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Are there differences in the relationship between respiratory rate and oxygen saturation between COVID-19 and non-COVID-19 patients? - Insights from a cohort-based correlational study

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Running Title: Silent hypoxemia in COVID-19

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Competing Interest None declared.

ABSTRACT

Background

Physicians have observed COVID-19 patients without respiratory distress despite marked hypoxemia and extensive radiographic abnormalities, a controversial phenomenon called “silent hypoxemia”. We aimed to compare the relationship between respiratory rate (RR) and peripheral oxygen saturation (SpO₂) in COVID-19 *versus* non-COVID-19 patients when breathing air on admission.

Methods

We conducted a retrospective multicenter emergency department cohort correlational study. We used the SIESTA (Spanish Investigators on Emergency Situations TeAm) network cohort of COVID-19 patients admitted in 61 Spanish emergency departments between March and April 2020. The non-COVID-19 cohort included patients with lower respiratory tract bacterial infections admitted between January 2016 and April 2018.

We built a multivariable linear model to investigate the independent predictive factors related to RR and a logistic multivariate regression model to analyze the presence of “silent hypoxemia”.

Results

We included 1,094 COVID-19 patients and 477 non-COVID-19 patients. On admission, RR was lower (20 ± 7 *versus* 24 ± 8 /min, $p<0.0001$), while SpO₂ higher (95 ± 5 *versus* $90\pm 7\%$, $p<0.0001$) in COVID-19 *versus* non-COVID-19 patients. RR was negatively associated with SpO₂ (RR decreasing with increasing age, $\beta=-0.37$, 95%-confidence interval (95%CI) [-0.43;-0.31], $p<0.0001$), positively associated with age (RR increasing with increasing age, $\beta= 0.05$, 95%CI [0.03;0.07], $p<0.0001$) and negatively associated with COVID-19 status (RR lower in COVID-19 patients, $\beta=-1.90$, 95%CI [-2.65;-1.15], $p<0.0001$). The negative RR/SpO₂ correlation differed between <80 and ≥ 80 -year-old COVID-19 patients ($p=0.04$).

≥ 80 -year-old COVID-19 patients had lower RR than ≥ 80 -year-old non-COVID-19 patients at SpO₂ values $< 95\%$ (22 ± 7 versus 24 ± 8 /min, $p=0.004$). “Silent hypoxemia” defined as RR <20 /min with SpO₂ $<95\%$ was observed in 162 (14.8%) COVID-19 patients and in 79 (16.6%) non-COVID-19 patients ($p=0.4$). “Silent hypoxemia” was associated with age ≥ 80 years (odds ratio=1.01 [1.01; 1.03], $p<0.0001$) but not with gender, comorbidities, and COVID-19 status.

Conclusion

The RR/SpO₂ relationship before oxygen administration does not differ between COVID-19 and non-COVID-19 patients, except in elderly patients.

Keywords: COVID-19; SpO₂; Respiratory rate; Hypoxemia; Silent

Key messages

What is already known on this subject

➔ COVID-19 patients may initially present to the emergency department with minimal to no dyspnea despite profound hypoxemia and extensive radiographic abnormalities. This phenomenon has been called “silent hypoxemia”.

What this study adds

➔ This study has demonstrated that the relationship between respiratory rate and peripheral oxygen saturation (before oxygen administration) in patients younger than 80 years old is comparable between COVID-19 and non-COVID-19 patients admitted with respiratory disease.

➔ “Silent hypoxemia”, *a posteriori* defined as respiratory rate $<20/\text{min}$ and a peripheral oxygen saturation $<95\%$, was associated with increasing age, but not with gender, comorbidities, or COVID-19 disease.

How this study might affect research, practice or policy

➔ In COVID-19 and other lower respiratory tract infections, the absence of clear dyspnea does not rule out the presence of profound hypoxemia and/or extensive radiographic abnormalities.

INTRODUCTION

Mechanisms leading to hypoxemia in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-infected patients are not fully understood. SARS-CoV-2-attributed pneumonia is characterized by atypical presentations of acute respiratory distress syndrome (ARDS), with a significant number of SARS-CoV-2-infected patients showing severe hypoxemia despite preserved lung compliance at least at the initial stage when admitted to the hospital.¹ Clinicians have observed patients with minimal to no dyspnea despite profound hypoxemia and extensive radiographic abnormalities, a phenomenon called “silent hypoxemia”, referring to the absence of respiratory distress.^{2,3} Various underlying pathophysiologic hypotheses have been speculated to explain these observations including inadequate nervous system sensing in response to hypoxemia,⁴ micro-thrombi in pulmonary vasculature,⁵ pulmonary angiopathy with abnormal vasodilatation of capillaries,^{6,7} and altered relationship between oxygen delivery and transport.⁸

Aiming to identify possible SARS-CoV-2-attributed particularities in the ventilation pattern observed at the bedside, we studied the relationship between respiratory rate (RR) and peripheral oxygen saturation (SpO₂) measured using pulse oximetry when breathing room air on admission in coronavirus disease-2019 (COVID-19) in comparison to non-COVID-19 patients.

METHODS

STUDY POPULATION

We performed a retrospective multicenter emergency department (ED) cohort correlational study. We used the SIESTA (Spanish Investigators on Emergency Situations TeAm) network cohort, which included 1,198 consecutive COVID-19 patients admitted in 61 Spanish EDs between March and April 2020 for which extensive details have been previously published.⁹

Diagnosis was obtained using RT-PCR (Cobas[®] SARS-CoV-2 Test, Roche, Spain) performed on nasopharyngeal swabs. The non-COVID-19 cohort included patients with lower respiratory tract bacterial infections admitted in 54 Spanish EDs in a period preceding COVID-19 outbreak, between January 2016 and April 2018.¹⁰ Among the SIESTA cohort and the non-COVID-19 cohort, 1,094 patients and 477 patients, respectively, had more than 95% of data compiled necessary for the present study (variables shown in Table 1) and were subsequently included. SpO₂ was measured by pulse oximetry, almost systematically at room air. For each patient, we selected the SpO₂ value at ED arrival or, alternatively, the first value registered by emergency medical service on the scene.

This study was performed in agreement with the 2013 Declaration of Helsinki of the World Medical Association. The ethics committee for clinical investigation of the University Hospital Clinics of Barcelona, Spain approved the study (Protocol N^o HCB/2020/0534).

DEFINITIONS

Silent hypoxemia was defined *a posteriori* as SpO₂ <95% and respiratory rate (RR) <20/min based on the hemoglobin dissociation curve and clinical practice.

To assess a possible effect of older age on the RR/SpO₂ relationship, an arbitrary cut-off of 80 years, corresponding to the third quartile of the age distribution in the whole study population was defined. We also stratified the correlation analysis according to gender and presence of silent hypoxemia.

STATISTICAL ANALYSES

Data are presented as percentages or mean \pm SD as required. There were no missing data for the variables analyzed in regression models (age, gender, COVID-19 status, COPD, chronic heart failure, cerebrovascular disease, RR and SpO₂). Univariate comparisons between groups were performed using Fisher exact or Student t-tests as appropriate. We built a multivariable linear model to investigate the independent predictive factors related to RR and

a multivariate logistic regression model to analyze the presence of silent hypoxemia. Pearson correlations between RR and age, SpO₂ and age, and RR and SpO₂ were tested in COVID-19 and non-COVID-19 patients. Pearson coefficients of correlation (Rho) were compared following the Fisher z-transformation. Data manipulation and statistical analyses were performed using the R statistical programming language (R Core Team [2021], 4.0.4-environment; R: A language and environment for statistical computing [R Foundation for Statistical Computing, Vienna, Austria]). This report was prepared in compliance with the STROBE checklist (Strengthening the Reporting of Observational Studies in Epidemiology) for observational studies. Given the absence of published data regarding a potential difference in the RR/SpO₂ relationship between COVID-19 and non-COVID-19, and the nature of the data concerned (comparison of correlation coefficients), no sample size calculation was performed prior to data analysis.

PATIENT AND PUBLIC INVOLVEMENT

Patients and/or the public were not involved in the design or conduct or reporting or dissemination plans of this research. In accordance with the ethical standards of Spanish legislation, informed consent was waived due to the non-interventional study design that did not modify existing diagnostic or therapeutic strategies. Only the non-opposition of the patient or their legal representative was collected.

RESULTS

PATIENTS' CHARACTERISTICS

We included 1,094 consecutive COVID-19 patients and 477 consecutive non-COVID-19 patients (figure 1). COVID-19 patients were significantly younger than non-COVID-19 patients (63±18 years *versus* 74±14 years, $p < 0.0001$), with a lower proportion of males (56%

versus 64%, $p=0.005$; [table 1](#)). Chronic obstructive pulmonary disease and chronic heart failure were significantly less frequent in patients with COVID-19 versus those without COVID-19.

RELATIONSHIP BETWEEN RESPIRATORY RATE AND OXYGEN SATURATION

On admission, RR was significantly lower (20 ± 7 *versus* 24 ± 8 /min, $p<0.0001$), while SpO₂ significantly higher (95 ± 5 *versus* $90\pm 7\%$, $p<0.0001$) in COVID-19 *versus* non-COVID-19 patients. Both RR and SpO₂ were correlated with age, positively for RR (RR increasing with increasing age) ($Rho=0.27$, 95%-confidence interval (95%CI) [0.22; 0.31], $p<0.0001$) and negatively for SpO₂ (SpO₂ decreasing with increasing age) ($Rho=-0.34$, 95%CI [-0.39; -0.30], $p<0.0001$).

Overall, there was a weak negative but highly significant correlation between RR and SpO₂ (RR decreasing with increasing SpO₂, $Rho=-0.39$, 95%CI [-0.43; -0.35], $p<0.0001$), which remained after inclusion of age, gender and comorbidities as covariates ($\beta=-0.39$, 95%CI [-0.44; -0.33], $p<0.0001$). In a multivariate model including also COVID, RR was again negatively associated with SpO₂ (RR decreasing with increasing SpO₂, $\beta = -0.37$, 95%CI [-0.43; -0.31], $p<0.0001$), positively associated with age (RR increasing with increasing age, $\beta=0.05$, 95%CI [0.03; 0.07], $p<0.0001$) but also negatively associated with COVID-19 status (RR lower in COVID-19 patients, $\beta=-1.90$, 95%CI [-2.65; -1.15], $p<0.0001$). Chronic obstructive pulmonary disease, chronic heart failure and cerebrovascular disease had no effect in the model.

In COVID-19 and non-COVID-19 patients, SpO₂ and RR were negatively correlated ($Rho=-0.33$, 95%CI [-0.38; -0.28], $p<0.0001$ and $Rho=-0.34$, 95%CI [-0.42; -0.26], $p<0.0001$, respectively); the difference between these two correlations was not significant (comparison of Pearson coefficients between groups, $p=0.90$; [figure 2A](#)).

After stratification for SpO₂ levels using the median value of 95% as threshold, a negative RR/SpO₂ correlation was found in both COVID-19 ($Rho=-0.29$, 95%CI [-0.36; -0.21],

$p < 0.0001$) and non-COVID-19 patients (Rho=-0.27, 95%CI [-0.36; -0.18], $p < 0.0001$) with $SpO_2 \leq 95\%$ (figure 2B). By contrast, no correlation was found in COVID-19 (Rho=-0.008, 95%CI [-0.07; 0.09], $p=0.85$) and non-COVID-19 patients (Rho=-0.07, 95%CI [-0.26; 0.12], $p=0.47$) with $SpO_2 > 95\%$.

To further explore whether SpO_2 level might influence the RR/ SpO_2 relationship in COVID-19 and non-COVID-19 patients, we performed a multivariate analysis searching for an interaction term between SpO_2 and COVID-19 status on RR. No interaction was found in the total patient sample (beta=-0.007, 95%CI [-0.13; 0.11], $p=0.90$).

The negative RR/ SpO_2 correlation was different between <80- and ≥ 80 -year-old COVID-19 patients (comparison of Pearson coefficients between groups, $p=0.04$; figure 3). In a multivariate model including age and comorbidities, there was an interaction between SpO_2 and COVID status (beta=0.25, 95%CI [-0.0003; 0.49], $p=0.0499$), reaching statistical significance in the ≥ 80 -year-old COVID-19 patients. These patients exhibited lower RR than ≥ 80 -year-old non-COVID-19 patients at SpO_2 values $< 95\%$ (22 ± 7 versus 24 ± 8 /min, $p=0.004$).

“SILENT HYPOXEMIA”

Defined as RR < 20 /min together with $SpO_2 < 95\%$, “silent hypoxemia” was found in 162 (14.8%) COVID-19 patients versus 79 (16.6%) non-COVID-19 patients ($p=0.4$). Overall, 242 (22%) patients had $SpO_2 < 95\%$ with RR ≥ 20 /min in the COVID-19 group versus 262 (55%) in the non-COVID-19 group ($p < 0.0001$). In a multivariate model, silent hypoxemia was only significantly associated with age (silent hypoxemia more frequent with increasing age, odds ratio=1.01 [1.01; 1.03], $p < 0.0001$) but not with gender, comorbidities or COVID-19 status.

DISCUSSION

Clinical presentation in COVID-19 is highly variable with some patients exhibiting no respiratory distress despite profound hypoxemia, a phenomenon referred to as “silent

hypoxemia”.²⁻⁴ Whether this entity is physiological or paradoxical remains controversial. To date, no study has compared the relationship between hypoxemia and respiratory status in COVID-19 *versus* other etiologies of acute lung injury. Differences could only be investigated in COVID-19 and non-COVID-19 patient cohorts with data obtained at the first medical contact before oxygen administration, like in our series.

Overall, we observed no significant differences in the RR/SpO₂ relationship between COVID-19 and non-COVID-19 patients on admission. However, ≥80-year-old COVID-19 patients with low SpO₂ exhibited lower variations in RR relative to changes in SpO₂. Our findings did not support better tolerance of hypoxemia in COVID-19 patients except those of ≥80-year-old.

STUDY LIMITATIONS

Our study had limitations. Our patient groups were not admitted in the same period. Arterial blood gas analysis before oxygen administration was mostly unavailable, and therefore, arterial pressure of carbon dioxide, a major determinant of respiratory function, could not be compared between COVID-19 and non-COVID-19 patients. We used RR as surrogate of respiratory distress, which may not adequately represent clinical tolerance to hypoxemia. Although our non-COVID-19 group included various etiologies of lower respiratory tract infections not restricted to viral infections, patterns of hypoxemia without high RR did not differ between COVID-19 and non-COVID-19 patients. Moreover, measurements of RR relying on human observations are notoriously subject to errors.¹¹ Last, our study population lacked in-depth clinical characteristics. The differences observed in the RR/SpO₂ relationship between COVID-10 and non-COVID-19 patients, especially in the elderly group, may be explained by a greater proportion of patients with underlying conditions affecting oxygen and carbon dioxide physiology, as lower SpO₂ values have been reported in older patients.¹²

CONCLUSIONS

The RR/SpO₂ relationship before oxygen administration, investigated in a nationwide multicenter emergency department cohort, does not differ between COVID-19 and non-COVID-19 patients, except in the elderly patients. Mechanisms underlying these findings are currently unexplained.

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Table 1 Patient characteristics on admission to the emergency department

Characteristics	COVID-19 patients (n=1,094)	Non-COVID-19 patients (n=477)	P-value
Demographics			
Age (years)	63±18	74±14	<0.0001
Age ≥ 80 years, N (%)	218 (20)	195 (41)	<0.0001
Male gender, N (%)	616 (56)	305 (64)	0.005
Diabetes, N (%)	212 (19)	150 (31)	<0.0001
Associated conditions			
COPD, N (%)	106 (10)	235 (49)	<0.0001
Chronic Heart Failure, N (%)	82 (8)	74 (16)	<0.0001
Cerebrovascular disease, N (%)	69 (6)	41 (9)	0.13
Vital parameters			
Body temperature (°C)	36.8±0.9	37.3±1.0	<0.0001
Fever, N (%)	699 (64)	162 (34)	<0.0001
Systolic blood pressure (mmHg)	136±27	128±10	<0.0001
Heart rate (bpm)	89±17	98±22	<0.0001
Respiratory rate (/min)	20±7	24±8	<0.0001
SpO ₂ (%)	95±5	90±7	<0.0001
Laboratory blood tests			
Leucocytes (G/L)	7.2±3.7	13.9±10.0	<0.0001
C-reactive protein (mg/L)	7.3±7.9	19.2±10.0	<0.0001
Chest X-ray			
Lung opacities, N (%)	651 (60)	207 (43)	<0.0001

Data are presented as n (%) or mean \pm SD. Comparisons were performed using exact Fisher tests for categorical and Student t-tests for continuous variables.

Abbreviations: COPD, chronic pulmonary obstructive disease; COVID-19, coronavirus disease-2019; SpO₂, peripheral oxygen saturation.

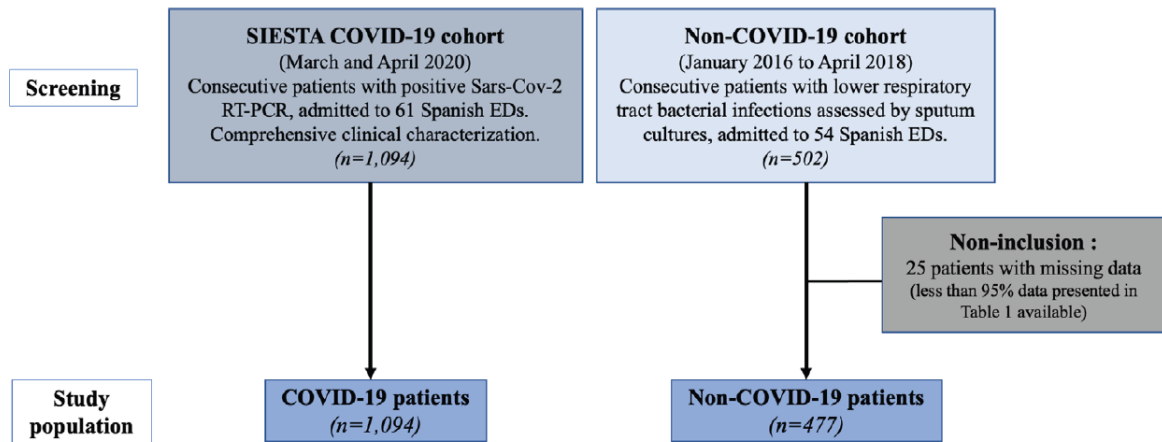


Figure 1. Study flowchart.

COVID-19, coronavirus disease-2019; ED, Emergency department; RT-PCR, reverse transcriptase - polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2

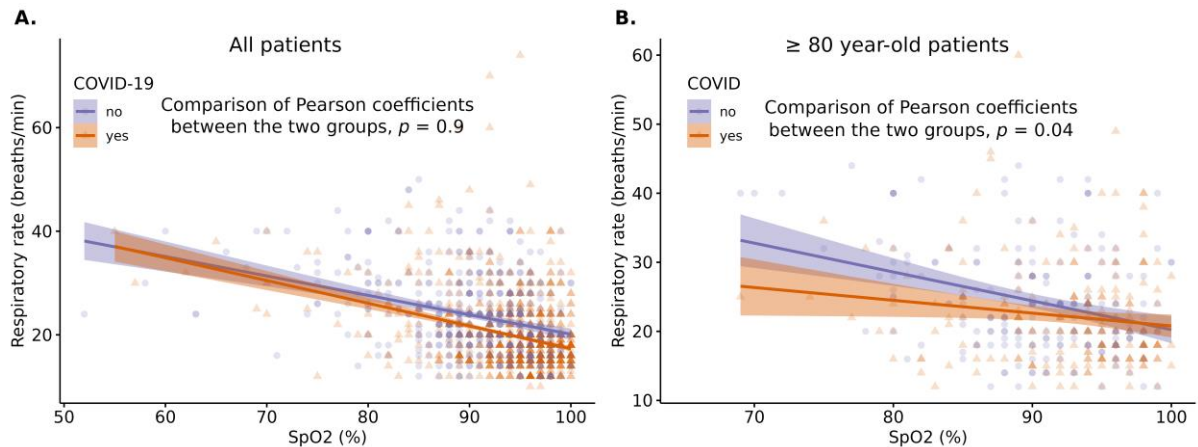


Figure 2. Correlations between respiratory rate and pulse oximetry oxygen saturation.

Pearson correlations between respiratory rate (RR) and pulse oximetry oxygen saturation (SpO₂) in COVID-19 (orange, triangles) and non-COVID-19 patients (purple, circles) in the whole study population (**A**) and the subgroup of patients aged over 80 years (**B**). In the whole population, RR and SpO₂ negatively correlated (Rho coefficients, -0.33 and -0.34, respectively) with no significant difference between both groups (Pearson coefficients difference, $p=0.90$). In the subgroup of patients aged over 80 years, COVID-19 patients had a significantly lower correlation between RR and SpO₂ than non-COVID-19 patients (comparison of Pearson coefficients between groups, $p=0.04$).

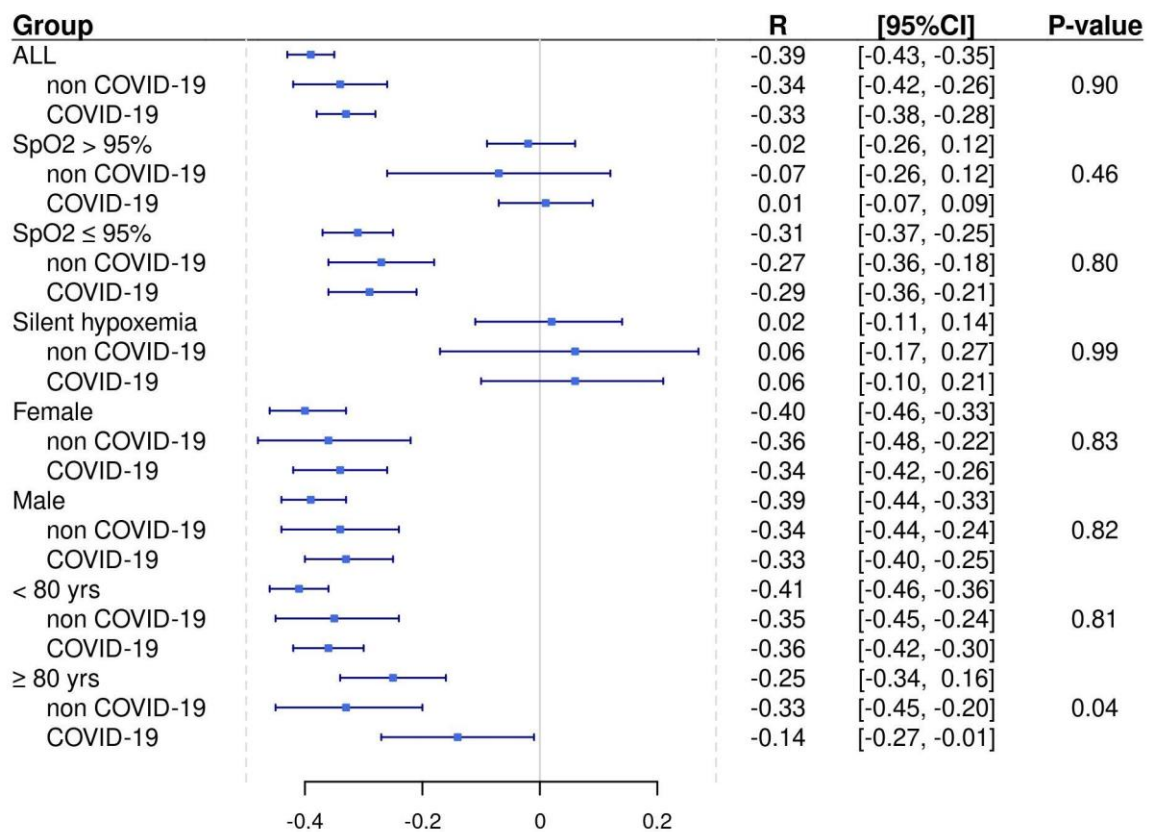


Figure 3. Comparison of Pearson coefficients between groups.

Forrest-plot of Pearson correlation coefficients between RR and SpO₂ in COVID-19 and non-COVID-19 patients. Reported p-values are those obtained for comparisons of Pearson coefficients between groups. There were no significant differences in Pearson coefficients between COVID-19 and non-COVID-19 except in patients aged over 80 years, with significantly lower correlation between RR and SpO₂ in COVID-19 *versus* non-COVID-19 patients (significantly higher Pearson coefficient, p=0.04).