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Risk factors associated with asymptomatic hypoxemia among COVID-19 patients: a retrospective study using the nationwide Japanese registry, COVIREGI-JP

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**Abstract**

Deaths of home-care patients with coronavirus disease (COVID-19) have become a social problem. One of their causes is hypoxemia without dyspnea which delays seeking medical attention. This was a retrospective study including patients registered in the COVID-19 Registry Japan, in which hospitalized patients with COVID-19 in 227 participating healthcare facilities were enrolled. The enrolled patients were divided into two groups: non-dyspneic patients with a peripheral capillary oxygen saturation (SpO\(_2\)) \(\leq 93\%\) on admission (the hypoxemia without dyspnea group) and non-dyspneic patients with an SpO\(_2\) > 93\% (the control group). We conducted a multivariate logistic regression analysis to identify the factors associated with hypoxemia without dyspnea. 21544 patients were enrolled, 1035 (4.8\%) patients were in the hypoxemia without dyspnea group, and 20509 (95.2\%) patients were in the control group. The median respiratory rate (RR) of the hypoxemia without dyspnea group was higher than that of the control group (31/min vs. 18/min, \(p < 0.001\)). Age > 65, male, body mass index > 25, smoking, chronic obstructive pulmonary disease, other chronic lung disease, and diabetes mellitus were the independent factors associated with hypoxemia without dyspnea. Patients with those background should be closely monitored. RR is an important indicator of hypoxemia, even in the absence of dyspnea.

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**Keywords:** COVID-19, Silent hypoxia, Risk factors, Respiratory rate, Registry

**Introduction**

The main symptoms of COVID-19 are fever and respiratory symptoms [1]. Despite the absence of dyspnea, some patients with COVID-19 may have markedly reduced oxygen saturations, measured using pulse oximetry. This is referred to as “silent hypoxia” [2].

In Japan, every time there was a major COVID-19 wave, the medical facilities became overwhelmed, resulting in a rapid increase in the number of patients receiving treatment at home. As a result, several deaths were registered among the home care patients, which have become a social problem.

One of the causes of the death of home care patients with COVID-19 is silent hypoxia because the absence of difficulty of breathing despite the presence of hypoxemia delays seeking medical attention. Furthermore, patients with both COVID-19 and silent hypoxia are known to have poor outcomes [3]. Therefore, hypoxemia among patients with COVID-19 without dyspnea should be identified and monitored carefully. In this study, we identified the risk factors for hypoxemia among patients with COVID-19 without dyspnea.

**Material and methods**

**Study design**

This was a retrospective study including patients registered in a nationwide Japanese registry, the COVID-19 Registry Japan (COVIREGI-JP). In this registry, patients who were diagnosed with COVID-19 (positive severe acute respiratory syndrome coronavirus-2 rapid antigen or polymerase chain reaction test) and hospitalized in the...
Patients’ demographics, and outcome.

| Demographics | Sub-categories | Total | the hypoxemia without dyspnea group | Control group |
|--------------|----------------|-------|-----------------------------------|--------------|
| Sex (6 missing) | Male | 11675 (54.2%) | 597 (57.7%) | 11078 (54.0%) |
| | Female | 9861 (45.8%) | 437 (42.3%) | 9424 (46.0%) |
| Age, years | Median [IQR] | 56 [39.73] | 73 [64.84] | 55 [38.72] |
| | Age (groups), years | 20–64 | 13172 (61.1%) | 271 (26.2%) | 12901 (62.9%) |
| | | ≥ 65 | 8372 (38.9%) | 764 (72.8%) | 7680 (37.1%) |
| Ethnicity | Japanese | 20559 (95.4%) | 1011 (97.7%) | 19548 (95.3%) |
| | Others | 985 (4.6%) | 24 (2.3%) | 961 (4.7%) |
| Smoking history (3560 missing) | Former or current | 7672 (42.7%) | 397 (48.2%) | 7275 (42.4%) |
| | Never | 10312 (57.3%) | 427 (51.8%) | 9885 (57.6%) |
| Alcohol consumption (4982 missing) | Daily or occasional | 9135 (55.2%) | 353 (46.8%) | 8782 (55.6%) |
| | Never | 7427 (44.8%) | 402 (53.2%) | 7025 (44.4%) |
| Body mass index (3837 missing), kg/m² | ≤ 25 | 12007 (67.8%) | 509 (63.4%) | 11498 (68.0%) |
| | > 25 | 5700 (32.2%) | 294 (36.6%) | 5406 (32.0%) |
| Comorbidities | Any | 3632 (16.9%) | 85 (8.2%) | 3547 (17.2%) |
| | No | 17912 (83.1%) | 950 (91.8%) | 16962 (82.7%) |
| Temperature (3 missing), °C | Median [IQR] | 38.5 | 37.4 [36.8, 38.0] | 38.6 [36.5, 37.4] |
| Respiratory rate (5883 missing), breaths/min | Median [IQR] | 18 [16.20] | 31 [17.22] | 18 [16.20] |
| Days from onset of symptoms to hospitalization (3124 missing) | Median [IQR] | 4.9 [2.7] | 5.4 [2.8] | 4.9 [2.7] |
| Oxygen administration during admission and modality (5 missing) | No oxygen therapy | 17021 (79.0%) | 284 (27.4%) | 16737 (81.6%) |
| | Oxygen therapy | 4518 (21.0%) | 751 (72.6%) | 3767 (18.4%) |
| | IVT/ECMO | 278 (1.2%) | 57 (5.1%) | 221 (1.0%) |
| Outcome (5 missing) | Death | 552 (2.6%) | 88 (8.5%) | 464 (2.3%) |
| | Discharged to home or transferred to facilities | 20987 (97.4%) | 944 (91.5%) | 20043 (97.7%) |

Abbreviations: IQR, interquartile range; IVT, Invasive ventilation therapy; ECMO, Extracorporeal membrane oxygenation.

Table 2
Factors associated with hypoxemia among patients with COVID-19 without dyspnea—Multivariable logistic regression (n = 13668).

| Variables | Odds ratio | 95% CI | p-value |
|-----------|------------|--------|---------|
| Age (> 65 years) | 3.56 | [2.92, 4.35] | < 0.001 |
| Male sex | 1.31 | [1.07, 1.60] | 0.0087 |
| Body mass index (> 25 kg/m²) | 1.39 | [1.16, 1.60] | < 0.001 |
| Smoking history | 1.23 | [1.01, 1.50] | 0.036 |
| Drinking alcohol | 0.848 | [0.702, 1.02] | 0.851 |
| Myocardial infarction | 1.1 | [0.664, 1.83] | 0.706 |
| Congestive heart failure | 3.44 | [0.765, 15.5] | 0.107 |
| Peripheral vascular disease | 0.643 | [0.323, 1.28] | 0.207 |
| Cerebrovascular disease | 1.15 | [0.852, 1.54] | 0.367 |
| Chronic obstructive pulmonary disease (COPD) | 2.01 | [1.30, 3.10] | 0.002 |
| Chronic lung disease (excluding COPD) | 1.9 | [1.06, 3.40] | 0.0305 |
| Bronchial asthma | 0.997 | [0.671, 1.48] | 0.987 |
| Hypertension | 1.18 | [0.972, 1.42] | 0.095 |
| Hyperlipidemia | 1.19 | [0.958, 1.47] | 0.138 |
| Severe renal dysfunction/Hemodialysis | 0.704 | [0.352, 1.41] | 0.320 |
| Liver dysfunction | 0.975 | [0.594, 1.60] | 0.919 |
| Diabetes mellitus | 1.51 | [1.24, 1.85] | < 0.001 |

Abbreviations: COVID-19, coronavirus disease 2019; CI, confidence interval.

Statistical analysis

Categorical variables are presented as count (%), and continuous variables are presented as median and interquartile range (IQR). Fisher’s exact test was used for categorical variables, and the t-test was used for continuous variables. To identify the factors associated with hypoxemia among patients with COVID-19 without dyspnea,
we conducted a multivariate logistic regression analysis and obtained the adjusted odds ratio (OR) with 95% confidence intervals (CIs). Age, sex, body mass index (BMI), smoking, drinking, and comorbidities were independent variables. These variables were limited to those that could be obtained via telephone interviews by health center personnel. All analyses were performed using EZR ver. 1.54 [6].

Results

In total, 21544 patients were enrolled. Of these, 1035 (4.8%) patients were in the hypoxemia without dyspnea group, and 20509 (95.2%) patients were in the control group. The patients’ backgrounds on admission and the outcomes are shown in Table 1. The median respiratory rate (RR) of the hypoxemia without dyspnea group was higher than that of the control group (31/min vs. 18/min, p < 0.001). The median SpO2 in the hypoxemia without dyspnea group was lower than that in the control group (91% vs. 97%).

The odds ratios and 95% confidence intervals of the factors associated with hypoxemia without dyspnea from the multivariable logistic regression analysis are shown in Table 2. The hypoxemia without dyspnea was associated with age > 65 years (95% CI: 2.920–4.350, p < 0.001), male sex (95% CI: 1.070–1.600, p = 0.008), BMI > 25 kg/m2 (95% CI: 1.160–1.600, p < 0.001), smoking history (95% CI: 1.010–1.500, p = 0.036), chronic obstructive pulmonary disease (COPD) (95% CI: 1.300–3.100, p = 0.002), other chronic lung disease (95% CI: 1.060–3.400, p = 0.031), and diabetes mellitus (CI: 1.240–1.850, p < 0.001).

Discussion

One of the most important findings in our study was that age > 65 years, male sex, BMI > 25 kg/m2, smoking history, COPD, other chronic lung disease, and diabetes mellitus were independent factors associated with hypoxemia without dyspnea. Patients with COVID-19 having one of those characteristics may have hypoxemia and remain non-dyspneic. Thus, close monitoring of such patients is necessary. Specifically, they should be provided transcutaneous oximeters so that they can self-monitor their SpO2 regularly. Knowledge of the risk factors of hypoxemia among patients with COVID-19 without dyspnea will ease their identification and monitoring at health centers.

This study also revealed that the mean RR in the hypoxemia without dyspnea group was significantly higher than that in the control group (31/min vs 18/min, p < 0.001). This finding implies that tachypnea is an important indicator of hypoxemia, even in the absence of dyspnea. Besides, RR is an indicator of a severe derangement in many body systems, not just the respiratory system [7]. As such, it is important for patients with COVID-19 and their families to know how to predict hypoxemia even without transcutaneous oximetry; this will ensure prompt medical attention before the disease becomes severe.

This study had several limitations. First, this study was conducted in Japan, and thus the findings may not be generalizable to other countries. Second, the median SpO2 in the hypoxemia without dyspnea group was 91%. It is likely that patients with COVID-19 who were very distressed could not complain of dyspnea. Therefore, patients with severe disease may have been enrolled in the hypoxemia without dyspnea group. Third, patients with COPD or chronic lung disease rarely complain of dyspnea, even in the presence of hypoxemia. Thus, it is difficult to determine whether the absence of dyspnea was due to silent hypoxia or to the original lung disease. Forth, only hospitalized COVID-19 patients were included in this study. Thus, home-care patients were not evaluated in this study. Lastly, the method of SpO2 measurement was not standardized among the facilities.

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CRediT authorship contribution statement

Yutaro Akiyama: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. Shinichiro Morioka: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration. Yusuke Asai: Methodology, Formal analysis, Data curation. Nobuaki Matsunaga: Data curation, Writing – review & editing. Kiyoko Hayakawa: Conceptualization, Methodology, Writing – review & editing. Norio Ohmagari: Conceptualization, Writing – review & editing, Supervision.

Conflict of Interest

All authors report no conflicts of interest relevant to this article.

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