Are there differences in the relationship between respiratory rate and oxygen saturation between patients with COVID-19 and those without COVID-19? Insights from a cohort-based correlational study

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ABSTRACT

Background Physicians have observed patients with COVID-19 without respiratory distress despite marked hypoxaemia and extensive radiographic abnormalities, a controversial phenomenon called 'silent hypoxaemia'. We aimed to compare the relationship between RR and peripheral oxygen saturation (SpO_2) in patients with COVID-19 versus patients without COVID-19 when breathing air on admission.

Methods We conducted a retrospective multicentre ED cohort correlational study.
We used the Spanish Investigators on Emergency Situations TeAm network cohort of patients with COVID-19 admitted to 61 Spanish EDs 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 analyse the presence of 'silent hypoxaemia'.

Results We included 1094 patients with COVID-19 and 477 patients without COVID-19. On admission, RR was lower (20±7 vs 24±8/min, p<0.0001), while SpO_2 higher (95±5% vs 90±7%, p<0.0001) in patients with COVID-19 versus patients without COVID-19. RR was negatively associated with SpO_2 (RR decreasing with increasing age, 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) and negatively associated with COVID-19 status (RR lower in patients with COVID-19, beta=−1.90, 95% CI (−2.65; −1.15), p<0.0001). The negative RR/SpO_2 correlation differed between patients with COVID-19 aged <80 and ≥80 years old (p=0.04). Patients with COVID-19 aged ≥80 years old had lower RR than patients without COVID-19 aged ≥80 years old at SpO_2 values <95% (22±7 vs 24±8/min, p=0.004). 'Silent hypoxaemia' defined as RR <20/min with SpO_2 <95% was observed in 162 (14.8%) patients with COVID-19 and in 79 (16.6%) patients without COVID-19 (p=0.4). 'Silent hypoxaemia' was associated with age ≥80 years (OR=1.01 (1.01; 1.03), p<0.0001) but not with gender, comorbidities and COVID-19 status.

Conclusion The RR/SpO_2 relationship before oxygen administration does not differ between patients with COVID-19 and those without COVID-19, except in elderly patients.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with COVID-19 may initially present to the ED with minimal to no dyspnoea despite profound hypoxaemia and extensive radiographic abnormalities. This phenomenon has been called 'silent hypoxaemia'.

WHAT THIS STUDY ADDS

⇒ This study has demonstrated that the relationship between RR and peripheral oxygen saturation (before oxygen administration) in patients younger than 80 years old is comparable between patients with COVID-19 and those without COVID-19 admitted with respiratory disease.

⇒ 'Silent hypoxaemia', a posteriori defined as RR <20/min and a peripheral oxygen saturation <95%, was associated with increasing age, but not with gender, comorbidities or COVID-19.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

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

INTRODUCTION

Mechanisms leading to hypoxaemia in SARS-CoV-2-infected patients are not fully understood. SARS-CoV-2-attributed pneumonia is characterised by atypical presentations of acute respiratory distress syndrome, with a significant number of SARS-CoV-2-infected patients showing severe hypoxaemia despite preserved lung compliance at least at the initial stage when admitted to the hospital.[1] Clinicians have observed patients with minimal to no dyspnoea despite profound hypoxaemia and extensive radiographic abnormalities, a phenomenon called 'silent hypoxaemia', referring to the absence of respiratory distress.[2 3] Various underlying pathophysiological hypotheses have been speculated to explain these observations including inadequate nervous system sensing in response to hypoxaemia,[4]

Table 1 Patient characteristics on admission to the ED

Characteristics	Patients with COVID-19 (n=1094)	Patients without COVID-19 (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 BP (mm Hg)	136±27	128±10	<0.0001
HR (bpm)	89±17	98±22	<0.0001
RR (/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
CXR			
Lung opacities, N (%)	651 (60)	207 (43)	<0.0001

Data are presented as n (%) or mean±SD. Comparisons were performed using Fisher's exact tests for categorical and Student's t-tests for continuous variables.
bpm, beats per minute; COPD, chronic obstructive pulmonary disease; SpO_2, peripheral oxygen saturation;

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 RR and peripheral oxygen saturation (SpO_2) measured using pulse oximetry when breathing room air on admission in COVID-19 in comparison with patients without COVID-19.

METHODS

Study population

We performed a retrospective multicentre ED cohort correlational study. We used the SIESTA (Spanish Investigators on Emergency Situations TeAm) network cohort, which included 1198 consecutive patients with COVID-19 admitted to 61 Spanish EDs between March and April 2020 for which extensive details have been previously published.[9] Diagnosis was obtained using reverse transcriptase-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 to 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, 1094 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.

SpO_2 was measured by pulse oximetry, almost systematically at room air. For each patient, we selected the SpO_2 value at ED arrival or, alternatively, the first value registered by emergency medical service on the scene.

Definitions

Silent hypoxaemia was defined a posteriori as SpO_2 <95% and RR <20/min based on the haemoglobin dissociation curve and clinical practice.

To assess a possible effect of older age on the RR/SpO_2 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 hypoxaemia.

Statistical analyses

Data are presented as percentages or mean±SD as required. There were no missing data for the variables analysed in regression models (age, gender, COVID-19 status, chronic obstructive pulmonary disease (COPD), chronic heart failure, cerebrovascular disease, RR and SpO_2). Univariate comparisons between groups were performed using Fisher's exact or Student's 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 analyse the presence of silent hypoxaemia. Pearson correlations between RR and age, SpO_2 and age, and RR and SpO_2 were tested in patients with COVID-19 and those without COVID-19. Pearson coefficients of correlation (r) were compared following the Fisher z-transformation. Data manipulation and statistical analyses were performed using the R statistical programming language (R Core Team (2021), V.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 Strengthening the Reporting of Observational Studies in Epidemiology checklist for observational

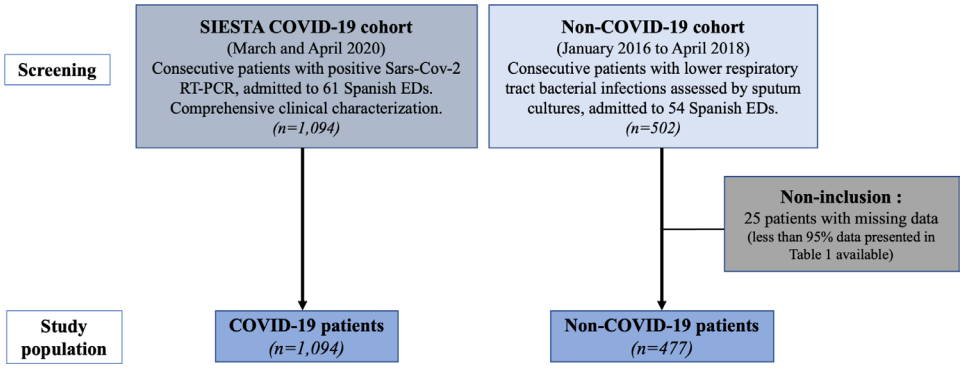

Figure 1 Study flow chart. RT-PCR, reverse transcriptase-PCR; SIESTA, Spanish Investigators on Emergency Situations TeAm.

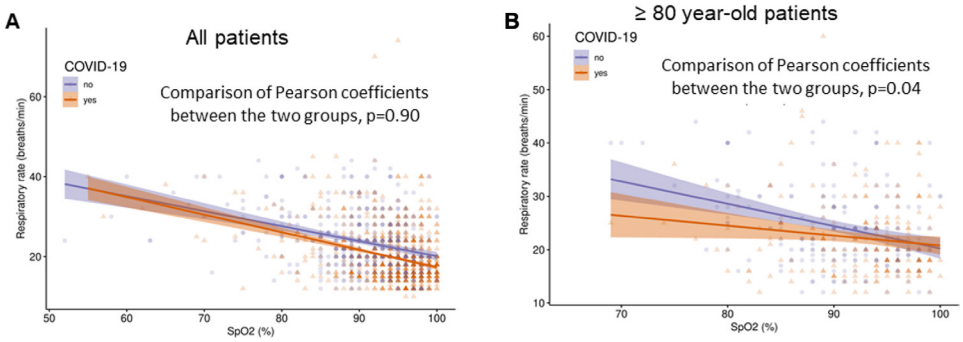

Figure 2 Correlations between RR and pulse oximetry oxygen saturation (SpO_2). Pearson correlations between RR and pulse oximetry SpO_2 in patients with COVID-19 (orange, triangles) and patients without COVID-19 (purple, circles) in the whole study population (A) and the subgroup of patients aged over 80 years (B). In the whole population, RR and SpO_2 negatively correlated (r 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, patients with COVID-19 had a significantly lower correlation between RR and SpO_2 than patients without COVID-19 (comparison of Pearson coefficients between groups, p=0.04).

studies. Given the absence of published data regarding a potential difference in the RR/SpO_2 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 1094 consecutive patients with COVID-19 and 477 consecutive patients without COVID-19 (figure 1). Patients with COVID-19 were significantly younger than patients without COVID-19 (63±18 years vs 74±14 years, p<0.0001), with a lower proportion of males (56% vs 64%, p=0.005; table 1). COPD and chronic heart failure were significantly less frequent in patients with COVID-19 versus those without COVID-19.

Relationship between RR and SpO_2

On admission, RR was significantly lower (20±7 vs 24±8/min, p<0.0001), while SpO_2 significantly higher (95±5% vs 90±7%,

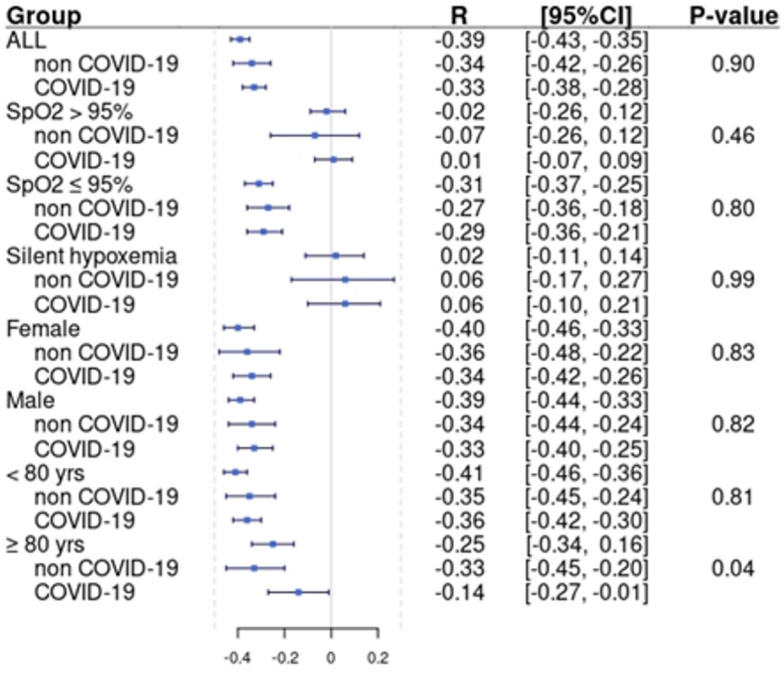

Figure 3 Comparison of Pearson coefficients between groups. Forest plot of Pearson correlation coefficients between RR and SpO_2 in patients with COVID-19 and those without COVID-19. Reported p values are those obtained for comparisons of Pearson coefficients between groups. There were no significant 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 SpO_2 in patients with COVID-19 versus patients without COVID-19 (significantly higher Pearson coefficient, p=0.04). SpO_2, peripheral oxygen saturation.

p<0.0001) in patients with COVID-19 versus patients without COVID-19. Both RR and SpO_2 were correlated with age, positively for RR (RR increasing with increasing age) (r=0.27, 95% CI (0.22; 0.31), p<0.0001) and negatively for SpO_2 (SpO_2 decreasing with increasing age) (r=−0.34, 95% CI (−0.39; −0.30), p<0.0001).

Overall, there was a weak negative but highly significant correlation between RR and SpO_2 (RR decreasing with increasing SpO_2, r=−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-19, RR was again negatively associated with SpO_2 (RR decreasing with increasing SpO_2, 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 patients with COVID-19, beta=−1.90, 95% CI (−2.65; −1.15), p<0.0001). COPD, chronic heart failure and cerebrovascular disease had no effect in the model.

In patients with COVID-19 and those without COVID-19, SpO_2 and RR were negatively correlated (r=−0.33, 95% CI (−0.38; −0.28), p<0.0001and r=−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 SpO_2 levels using the median value of 95% as threshold, a negative RR/SpO_2 correlation was found in both patients with COVID-19 (r=−0.29, 95% CI (−0.36; −0.21), p<0.0001) and patients without COVID-19 (r=−0.27, 95% CI (−0.36; −0.18), p<0.0001) with SpO_2 ≤95% (figure 2B). By contrast, no correlation was found in patients with COVID-19 (r=−0.008, 95% CI (−0.07; 0.09), p=0.85) and patients without COVID-19 (r=−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 patients with COVID-19 and those without COVID-19, 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 patients with COVID-19 aged <80 and ≥80 years old (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-19 status (beta=0.25, 95% CI (−0.0003; 0.49), p=0.0499), reaching statistical significance in the patients with COVID-19 aged ≥80 years old. These patients exhibited lower RR than patients without COVID-19 aged ≥80 years old at SpO_2 values <95% (22±7 vs 24±8/min, p=0.004).

'Silent hypoxaemia'

Defined as RR <20/min together with SpO_2 <95%, 'silent hypoxaemia' was found in 162 (14.8%) patients with COVID-19 vs 79 (16.6%) patients without COVID-19 (p=0.4). Overall, 242 (22%) patients had SpO_2 <95% with RR ≥20/min in the COVID-19 group vs 262 (55%) in the non-COVID-19 group (p<0.0001). In a multivariate model, silent hypoxaemia was only significantly associated with age (silent hypoxaemia more frequent with increasing age, OR=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 hypoxaemia, a phenomenon referred to as 'silent hypoxaemia'.[2–4] Whether this entity is physiological or paradoxical remains controversial. To date, no study has compared the relationship between hypoxaemia and respiratory status in COVID-19 versus other aetiologies of acute lung injury. Differences could only be investigated in cohorts of patients with COVID-19 and patients without COVID-19 with data obtained at the first medical contact before oxygen administration, like in our series.

Overall, we observed no significant differences in the RR/SpO_2 relationship between patients with COVID-19 and those without COVID-19 on admission. However, patients with COVID-19 aged ≥80 years old with low SpO_2 exhibited lower variations in RR relative to changes in SpO_2. Our findings did not support better tolerance of hypoxaemia in patients with COVID-19 except those aged ≥80 years old.

Study limitations

Our study had limitations. Our patient groups were not admitted in the same period. ABG 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 patients with COVID-19 and those without COVID-19. We used RR as surrogate of respiratory distress, which may not adequately represent clinical tolerance to hypoxaemia. Although our non-COVID-19 group included various aetiologies of lower respiratory tract infections not restricted to viral infections, patterns of hypoxaemia without high RR did not differ between patients with COVID-19 and those without COVID-19. 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/SpO_2 relationship between patients with COVID-10 and those without COVID-19, 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 SpO_2 values have been reporter in older patients.[12]

CONCLUSIONS

The RR/SpO_2 relationship before oxygen administration, investigated in a nationwide multicentre ED cohort, does not differ between patients with COVID-19 and patients without COVID-19, except in the elderly patients. Mechanisms underlying these findings are currently unexplained.

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Contributors ML, CV, OM and BM have made substantial contributions to the conception and design of the study. OM, JGdC, AA-A, JJ and PP have contributed to acquisition of data. ML, CV and BM performed the analysis and the interpretation of data. All authors read and approved the final manuscript.

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Competing interests None declared.

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.

Patient consent for publication Not required.

Ethics approval 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 no: HCB/2020/0534).

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REFERENCES

1 Gattinoni L, Chiumello D, Caironi P, *et al*. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med* 2020;46:1099–102.
2 Tobin MJ, Laghi F, Jubran A. Why COVID-19 silent hypoxemia is baffling to physicians. *Am J Respir Crit Care Med* 2020;202:356–60.
3 Allali G, Marti C, Grosgurin O, *et al*. Dyspnea: the vanished warning symptom of COVID-19 pneumonia. *J Med Virol* 2020;92:2272–3.
4 Swenson KE, Ruoss SJ, Swenson ER. The pathophysiology and dangers of silent hypoxemia in COVID-19 lung injury. *Ann Am Thorac Soc* 2021;18:1098–105.
5 Ackermann M, Verleden SE, Kuehnel M, *et al*. Pulmonary vascular Endothelialitis, thrombosis, and angiogenesis in COVID-19. *N Engl J Med* 2020;383:120–8.
6 Reynolds AS, Lee AG, Renz J, *et al*. Pulmonary vascular dilatation detected by automated transcranial Doppler in COVID-19 pneumonia. *Am J Respir Crit Care Med* 2020;202:1037–9.
7 Patel BV, Arachchillage DJ, Ridge CA, *et al*. Pulmonary Angiopathy in severe COVID-19: physiologic, imaging, and hematologic observations. *Am J Respir Crit Care Med* 2020;202:690–9.
8 Liu W, Li H. COVID-19: attacks the 1-beta chain of hemoglobin and captures the Porphyrin to inhibit human Heme metabolism. *ChemRvix* 2020.
9 Gil-Rodrigo A, Miró Ò, Piñera P, *et al*. Analysis of clinical characteristics and outcomes in patients with COVID-19 based on a series of 1000 patients treated in Spanish emergency departments. *Emergencias* 2020;32:233–41.
10 González Del Castillo J, Julián-Jiménez A, Gamazo-Del Rio JJ, *et al*. A multidrug-resistant microorganism infection risk prediction model: development and validation in an emergency medicine population. *Eur J Clin Microbiol Infect Dis* 2020;39:309–23.
11 Fogarty AW, Card T, Shaw D, *et al*. Error in respiratory rate measurement by direct observation impacts on clinical early warning score Algorithms. *Emerg Med J* 2023;40:458–9.
12 Rodríguez-Molinero A, Narvaiza L, Ruiz J, *et al*. Normal respiratory rate and peripheral blood oxygen saturation in the elderly population. *J Am Geriatr Soc* 2013;61:2238–40.