolidation on CT and showed a moderate to high COVID-19 CT severity score (median: 13.5, IQR: 10.8–15.3). The median FIO2 of the maximum oxygen required was 55 (IQR: 28–70)%. Two patients (25.0%) were intubated, and one patient (12.5%) underwent extracorporeal membrane oxygenation. Some COVID-19 patients with "silent hypoxia" may develop severe disease. Close and accurate monitoring of patients using arterial blood gas and pulse oximetry is necessary, regardless of their symptoms.

1. Manuscript

Since its emergence in December 2019, many unique features of coronavirus disease 2019 (COVID-19), diseases caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have been reported [1,2]. Among them, some patients with hypoxia have been labeled with a condition called "silent hypoxia/hypoxemia" or "happy hypoxia/hypoxemia" because they do not experience dyspnea [3]. One French study reported that the prognosis of these patients was worse than those who experienced dyspnea, partially because of their delayed attention to the necessary medical care [4]. There have been several studies proposing possible mechanisms behind this phenomenon, including direct viral entry into respiratory control centers [5] and altered ventilation/perfusion (V_A/Q) due to pulmonary micro-thrombosis [6]. However, detailed clinical and radiological

characteristics of these patients in Asian population are still not understood well. Therefore, we aimed to describe the clinical and radiological findings of Japanese COVID-19 patients with "silent hypoxia".

This study was approved by the ethics committee of National Center for Global Health and Medicine (NCGM) (NCGM-G-003665-00) and was implemented in accordance with the 1964 Declaration of Helsinki. A retrospective cohort study of all COVID-19 patients was conducted between January 31 and August 31, 2020, at the NCGM, Tokyo, Japan. All COVID-19 patients were diagnosed by quantitative reverse transcription polymerase chain reaction (qRT-PCR) for SARS-CoV-2 using nasopharyngeal swabs, according to the protocol recommended by the National Institute of Infectious Disease in Japan [7]. Enrolled patients were those who reported no dyspnea on admission, even though their oximetry saturation was <94% [3]. All data were extracted from the COVID-19 Registry Japan (COVIREGI-JP) of the NCGM, with permission. The

study data of COVIREGI-JP were collected and managed using the Research Electronic Data Capture, a secure, web-based data capture application hosted at the Japan Clinical Research Assist Center data center of the NCGM [8]. The parameters retrieved from the database included (i) demographics and comorbidities; (ii) number of days from symptom onset to hospital admission and CT scan; (iii) clinical symptoms; (iv) laboratory findings; (v) radiological findings on CT scan, including COVID-19 severity score [9]; and (vi) clinical outcomes.

During the study period, 270 patients were hospitalized in the NCGM. Among them, eight (3.0%) met the criteria for "silent hypoxia". The median age was 61 (interquartile range [IQR]: 48.8–72.3) years, and five (62.5%) were male. The median days from symptom onset to hospital admission and CT were 6 (IQR: 4.5–6.3) and 6 (IQR: 4.5–7.5) days, respectively. All patients had consolidation on CT, and the COVID-19 CT severity score was moderate to high (median 13.5, IQR: 10.8–15.3) (Table 1). Laboratory results associated with poor prognosis were markedly elevated in our cohort; the median of C-reactive protein (CRP) was 5.5 (IQR: 4.6–7.5) mg/dL, and the median of D-dimer was 1500 ng/mL (IQR: 800–3800). Fig. 1 shows an example of the CT image of a patient with "silent hypoxia". The patient was a 86-year-old-female with a chief complaint of fever, denying dyspnea. Chest X-ray on admission showed bilateral grand-glass opacity (GGO) and consolidation with a predominantly peripheral distribution. Her oximetry saturation was 90% on admission, body temperature was 37.6 °C, and blood pressure was 136/61 mmHg. Chest CT scan taken on day 10 showed bilateral GGO and consolidation with a predominantly peripheral distribution with CT severity score of 16. Although her oximetry saturation was 93% on 0.5 L oxygen on that day, she did not report dyspnea. In our cohort, while oxygen was not administered to one (12.5%) patient

Fig. 1. Example of the CT image of a patient with "silent hypoxia". Oximetry saturation of the patient was 90% on admission, and body temperature was 37.6 °C. Chest CT scan taken on day 10 showed bilateral GGO and consolidation with a predominantly peripheral distribution with CT severity score of 16. Although her oximetry saturation was 93% on 0.5 L oxygen on that day, she did not report dyspnea.

whose oximetry saturation was 93% at the lowest, the median FIO2 of maximum oxygen required was 55 (IQR: 28–70) %. During the clinical course, two patients (25.0%) were intubated, and one patient (12.5%) underwent extracorporeal membrane oxygenation (ECMO). The median total length of hospital stay was 26.5 (IQR: 19.8–38.8) days, and no patient died (Table 2).

Our study showed that the clinical characteristics of COVID-19 patients with "silent hypoxia" varied, and their outcomes can be severe. In our cohort, two patients were intubated, and one patient required ECMO, with no in-hospital death. Interestingly, CT revealed moderate to severe pneumonia, with a median chest CT score of 13.5 (IQR: 10.8–15.3), which is disproportionate to the absence of dyspnea. As previously suggested from a report from France [4], Japanese patients with "silent hypoxia" might also have poor prognosis. Our study also implies that this poor prognosis might not be due to the patient delay, because all patients in our study presented themselves within seven days, suggesting pathophysiological process producing "silent hypoxia" is essentially aggravating the disease severity. Several pathophysiological hypotheses behind "silent hypoxia" have been proposed. Some reports pointed out that baseline characteristics, such as age and diabetes, may affect perception of the lack of oxygen. However, in our cohort, the youngest patient was 33 years old, and 7 out of 8 patients (87.5%) did not have diabetes. Thus, our results implicate that more complicated mechanisms beyond comorbidities are involved in this condition. One report claims that SARS-CoV-2 may cause neuronal damage in the corticolimbic network, altering the perception of dyspnea and respiration control [5]. Histopathological examination of COVID-19 patient brain specimens revealed neuron loss in the cerebral cortex, hippocampus,

Table 1

Baseline characteristics of COVID-19 patients who presented with silent hypoxia (n=8).

	All patients (n = 8)
Age, years	61.00 (48.75–72.25)
Male	5 (62.50)
Body mass index, kg/m^2	22.69 (18.15–25.99)
Smoking	2 (25.00)
Days from onset to admission	6 (4.50–6.25)
Comorbidities	
Hypertension	4 (50.00)
Diabetes	1 (12.50)
Respiratory disorders	1 (12.50)
Symptoms	
Fever	8 (100)
Cough	3 (37.50)
Short breath	0 (0.00)
Dysosmia	0[a] (0.00)
Laboratory data	
White blood cell, $\times 10^3$/μL	5.04 (3.65–6.88)
Lymphocyte, %	14.55 (13.43–21.57)
AST, U/L	36.50 (33.75–80.00)
ALT, U/L	37.00 (24.25–70.50)
LDH, IU/L	328 (318–430)
CRP, mg/dL	5.53 (4.57–7.53)
D-Dimer, ng/mL	1500 (800–3800)
CT findings	
Days from onset to receiving CT	6 (4.5–7.5)
COVID-19 CT score	13.50 (10.75–15.25)
Ground Grass Opacities	8 (100)
Consolidation	6 (75.00)
Pulmonary emphysema	1 (12.50)
Pulmonary fibrosis	3 (37.50)
Plural effusion	3 (37.50)
Fatty liver	5 (50.00)

Unless otherwise stated, data are presented as n (%).
Continuous variable data are presented as median (interquartile range). COVID-19; coronavirus disease 2019, AST; aspartate aminotransferase, ALT; alanine aminotransferase, LDH; lactate dehydrogenase, CRP; C-reactive protein, CT; computerized tomography.
[a] One patient lacked information on the presence of dysosmia.

Table 2

Clinical outcomes of COVID-19 patients who presented with silent hypoxia (n = 8).

	All patients (n = 8)
Number of patients administered oxygen	7 (85.0)
Maximum FIO$_2$ of required oxygen, %*	55 (28–70)
Days from onset to requiring maximum oxygen*	9 (8–9.5)
Intubation	2 (25.0)
ECMO required	1 (12.5)
ICU admission	2 (25.0)
Total length of hospital stays, days	26.5 (19.8–38.8)
In-hospital mortality	0 (0)

Unless otherwise stated, data are presented as n (%).

and cerebellar Purkinje cell layer; SARS-CoV-2 was also detected in several brain sections [10]. Additionally, pulmonary microthrombosis in COVID-19 patients without large decrements in lung compliance disrupts the V_A/Q relationship, resulting in reduced increases in breathing to achieve appropriate oxygenation [6]. Elevated D-dimer level in our study might reflect this. Our study has several limitations. First, because of the small sample size, we were not able to conduct a case-control study, which hindered us from identifying any patterns or factors related to silent hypoxia when compared with patients experiencing dyspnea. Second, we did not clarify the mechanisms of "silent hypoxia". Lung and brain biopsies were not performed, thus, we do not know whether the patients had actual neuronal damage or micro-thrombosis in the lungs, as reported earlier [5,10]. Third, we did not evaluate patients who presented "silent hypoxia" after admission, as the clinical information which we were able to extract from our database was symptoms and oximetry saturation on admission. The database does not hold information on whether the patients developed dyspnea or not during the hospital course. Because COVID-19 is known to progress during day 7–10 after onset, we might have been able to include some patients in this study if we were able to extract information on patients who developed "silent hypoxia" after hospitalization.

In conclusion, COVID-19 patients with "silent hypoxia" may present with or progress to severe COVID-19 pneumonia disproportionate to their symptoms. Therefore, close monitoring of arterial blood gas and pulse oximetry is necessary. Further large-scale studies are needed to clarify the characteristics and risk factors of "silent hypoxia" COVID-19 patients.

Authorship statement

MI was responsible for the organization and coordination of the study. AO was the chief investigator and responsible for the data analysis and writing the original manuscript. MH is also responsible for data analysis and reviewing the manuscript. LS, YA, SM, SS, TT, MY, KT, IS, and NO were responsible for reviewing the study design and the manuscript. NO is also responsible for financial support. All authors contributed to the writing of the final manuscript. All members contributed to the management or administration of the trial.

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Declaration of competing interest

All authors declare no conflicts of interest from this study.

Acknowledgments

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