Asymptomatic hypoxia in COVID-19 is associated with poor outcome

Philippe Brouqui, Sophie Amrane, Matthieu Million, Sébastien Cortaredona, Philippe Parola, Jean-Christophe Lagier, Didier Raoult

Asymptomatic hypoxia in COVID-19 is associated with poor outcome

Philippe Brouqui[1,2*], Sophie Amrane[1,2], Matthieu Million[1,2], Sébastien Cortaredona[2,3], Philippe Parola[2,3], Jean-Christophe Lagier[1,2] and Didier Raoult[1,2]

1. Aix Marseille Université, IRD, MEPHI, Marseille, France
2. IHU-Mediterranée Infection, Marseille, France
3. Aix Marseille Université, IRD, AP-HM, SSA, VITROME, Marseille, France

**Corresponding author: philippe.brouqui@univ-amu.fr*

Acknowledgments

The English language in this text was edited by American Journal Experts.

Keywords: COVID-19; hypoxemia; hypoxia; hypocapnia; silent; happy; low dose CT-scan; D-dimers; 02 sat

Abstract:

Objectives

Describe and evaluate the outcome of COVID patient without shortness of breath

Design and methods

We retrospectively collected data from COVID-19 patients diagnosed and cared for in Marseille France. We selected data from patients who had at admission, a low dose CT scanner, dyspnea status and oxygen saturation available. Blood-gas was analyzed in a sample subset of patients.

Results

Among 1712 patients with COVID-19 we report that 1107 (64.7%) do not complaint of a shortness of breath at admission. The LDCT scan showed signs compatible with pneumonia in 757/1,107 (68.4%) of patients without dyspnea. In a subset of patients who had underwent at least one blood gas analysis (n=161) and presented without dyspnea at admission, 28.1% (27/96) presented with a hypoxemia/hypocapnia syndrome. Asymptomatic hypoxia was associated with a very poor outcome (33.3% were transferred to ICU and 25.9% died)

Conclusion

The absence of shortness of breath in old patient with co-morbidity merit medical attention and should not be considered as a good sign of wellbeing. The poor prognosis of asymptomatic hypoxia, highlight the severity of this mild clinical presentation. In these patient's pulse oximetry is an important mean to predict the outcome along with news score and LDCT scanner.

Introduction

Recently, a new coronavirus named SARS-CoV-2 emerged in China at the end of December 2019 and rapidly spread throughout the world, producing millions of victims and several hundred thousand deaths (1). The early descriptive reports of the clinical presentation of the disease resulting from SARS-CoV-2 infection, named COVID-19, revealed that a third of patients did not have dyspnea (2). Shortness of breath has been reported in 18.7% of 1,099 patients hospitalized with COVID-19, many of whom showed an abnormal CT scan (86%) and received supplemental oxygen (41%) (3). In patients with objective radiographic findings consistent with COVID-19 pneumonia, only 50% report shortness of breath (1). Despite this accumulating knowledge, the criteria for clinical screening and care management in most countries, including France, are still based upon 3 symptoms: fever, cough and dyspnea. Asymptomatic patients are requested to self-isolate at home, while those that become symptomatic are invited to contact their health care provider (4). However, some patients with COVID-19 deteriorate rapidly and seemingly without warning. For example, in Marseille, France, more than two thirds of patients hospitalized in intensive care units (ICUs) come directly from home or are admitted to the ICU after less than three days of standard ward hospitalization. Additionally, many patients who go on to develop respiratory failure experienced hypoxemia and hypocapnia without signs of respiratory distress, especially elderly patients. This is called "happy hypoxemia" or “silent hypoxemia” and was previously described in patients during the initial Wuhan outbreak (5). The cause of this asymptomatic hypoxia is not yet clear. Anosmia-hyposmia has been reported as a frequent clinical sign in COVID (6) but whether SARS Cov2 access to the brain and contribute to the association between dyspnea and anosmia-hyposmia remained to be determined (7). Some have links happy hypoxemia with the development of thrombi within the pulmonary vasculature (8).

The discrepancy between respiratory clinical signs and the pulmonary lesions observed with a low-dose computed tomography (LDCT) scanner were reported in the early epidemic by Chinese authors (1;2;9) but was not taken into account, and decisions based on home interviews of patients only considered dyspnea to justify hospital care. Massive test implementation and careful observation of positive patients, regardless of whether they were apparently symptomatic, allowed us to show that some patients who were classified as asymptomatic actually had hypoxia and others had lung damage visible on CT scan (10). In this work, which is derived from a report based on a cohort of 3,737 patients , we wanted to focus on the relationship between dyspnea, hypoxemia and lung lesions identified in LDCT scans.

Patients and methods

The patients

We retrospectively collected data from the information system of our hospital related to COVID-19 patients diagnosed and cared for in the infectious disease institute (IHU Mediterranée Infection) in Marseille France from March 3rd until April 27th. All patient care were diagnosed by PCR of a nasopharyngeal sample and were over 18 y-o (10;11). We selected data from patients who had in their record at admission, all of the following items: a low dose CT Scanner, dyspnea status and oxygen saturation available (1,712 patients). Blood-gas were analyzed in a sample subset (161 patients). Dyspnea is a subjective sign which was recorded at interview and was defined as shortness of breath. O_2 desaturation was defined as SaO_2<=95%. A low-dose CT scanner was proposed for all patients as soon as possible after admission when possible, and radiological lesions were classified into four categories: normal, minimal grade 1, intermediate grade 2 or severe grade 3 (12). Hypoxemia was defined as pO2_mmHg<= 80, and hypocapnia as pCO2_mmHg<=35. Demographics, chronic conditions (cancer, diabetes mellitus, chronic heart disease, hypertension, chronic respiratory

disease and obesity), concomitant medication, and signs and symptoms, including fever, cough, anosmia, ageusia, dyspnea, oxygen saturation, and blood gas analysis were extracted from the hospital information system (10) . Severity was assessed using the national early warning score adapted to COVID-19 patients (NEWS-2) (12).

Statistics

Categorical variables are presented as n (%). We used Chi-squared test, Fisher's exact test, univariate logistic regressions and estimated odds ratios (ORs) with 95% confidence intervals (CIs) to compare differences between patients with dyspnea and patients without dyspnea. To compare the prognosis performance of the LDCT scanner score and O_2 saturation on clinical outcomes (transfer to ICU/death) among patients with no dyspnea, we performed multivariate logistic regressions. Models were adjusted on the following covariates: age, sex, time from symptom onset to admission, comorbidities (cancer, diabetes mellitus, cardiac diseases, hypertension, chronic respiratory diseases, obesity) and clinical classification at inclusion (NEWS score). Four separate models were carried out. In the reference model (model A), all covariates previously listed were included. In Model B, we added to this list the LDCT scanner severity score. In model C, we added O_2 saturation. Model D included both O_2 saturation and the LDCT scanner severity. We calculated the Akaike information criterion (AIC) and computed the C-statistic for each model. The C-statistic is equal to the area under the receiver operating characteristic (ROC) curve and ranges from 0.5 to 1. A two-sided α value of less than 0·05 was considered statistically significant. To investigate associations between clinical data, biological data, radiological data and clinical outcomes (death and/or ICU stay), we performed univariate logistic regressions and Principal Component Analysis (PCA) in a subset of 161 patients who had underwent at least one blood gas analysis. Hierarchical Clustering on Principal Components (HCPC) was performed to identify clusters of patients. Analyses were carried out using SAS 9.4 statistical software (SAS Institute, Cary,

NC). PCA and HCPC were performed using R Statistical Software and the FactoMineR package (13).

Results

Among 3,737 patients diagnosed with SARS-CoV-2 infection in our institute, we selected 1,712 with available dyspnea, O_2 saturation and LDCT scan information obtained within the first 48 or 72 hours. Among them, 1,107/1,712 (64.7%) presented with no dyspnea, and 605/1,712 (35.3%) presented with dyspnea. Underlying conditions and clinical symptoms are comprehensively described in **Table 1**. The prevalence of poor clinical outcome (transfer to intensive care unit and/or death) significantly increased among patients with dyspnea.

The LDCT scan showed signs compatible with pneumonia in 757/1,107 (68.4%) of patients without dyspnea, with 525/757 (69.4%) of patients exhibiting minimal grade 1 lesions, 194/757 (25.6%) of patients exhibiting intermediate grade 2 lesions, and 38/757 (5.0%) of patients exhibiting severe grade 3 lesions (**Figure 1, Table 2**). Compared to patients without dyspnea, lesions of grades 2 and 3 were significantly more frequent in patients with dyspnea (OR 95% CI: 1.58; 1.24-2.01 and OR 95% CI: 2.15; 1.38-3.37, respectively). 157/1107 (14.2%) of patients without dyspnea had an O_2 sat $\leq$95. Among them, 84 had an O_2 sat $\leq$94, 48 had an O_2 sat $\leq$93, 26 had an O_2 sat $\leq$92, 12 had an O_2 sat $\leq$91 and 6 had an O_2 sat $\leq$90. Compared with patients without dyspnea, oxygen saturation was significantly worse in patients with dyspnea (**Table 2**).

Among the 1,107 without dyspnea, those which LDCT grade 2 and 3 lesions had significantly higher odds of having a poor clinical outcome during follow-up (OR 95% CI: 9.45; 3.02-29.62) (**Table 3**). Compared to the model with O_2 sat (OR 95% CI: 0.78; 0.65-0.93), the model with LDCT scan score achieved a better goodness-of-fit (lower AIC).

In the subset of patients who had underwent at least one blood gas analysis (n=161) and presented without dyspnea at admission, 28.1% (27/96) presented with a

hypoxemia/hypocapnia syndrome defining asymptomatic hypoxia **Figure 2**. HCPC analysis distinguished three clusters. Hypoxemia/hypocapnia syndrome (yellow dots) was clustered with death/ICU, elevated NEWS score, age, male and elevated D-dimers. Hypoxemia/hypocapnia was associated with aging, male, and chronic heart disease but not with diabetes mellitus. Hypoxemia/hypercapnia (33%) clustered with favorable outcome and was associated with younger age. Hyperoxemia/ hypocapnia (22%) was associated with women and younger age. Hyperoxemia/hypercapnia (15%) was surprisingly associated with cancer (**Figure 3, Table 4**). Hypoxemia/hypocapnia syndrome was strongly associated with death/ICU (OR 95% CI: 4.37; 2.12-9.03) ($p<0.0001$) and elevated D-dimers >2.5 mg/l (OR 95% CI: 6.26; 1.99-19.75) ($p=0.002$).

Discussion

In patient with COVID 19 dyspnea is linked to poor outcome and merit attention and urgent care. However, it is important to underling that among 1712 patients with COVID-19, 64.7% (1107) do not complaint of shortness of breath at admission and that 23 of them were transferred to ICU and /or died highlighting the severity of this clinical presentation. In these patients, News score, LDCT of the thorax and pulse oximetry are important means to predict death. Moreover, among patient without dyspnea 28.1% presented with hypoxemia/hypocapnia syndrome (happy or silent hypoxemia) which was also strongly associated with a poor outcome. Due to inclusion criteria, our studied population was significantly more severe and had a longer time from symptom onset to admission suggesting a selection bias. Consequently our results cannot be extrapolated to the whole population of patients with COVID-19.

To the best of our knowledge, this work is the most comprehensive comparison of dyspneic and non-dyspneic COVID-19 patients and their blood gas analysis results and lung lesion findings visualized on a low-dose CT scan. Asymptomatic hypoxia has only been

reported recently in COVID-19 patients (5,7). Hypoxia with accompanying hypocapnia generates no sensation of breathlessness, on the contrary, it may feel comfortable (14), and COVID-19 patients do not necessarily appear dyspneic until late in the course of the disease (5). Physicians treating COVID-19 patients, including us, have reported caring for patients who presented well and then suddenly, within a few hours, progressed to severe respiratory distress (14).

The subjective sensation of dyspnea is driven by the respiratory center in our brain that is sensitive to increased CO2 and to a lesser degree, decreased O2 (7). Our respiratory center can become desensitized as we age and from chronic conditions such as diabetes (15). Patients with diabetes were noted to be 1.8 times more likely to have an impaired ability to perceive respirations than nondiabetic controls. Therefore, it was suggested that patients who are presenting with silent hypoxemia are most likely the elderly and those with chronic diseases and consequently the poorest outcomes. In our cohort, age but not diabetes was associated with dyspnea and hypoxemia. While pulse oximetry is underestimating true pO2_mmHg, in patient feeling comfortable at admission we show that it predicts well the outcome. As consequence in patient with COVID but without shortness of breath, pulse oximetry should be added to the News score and to LDCT to monitor the care.

The incidence of thrombotic complications in ICU patients with COVID-19 infection is remarkably high (16). This has been well established by a recent study of necropsied patients, which reported that although the predominant patterns of lung lesions are diffuse alveolar, damage associated with the presence of platelet-fibrin thrombi in small arterial vessels is consistent with coagulopathy and appears extremely common (17). Hypoxemia and elevated D-dimers strongly suggest that the resulting lung damage is due in part to arterial microemboli and might explain the severity of clinical presentation and the subsequent death.

These findings reinforce the recommendation to apply thrombosis prophylaxis in these patients (16).

It appears now clear that dyspnea is not a key criterion of initial severity in patients with COVID-19. As recommended by the CDC and many other heath policies throughout the world, “Patients with a mild clinical presentation (absence of viral pneumonia and hypoxia) may not initially require hospitalization, and many patients will be able to manage their illness at home” (4). We believe that it is necessary to systematically ask for shortness of breath that is a subjective sensation not related with respiratory frequency and very frequently reported. Among patients feeling well and without dyspnea, a third (28.1%) might present with hypoxemia at admission. This absence of shortness of breath merit medical attention and it should not be considered as a good sign of wellbeing. We suggest that for these patients with “a mild clinical presentation” it is particularly important to achieve in a regular basis oxygen saturation with pulse oximetry completed with blood gas analysis if necessary, to allow early diagnosis of asymptomatic hypoxia and a more appropriate care to reduce the poor outcome.

Table 1. Clinical characteristics of patients according to dyspnea status (n=1,712)

	No dyspnea[a] (n=1107, 65%)		Dyspnea[a] (n=605, 35%)		p-value[b]	All (n=1712)	
	n	%	n	%		n	%
Sex							
Men	529	47.8	257	42.5	0.035	786	45.9
Age at inclusion							
<45 y.o	361	32.6	203	33.6	0.314	564	32.9
45-54 y.o	273	24.7	157	26.0		430	25.1
55-64 y.o	239	21.6	143	23.6		382	22.3
65-74 y.o	122	11.0	53	8.8		175	10.2
≥75 y.o	112	10.1	49	8.1		161	9.4
Time from symptom onset to admission							
<3 days (or no symptom)	234	21.1	59	9.8	<0.001	293	17.1
3-5 days	324	29.3	177	29.3		501	29.3
>5 days	549	49.6	369	61.0		918	53.6
Risk factors							
Hypertension	248	22.4	135	22.3	0.966	383	22.4
Diabetes mellitus	152	13.7	73	12.1	0.330	225	13.1
Cancer	66	6.0	30	5.0	0.388	96	5.6
Chronic respiratory disease	116	10.5	93	15.4	0.003	209	12.2
Chronic heart diseases	109	9.8	37	6.1	0.008	146	8.5
Obesity	164	14.8	112	18.5	0.047	276	16.1
Clinical symptoms							
Fever	179	16.2	126	20.8	0.016	305	17.8
Cough	553	50.0	400	66.1	<0.001	953	55.7
Anosmia	350	31.6	258	42.6	<0.001	608	35.5
Ageusia	354	32.0	265	43.8	<0.001	619	36.2
NEWS score							
0-4	991	89.5	502	83.0	<0.001	1493	87.2
5-6	76	6.9	43	7.1		119	7.0
>6	40	3.6	60	9.9		100	5.8
Clinical outcomes							
Death	11	1.0	16	2.6	0.009	27	1.6
Transfer to intensive care unit	16	1.4	31	5.1	<0.001	47	2.7
Transfer to intensive care unit and/or death	23	2.1	44	7.3	<0.001	67	3.9

a: Dyspnea available within 48 h after admission.
b: Chi-squared / Fisher's exact test

Table 2. Dyspnea, LDCT scan severity scores and oxygen saturation in patients with COVID-19 pneumonia (n=1,712)

	No dyspnea[a] (n=1107, 65%)		Dyspnea[a] (n=605, 35%)		Odds ratio 95% confidence interval
	n	%	n	%	(Dyspnea vs no dyspnea)
LDCT scanner severity score					
Normal	350	31.6	162	26.8	0.79 0.64-0.99
Pneumonia	757	68.4	443	73.2	1.27 1.01-1.56
Limited grade 1	525	47.4	248	41.0	0.77 0.63-0.94
Medium grade 2	194	17.5	152	25.1	1.58 1.24-2.01
Severe grade 3	38	3.4	43	7.1	2.15 1.38-3.37
O2 Sat					
Lower equal 95	157	14.2	121	20.0	1.51 1.17-1.96
Lower equal 94	84	7.6	72	11.9	1.65 1.18-2.29
Lower equal 93	48	4.3	44	7.3	1.73 1.14-2.64
Lower equal 92	26	2.3	30	5.0	2.17 1.27-3.70
Lower equal 91	12	1.1	19	3.1	2.96 1.43-6.14
Lower equal 90	6	0.5	15	2.5	4.67 1.80-12.09

a: Dyspnea available within 48 h of admission and LDCT available within 72 hours after admission.

Table 3. Factors associated with poor clinical outcome during follow-up (death/transfer to ICU[a]) among patients without dyspnea – Multivariable logistic regressions (n=1,107)

	Model A OR 95%CI[c]	Model B OR 95%CI[c]	Model C OR 95%CI[c]	Model D OR 95%CI[c]
Sex (ref. Men)				
Women	1.40[0.54;3.63]	1.67[0.62;4.47]	1.44[0.55;3.80]	1.65[0.61;4.46]
Age (ref. 18-64)				
>64	1.14[0.35;3.69]	1.11[0.36;3.43]	1.19[0.37;3.86]	1.10[0.35;3.42]
Risk factors				
Diabetes mellitus	0.99[0.34;2.85]	0.72[0.23;2.23]	0.88[0.30;2.63]	0.72[0.23;2.25]
Hypertension	1.90[0.64;5.63]	1.79[0.60;5.32]	1.74[0.57;5.28]	1.65[0.54;5.00]
Cancer	1.21[0.33;4.47]	1.44[0.40;5.21]	1.05[0.29;3.90]	1.30[0.36;4.72]
Chronic heart diseases	3.92[1.34;11.50]	4.27[1.44;12.66]	3.83[1.28;11.43]	4.15[1.37;12.52]
Chronic respiratory disease	0.66[0.16;2.65]	1.15[0.28;4.70]	0.70[0.17;2.85]	1.02[0.25;4.20]
Obesity	1.27[0.39;4.16]	0.91[0.27;3.12]	1.11[0.33;3.75]	0.86[0.24;3.00]
Time from symptom onset to admission (ref. <3days (or no symptom))				
Between 3 and 5 days	1.66[0.46;5.96]	1.68[0.43;6.47]	1.44[0.40;5.26]	1.49[0.39;5.72]
>5 days	1.46[0.45;4.74]	0.82[0.23;2.92]	1.32[0.40;4.29]	0.74[0.21;2.66]
NEWS score (ref. 0-4)				
NEWS >4	15.40[4.99;47.49]	9.64[3.18;29.21]	9.02[2.72;29.96]	6.82[2.13;21.87]
LDCT scanner severity score (ref. normal/limited)				
Medium-severe		9.45[3.02;29.62]		7.88[2.48;25.00]
O2 Sat (min=63-max=100)			0.78[0.65;0.93]	0.82[0.67;1.00]
AIC / c- statistic (Area Under ROC Curve)	187 / 0.93	172 / 0.93	182 / 0.94	170 / 0.94

a: 23/1107 (2.1%) of patients were transferred to an ICU/and or died during follow-up
b: List of included risk factors: hypertension, obesity, cancer, diabetes, cardiac disease and chronic respiratory disease (see table 1).
c: Adjusted odds ratio with 95% confidence interval

Table 4. Clinical characteristics of patients according to hypoxemia/hypocapnia syndrome (n=161)

	hypoxemia/ hypocapnia (n=49, 30%)		hypoxemia/ hypercapnia (n=53, 33%)		hyperxemia/ hypocapnia (n=35, 22%)		hyperxemia/ hypercapnia (n=24, 15%)		All (n=161)	
	n	%	n	%	n	%	n	%	n	%
Sex										
Men	39	**79.6***	27	50.9	13	**37.1***	11	45.8	90	55.9
Age at inclusion										
<45 y.o	2	**4.1***	24	**45.3***	12	**34.3***	7	29.2	45	28.0
45-54 y.o	3	6.1	5	9.4	6	17.1	6	25	20	12.4
55-64 y.o	13	26.5	8	15.1	11	31.4	3	12.5	35	21.7
65-74 y.o	9	18.4	5	9.4	4	11.4	4	16.7	22	13.7
≥75 y.o	22	44.9	11	20.8	2	5.7	4	16.7	39	24.2
Time from symptom onset to admission										
<3 days (or no symptom)	11	22.5	9	17.0	6	17.1	8	33.3	34	21.1
3-5 days	12	24.5	17	32.1	12	34.3	5	20.8	46	28.6
>5 days	26	53.0	27	50.9	17	48.6	11	45.8	81	50.3
Risk factors										
Hypertension	20	40.8	14	26.4	11	31.4	9	37.5	54	33.5
Diabetes mellitus	8	16.3	8	15.1	2	5.7	5	20.8	23	14.3
Cancer	5	10.2	4	7.5	0	**0.0***	6	**25.0***	15	9.3
Chronic respiratory disease	5	10.2	5	9.4	3	8.6	2	8.3	15	9.3
Chronic heart diseases	16	**32.7***	8	15.1	3	8.6	4	16.7	31	19.3
Obesity	6	12.2	10	18.9	10	28.6	9	37.5	35	21.7
Clinical symptoms										
Fever	13	26.5	11	20.8	10	28.6	7	29.2	41	25.5
Cough	28	57.1	27	50.9	24	68.6	14	58.3	93	57.8
Dyspnea	22	44.9	19	35.8	18	51.4	6	25.0	65	40.4
Anosmia	8	16.3	14	26.4	13	37.1	5	20.8	40	24.8
Aguesia	12	24.5	11	20.8	13	37.1	5	20.8	41	25.5
NEWS score										
0-4	8	16.3	39	73.6	22	62.9	14	58.3	83	51.6
5-6	14	28.6	6	11.3	7	20.0	3	12.5	30	18.6
>6	27	55.1	8	15.1	6	17.1	7	29.2	48	29.8
Clinical outcomes										
Death	10	**20.4***	3	5.7	2	5.7	2	8.3	17	10.6
Transfer to intensive care unit	21	**42.9***	6	**11.3***	7	20.0	4	16.7	38	23.6
Transfer to intensive care unit and/or death	26	**53.1***	9	**17.0***	8	22.9	6	25	49	30.4

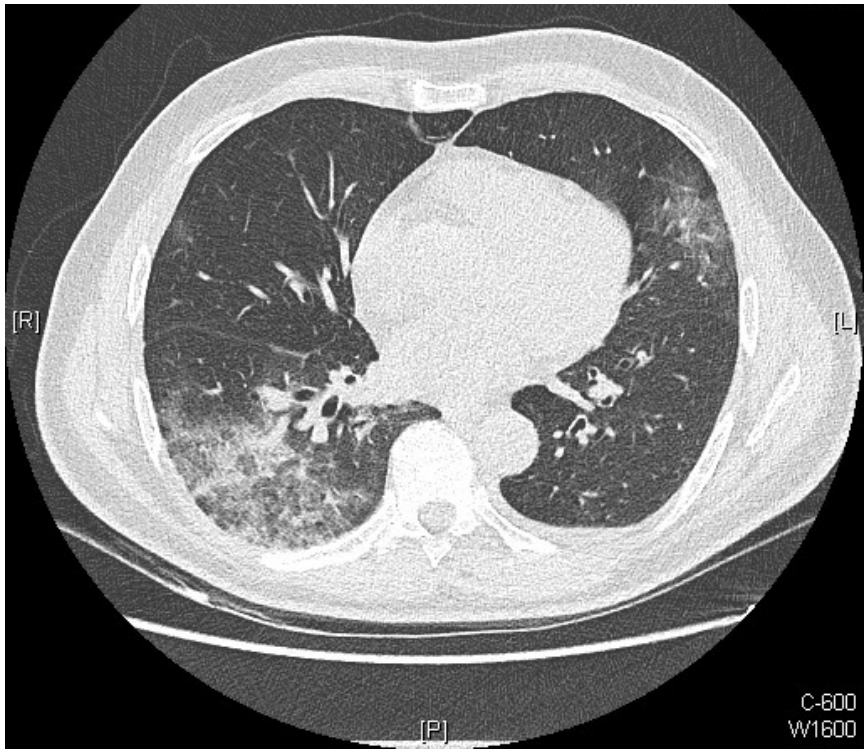
*: p<0.05 Fisher's exact test (versus rest of the sample).

Figure 1: LDCT scan at admission in a patient with silent COVID-19 pneumonia who abruptly needed O_2 support and ICU surveillance for 48 hours and his control LDCT at day 10 of treatment with hydroxychloroquine and azithromycin showing residual lesions with retraction, suggesting fibrosis

Figure 2: Venn diagram showing that in patient presenting with no dyspnea (27/96) 28.1% will have hypoxemia hypercapnia syndrome defining asymptomatic hypoxia (161 patients)

Figure 3. Associations between blood gas analysis, clinical data, biological data and clinical outcomes - Hierarchical Clustering on Principal Components (n=161)

Figure 1



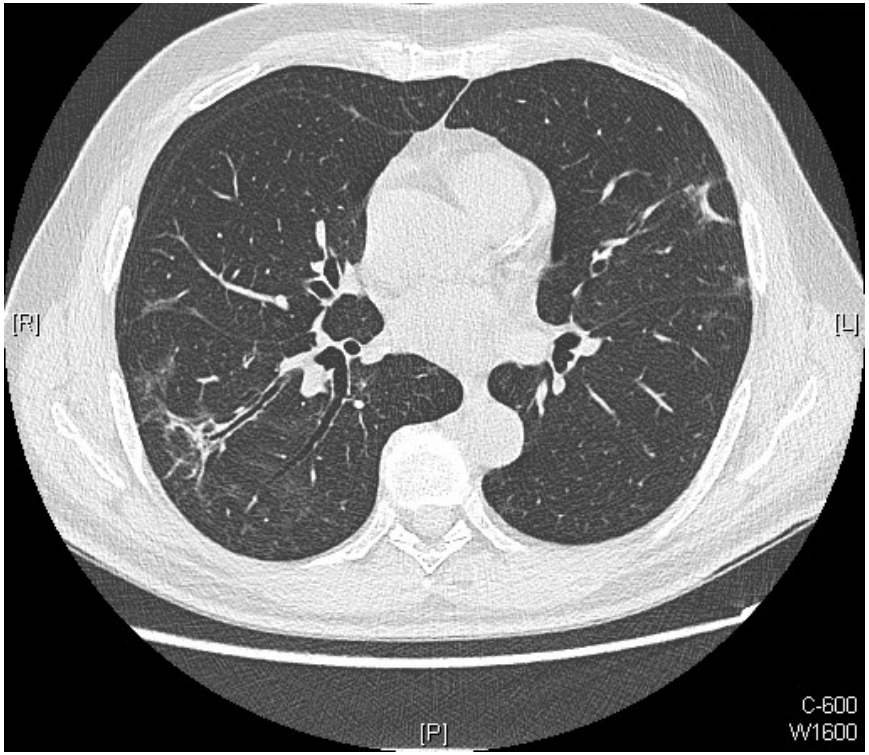


Figure 2:

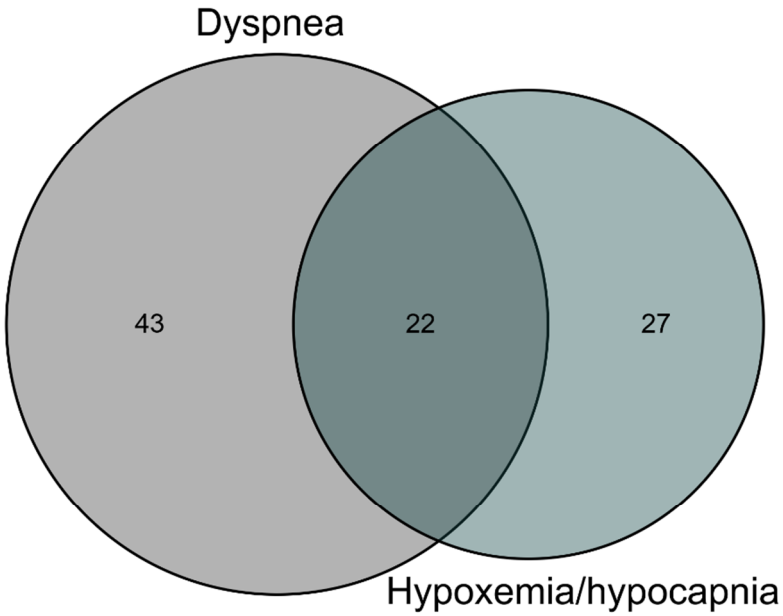
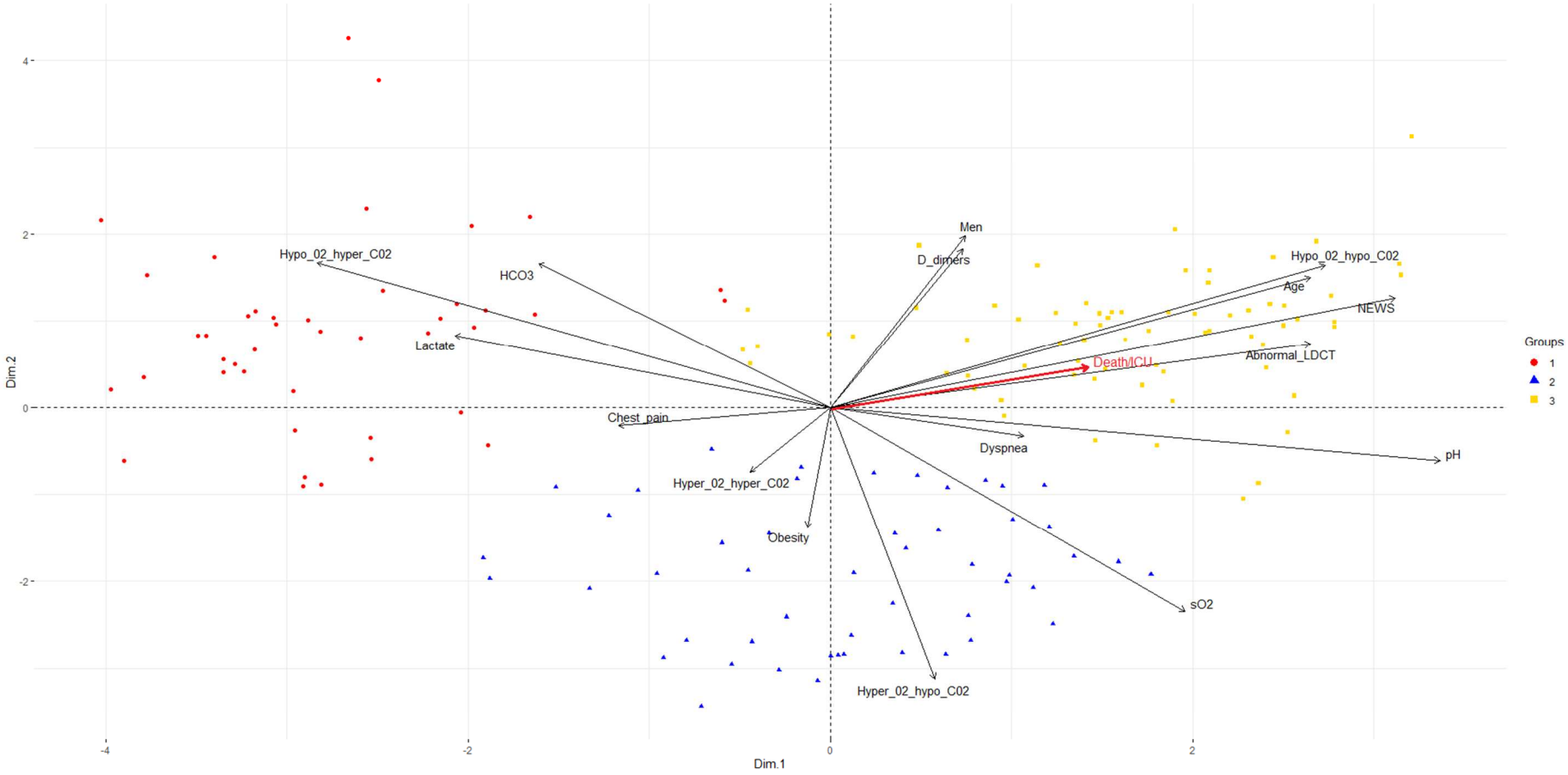


Figure 3:


Hypo_02_hyper_C02
HCO3
Lactate
Men
D_dimers
Hypo_02_hypo_C02
Age
NEWS
Abnormal_LDCT
Death/ICU
Chest_pain
Dyspnea
pH
Hyper_02_hyper_C02
Obesity
sO2
Hyper_02_hypo_C02
Dim.1
Dim.2
Groups
1
2
3

Conflict of interest

None of the authors report a conflict of interest that might interfere with the manuscript contents

Financial support

This study was supported by the National Research Agency under the program «Investissements d'avenir », reference ANR-10-IAHU-03.

Ethical approval

The noninterventional retrospective nature of the study was approved by our institutional review board committee (Mediterranée Infection N°: 2020-021). According to European General Data Protection Regulation No 2016/679, patients were informed of the potential use of their medical data and that they could refuse. The analysis of collected data followed the reference methodology MR-004 registered on N° MR 5010010520 in the AP-HM register.

Reference List

(1) Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020 Feb 15;395(10223):497-506.

(2) Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020 Mar 11.

(3) Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020 Apr 30;382(18):1708-20.

(4) Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19) : clinical managment and treatment. https://www cdc gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients html#clinical-management-treatment%3C 2020 June 2

(5) Xie J, Tong Z, Guan X, Du B, Qiu H. Clinical Characteristics of Patients Who Died of Coronavirus Disease 2019 in China. JAMA Netw Open 2020 Apr 1;3(4):e205619.

(6) Boudjema S, Finance J, Coulibaly F, Meddeb L, Tissot-Dupont H, Michel M, et al. Olfactory and gustative disorders for the diagnosis of COVID-19. Travel Med Infect Dis 2020 Sep 5;101875.

(7) Tobin MJ, Laghi F, Jubran A. Why COVID-19 Silent Hypoxemia Is Baffling to Physicians. Am J Respir Crit Care Med 2020 Aug 1;202(3):356-60.

(8) Couzin-Frankel J. The mystery of the pandemic's 'happy hypoxia'. Science 2020 May 1;368(6490):455-6.

(9) Guan W, Xian J. The progress of 2019 Novel Coronavirus (2019-nCoV) event in China. J Med Virol 2020 Feb 12.

(10) Lagier JC, Million M, Gautret P, Colson P, Cortaredona S, Giraud-Gatineau A, et al. Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: A retrospective analysis. Travel Med Infect Dis. In press 2020.

(11) La SB, Le BM, Andreani J, Hoang VT, Grimaldier C, Colson P, et al. Viral RNA load as determined by cell culture as a management tool for discharge of SARS-CoV-2 patients from infectious disease wards. Eur J Clin Microbiol Infect Dis 2020 Jun;39(6):1059-61.

(12) Liao X, Wang B, Kang Y. Novel coronavirus infection during the 2019-2020 epidemic: preparing intensive care units-the experience in Sichuan Province, China. Intensive Care Med 2020 Feb;46(2):357-60.

(13) Lê S, Josse J., usson F. FactoMineR: An R Package for Multivariate Analysis. Journal of Statistical Software 2008;25(1):1-18.

(14) Ottestad W, Seim M, Maehlen JO. COVID-19 with silent hypoxemia. Tidsskr Nor Laegeforen 2020 May 5;140(7).

(15) O'Donnell CR, Friedman LS, Russomanno JH, Rose RM. Diminished perception of inspiratory-resistive loads in insulin-dependent diabetics. N Engl J Med 1988 Nov 24;319(21):1369-73.

(16) Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers D, Kant KM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. Thromb Res 2020 Jul;191:148-50.

(17) Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. Lancet Infect Dis 2020 Jun 8.