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Frequency, characteristics, and outcome of patients with COVID-19 pneumonia and "silent hypoxemia" at admission: a severity-matched analysis

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Running title

"Silent hypoxemia" in COVID-19 pneumonia

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Abstract

Background: An aspect of COVID-19 baffling physicians is the presentation of patients with acute respiratory failure, but normal mental faculties and no perception of dyspnea (*i.e.* "silent hypoxemia"). The aim of this study was to investigate the frequency, characteristics, and outcome of COVID-19 patients with silent hypoxemic status and comparing them with a symptomatic severity-matched group.

Methods: This is a retrospective monocentric observational study involving all patients with PCR confirmed SARS-CoV-2 pneumonia, admitted at Papa Giovanni XXIII Hospital, Bergamo (Italy) from Emergency Department due to acute respiratory failure, during the first Italian pandemic peak (February-April 2020).

Results: Overall 28-day mortality in 1,316 patients was 26.9%. Patients who did not report dyspnea at admission (N 469, 35.6%) had a lower 28-day mortality (22.6 *vs*. 29.3%, p=0.009). The severity matching analysis (*i.e.* PaO_2/FiO_2 and imaging) led to the identification of two groups of 254 patients that did not differ for sex prevalence, age, BMI, smoking history, comorbidities, and $PaCO_2$ at admission. The use of CPAP during the first 24 hours, such as the need of endotracheal intubation (ETI) during the overall admission were significantly lower in matched patients with silent hypoxemia, whereas 28-day mortality resulted similar (p=0.21).

Conclusions: Lack of dyspnea is common in patients suffering from severe COVID-19 pneumonia leading to respiratory failure, since up to a third of them could be asymptomatic on admission. Dyspnea *per se* correlates with pneumonia severity, and prognosis. However, dyspnea loses its predictive relevance once other findings to evaluate pneumonia severity are available such as PaO_2/FiO_2 and imaging. Silent hypoxemic patients are less likely to receive CPAP during the first 24 hours and ETI during the hospitalization, in spite of a comparable mortality to the dyspneic ones.

Background

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the etiologic agent of Coronavirus Disease 2019 (COVID-19), causes an interstitial pneumonia possibly leading to respiratory failure and hospitalization. Since the beginning of the pandemic, it has become evident that increasing age, elevated inflammatory indicators and troponin, underlying cardiometabolic disease, low lymphocytes count, and severity of respiratory failure at presentation are some of the strongest predictors of mortality [1-5]. Respiratory impairment in COVID-19 can be severe, possibly meeting Acute Respiratory Distress Syndrome (ARDS) criteria [6]. A bewildering feature of COVID-19 respiratory failure, not previously reported in ARDS of other etiology, is the presentation of a proportion of patients with low blood oxygenation, but normal mental faculties and no perception of dyspnea nor signs of respiratory distress. This phenomenon has led to the introduction of the term "happy", "silent" or "apathetic" hypoxia or hypoxemia [7-10]. Dyspnea is a complex symptom defined as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations (*i.e.* work/effort to breath, difficult inspiration/air hunger, tight chest)" [11], however an accurate definition of silent hypoxemia is still lacking. Since the beginning of the pandemic, many case reports of severe hypoxemia without breathlessness perception have been published [12-14]. The physiological basis for this phenomenon are still controversial and are beyond the scope of this research. However, wanting to offer a brief overview, current literature is mainly focused on three hypothetical mechanisms, namely the partially preserved lung compliance at least in the early stages of the disease, the peculiar pulmonary vascular responses to hypoxia, and the nervous system sensing and response to hypoxemia respectively [15]. Tobin et *al*. reviewed some relevant mechanisms related to "happy hypoxia", such as the role of diabetes and age on control of breathing, the inaccuracy of pulse oximetry at low oxygen saturations, and the role of low carbon dioxide tension ($PaCO_2$) in blunting brain's response to hypoxia [9]. Additionally, other Authors highlighted the importance of vascular pulmonary disorder in COVID-19, characterized by an increased pulmonary blood flow with intrapulmonary right to left shunt with limited alveolar injury, leading them to consider this specific finding as an "Acute Vascular Distress Syndrome" (AVDS) [16]. Under this circumstance (*i.e*. shunt), hyperventilation will not increase PaO_2, but will decrease $PaCO_2$, abolishing further increase in ventilation and possibly explaining the absence of respiratory effort and dyspnea [17]. However, in contrast with other well

defined predictors of unfavorable outcomes, it is still debated whether “silent hypoxemia” is a predictor of a suddenly deteriorating scenario, and warrants invasive airway management, or whether close observation and monitoring represent an alternative strategy in light of potential hazards of endotracheal intubation (ETI) [10, 15, 18-24]. The aim of this study was to investigate the frequency, characteristics, and outcome of COVID-19 patients admitted at Papa Giovanni XXIII Hospital, Bergamo (Italy), from Emergency Department due to respiratory failure with silent hypoxemic status when compared with a symptomatic severity-matched group.

Methods

This is a retrospective monocentric observational study, approved by the local Ethics Committee (Comitato Etico di Bergamo, Italy. N°37/2020). In the light of the urgent need to treat critical patients, and to avoid paper contamination, verbal consent was obtained when feasible, according to local protocol.

Source of data

Data were derived from electronic medical records in all patients with laboratory-confirmed SARS-CoV-2 infection, hospitalized from emergency department for respiratory failure at Papa Giovanni XXIII Hospital (Bergamo, Italy) and its affiliate Hospital, San Giovanni Bianco, Italy during the first Italian pandemic peak. Respiratory failure was defined as a peripheral oxygen saturation (SpO_2) <90% or PaO_2 <60 mmHg when breathing room air. In a minority of the patients, latent respiratory failure was revealed by an informal rapid walking test in the emergency room (*i.e.* a fall of 3% or more in SpO_2 or its reduction below 90%) [24]. All adult patients hospitalized between February 23rd and April 7th, 2020 were enrolled. Follow-up ended on May 5th, 2020, to allow for a minimum of 28 days in all patients. The presence of dyspnea is one of the parameter systematically evaluated at admission in the emergency department by the attending physician. For discharged or transferred patients, survival status, as well as the date of death, was obtained from the Regional Healthcare Information System (SISS, Lombardy Region, Italy). Radiologic assessments and laboratory tests were performed according to local clinical practice, and based on clinical needs. The most intense level of oxygen or ventilatory support (*i.e.* low flow oxygen nasal cannula [1-5 L/min of oxygen], Venturi mask [FiO_2 ranging from 31 to 60%], Non-rebreather mask [reservoir 15 L/min of oxygen], continuous positive airway pressure [CPAP], non-invasive mechanical ventilation [NIV], or endotracheal intubation [ETI] and invasive mechanical ventilation) during the first 24 hours was recorded.

Laboratory confirmation of SARS-COV-2 infection

SARS-CoV-2 genome from nasal swabs and respiratory samples was detected by two different molecular methods (GeneFinder COVID-19-Elitech Group, Allplex™ 2019-nCoV Assay - Seegene Inc) according to the manufacturer's instructions. After the purification of viral RNA from clinical samples, the detection of

RdRp, E and N viral genes was obtained by real time Polymerase Chain Reaction (RT-PCR) according to WHO protocol.

Outcomes

The primary outcome was 28-day all-cause mortality, occurring either during in-hospital stay, or after discharge, in severity-matched groups (*i.e.* PaO_2/FiO_2, and radiological involvement) of COVID-19 admitted patients with and without dyspnea.

Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics of COVID-19 patients with or without dyspnea perception. Continuous variables were expressed as mean and standard deviation (SD) or as median and interquartile range [IQR], depending on their parametric or non-parametric distribution. Categorical variables were expressed as absolute counts and percentages. The chi-square test (or Fisher's exact test when appropriate) was used to test between-group differences for the categorical variables, whereas the t-test or the Wilcoxon-Mann-Whitney test (for normally and not normally distributed variables, respectively) were used to compare continuous variables. To obtain two comparable groups in terms of severity of the disease, a classical 1:1 matching was adopted. In particular, for each patient with dyspnea, a patient without dyspnea was matched among patients with the same PaO_2/FiO_2 ratio value (± 5), on a continuous scale, and the same chest X-ray result in terms of unilateral/bilateral abnormalities. All patients without matched controls were excluded from the analysis. Kaplan Meier survival curves were reported and stratified by the presence/absence of dyspnea with comparison by the log-rank test. Statistical analysis was performed using STATA software, release 16 (StataCorp LP, College Station TX, USA). All tests were two-sided and a p-value <0.05 was considered significant.

Results

Demographic and clinical characteristics of all 1,316 COVID-19 patients admitted from Emergency Department for respiratory failure are shown in the unmatched section of Table 1. The majority of the patients were male, with a mean age of 66 years. Study cohort was generally overweight (i.e. BMI >25 Kg/m^2). The most frequent comorbidities were systemic hypertension, diabetes and coronary artery disease. The median interval between symptoms onset and hospital presentation was 8 days [6-11] (Supplementary Table 1). Respiratory failure was assessed at admission by room air SpO_2 or by an arterial blood gas analysis (ABG). Median PaO_2/FiO_2 ratio at admission resulted 194 [108 – 271]. The 83.7% (N 1,101) of the patients required oxygen or ventilatory support during the first 24 hours since hospital admission, while the minority of the patients who did not required oxygen at rest had borderline gas exchange parameters, with latent respiratory failure revealed by an informal rapid walking test in the emergency room (*i.e.* a fall of 3% or more in SpO_2 or its reduction below 90%). Amongst patients needing oxygen supplementation, 66.2% were treated with different support, ranging between low-flow nasal cannula to non-rebreathing mask, in 32.2% of the patients CPAP or NIV was needed, while the 1.5% of patients underwent ETI directly. Laboratory findings at admission are reported in Supplementary Table 2. Standard panel of blood tests at admission showed an overall raised C reactive protein (median value 12.4 mg/dl [5.2 – 18.5]), normal white blood cells count (7,115 cells/mm^3 [5,350 – 9,870]) with reduced lymphocytes count (830 cells/mm^3 [580 – 1,150]). Median D-dimer value was raised (1,730 ng/ml [851 – 7,238], but it was investigated only in a third of the patients (N 348, 28.9%). A chest X-ray was available in 1176 patients, showing bilateral involvement in 86.4% of the cases (Table 3). Overall 28-day mortality was 26.9% (N 354), as shown in Table 3.

Features and outcome of unmatched patients according to dyspnea

In our cohort, over a third of the patients (N 469, 35.6%) did not report dyspnea at hospital admission despite the pneumonia and respiratory failure. In accordance with the unmatched analysis shown in Table 1, dyspneic patients were more often male, and overweight. Other common symptoms of COVID-19 (Table 2), such as fever, cough, myalgia, nausea, chest pain, hypo/anosmia, hypo/ageusia and diarrhea occurred similarly both in unmatched dyspneic and eupneic patients, while anorexia, asthenia, dizziness and vomiting resulted

more common in not dyspneic patients. When considering comorbidities (Table 1), patients on long-term oxygen therapy were more frequently dyspneic, while those suffering from atrial fibrillation reported shortness of breath less frequently. Patients with dyspnea generally had a more severe respiratory failure, as demonstrated by a significantly lower PaO_2/FiO_2 ratio, and a higher rate of CPAP/NIV use in the first 24 hours (Table 3). Of note, these patients were also more tachypneic and tachycardic. Furthermore, in this category of patients, bilateral radiological abnormalities, reported in Table 3, were considerably more frequent. Laboratory findings (Supplementary Table 2), although did not highlight striking differences between groups, seemed to show a tendency towards a greater impairment of liver function, greater inflammatory status with raised CRP value and more pronounced lymphopenia in dyspneic patients. Intervals between symptoms onset and clinically relevant episodes are shown in Supplementary Table 1. Dyspneic patients started CPAP or NIV support before the eupneic ones, respectively 2 days earlier when considering symptoms onset (11 days [8-14] *vs.* 9 days [7-13], p=0.033), and 1 day earlier when considering from hospitalization (2 days [1-4] *vs.* 1 day [0-2], p<0.001). Intervals between symptoms onset and Emergency Room (ER) presentation, as well as between escalation from CPAP/NIV to ETI, were comparable between groups. As shown in Table 3, clinical outcomes in the unmatched cohort pointed out that dyspneic patients globally had worst outcomes, with remarkably greater rate of CPAP, NIV, and ETI use, higher admission rate in ICU or Semi Intensive Care Respiratory Unit, and eventually a higher mortality rate (29.3% *vs.* 22.6%, p=0.009). Accordingly, Kaplan–Meier survival curve at 28-day found a higher mortality for patient with dyspnea at admission (Figure 1, p=0.001).

Features and outcome of matched dyspneic and not dyspneic hypoxemic patients

The matching analysis led to the identification of two groups of dyspneic (N 254), and not dyspneic (N 254) patients with comparable radiological impairment, and respiratory failure severity at admission, as previously described. Matched groups of patients had a median PaO_2/FiO_2 ratio of 229 [135 - 286], and bilateral chest X-ray involvement was reported in 81.1% of them (Table 3). No significant differences in terms of sex prevalence, age, BMI, smoking history and comorbidities were found, with the only exception of a higher percentage of patients with atrial fibrillation in the eupneic group (Table 1). Differences in symptoms at presentation (Table 2) were analogous of those in the unmatched analysis, with anorexia, asthenia, dizziness

and vomiting more commonly reported in not dyspneic patients, while chest pain was more frequently reported in the dyspneic ones. Intervals between symptoms onset or hospitalization and start of NIV/CPAP or ETI resulted comparable among categories, as well as intervals between CPAP/NIV and escalation to ETI (Supplementary Table 1). No statistically significant differences were observed in terms of symptoms onset and hospital presentation (9 days in not dyspneic patients vs. 8 days in dyspneic ones, p=0.084). During the first 24 hours (Table 3), only the use of CPAP was significantly higher in patients with dyspnea (32.6% *vs.* 17.1%, p<0.001), and blood lactates were slightly raised in patients with dyspnea. Laboratory findings (Supplementary Table 1) showed similar organ function indicators and CRP values between groups, statistically significant differences were found in the blood count, with higher white blood cells and platelets but lower lymphocytes in dyspneic patients. When considering clinical outcomes (Table 3), CPAP/NIV use, and ICU/Semi Intensive Respiratory Care Unit admittance rate did not differ significantly (p=0.21), as well as mortality. Accordingly, Kaplan–Meier survival analysis at 28-day in matched patients with and without dyspnea at admission did not find a significant difference (Figure 2, p=0.120). However, ETI rate during hospital stay resulted significantly higher in patients with shortness of breath at admission (17.7% *vs.* 10.2%, p=0.015).

Discussion

The main results from this study, specifically focused on dyspnea at presentation in patients with COVID-19 pneumonia admitted for respiratory failure, and their clinical outcomes, can be summarized as follows: 1) even in case of significant respiratory impairment needing hospitalization, over a third of the patients with COVID-19 could be asymptomatic for shortness of breath at admission; 2) dyspneic patients at presentation are more commonly male, with a higher BMI, and have a worst clinical course, with more severe respiratory failure, higher rate of CPAP, NIV and ETI need, and higher mortality; 3) however, when patients are matched for disease severity at presentation (*i.e.* PaO_2/FiO_2 ratio, and radiological impairment), mortality is comparable between dyspneic and not dyspneic patients; 4) patients without dyspnea had more frequently other symptoms (i.e., anorexia, asthenia, dizziness, and vomiting) compared to severity-matched patients without dyspnea; 5) matched patients who refer dyspnea at admission are more frequently treated with CPAP during the first 24 hours, and intubated during admission when compared with severity-matched patients who do not refer dyspnea at admission.

Silent hypoxemia is a topic of debate. As already mentioned, there is an increasing literature mainly consisting of case reports and reviews of the possible pathophysiological mechanisms, while there are fewer studies addressing the characteristics and outcomes of COVID-19 patients with and without dyspnea [24, 26]. To the best of our knowledge, this work is the first to specifically investigate COVID-19 patients with respiratory failure, with and without dyspnea, in a severity matched analysis providing new insights into the topic. It must be acknowledged that the vast majority of our cohort had significant respiratory failure, as evidenced by a median PaO_2/FiO_2 ratio of 194 [108-271], therefore we categorized patients on the basis of the presence or absence of dyspnea, considering them implicitly hypoxemic.

Shortness of breath at presentation in COVID-19 patients was described with variable prevalence depending on study population. Early Chinese report from Wuhan, reported shortness of breath only in 18.7% of hospitalized patients [27]. In a recent French study, specifically aimed at investigating asymptomatic hypoxemic COVID-19 patients, they reported dyspnea in 35% of their cohort (N 605) [24]. Conversely, in an Italian cohort of patients investigated by Busana et *al*., they found 68.1% (N 145) of dyspneic hypoxemic patients [26]. In our cohort, dyspneic patients at presentation were 64.4%. The high rate of dyspneic patients

in our cohort, as well as in the cohort of Busana et *al*., could account for a great prevalence of severe cases. This data is in accordance with other cohort of patients: in Guan study, dyspnea was more frequent in more severe patients (37.6% *vs* 15.1%) and even higher (53.7%) in patients admitted to the ICU [27]; in the Huang study dyspnea was 92% in ICU *vs* 37% of non-ICU patients [28]. Furthermore, many Authors have recently recognized that dyspnea was positively associated with progression to severe illness and death [29, 30].

In fact, considering only the presence or absence of dyspnea at the time of hospital admission, dyspneic patients have significantly worse clinical outcomes. These findings are in accordance with those of Busana et. *al* and Brouqui et *al*.. The former Author found an in-hospital mortality of 17.6% vs 29.7% (p 0.083) in silent and dyspneic hypoxemia respectively [26], while the latter described a composite outcome (*i.e.* death or transfer in ICU) which was unfavorable for dyspneic patients (*i.e*. 7.3% *vs* 2.1% in dyspneic and not dyspneic patients respectively) [24].

The link between disease severity and dyspnea is interestingly summarized by Ora et *al*., in accordance with previous considerations by Gattinoni *et al.* [31, 32]. The increase in dyspnea correlates with the increase in ventilation, therefore in the early stages of COVID-19 with preserved elastance, there is a good coupling between respiratory drive and mechanical response, without dyspnea. On the other hand, in the advanced stages characterized by high elastance, there are alterations of respiratory mechanics with mechanical constraint and neuromechanical dissociation and dyspnea will be described. Higher prevalence of unfavorable outcomes (*i.e.* CPAP, NIV, ETI, ICU transfer, death) in dyspneic patients, may be attributable to a more severe disease. Notably, no differences in terms of intervals between symptoms onset and ER presentation has been observed in our cohort. This seems to validate that dyspnea could be present at onset, but it is not the only hospital presentation leading cause, while fever and cough play an important role [33].

Pathophysiological mechanisms that may be responsible for the absence of dyspnea in patients with COVID-19 have been hypothesized, including viral neuroinvasion and damage of afferent fibers, similar to the mechanisms of ageusia and anosmia [34-36]. On the other hand, it should also be considered that central nervous system (CNS) involvement could lead to encephalitis and apathetic status [37, 38]. However, without making inferences regarding CNS involvement, symptoms such as hypo/anosmia and hypo/ageusia were

comparable in our cohort (Table 2). In this regard, what seems to emerge is a higher prevalence of extrapulmonary symptoms in patients with silent hypoxemia, a finding confirmed also by Busana et *al.*.

Moreover, is well known that dyspnea is linked to ventilatory impairment rather than oxygen level in blood, indeed has been already demonstrated that hypoxemia is only a weak stimulus for respiratory drive, and consequently for dyspnea, if it is not accompanied by an increase in CO_2 or a reduction in pH [8, 9, 39]. Regarding this aspect, cardiovascular compensation to hypoxemia is crucial for preservation of tissue oxygen delivery and preservation of acid-base balance [40]. Of note, as shown in the unmatched section of Table 3, not dyspneic patients had a remarkably lower respiratory rate (RR) than dyspneic ones, this data is consistent with findings of other similar research [26], however interestingly they did not differ in terms of RR when matched for severity.

Even when matched for severity, dyspneic patients are more likely to receive CPAP in the first 24 hours. This is probably due to the breathing mechanics alterations more frequently observed in dyspneic patients, which is a criterion to start ventilatory support [41]. When patients are matched for severity, mortality is similar between those presenting dyspneic and those not. This finding is of particular interest because warns clinicians also about patients who come to observation with impaired gases exchange but without shortness of breath. Finally, we observed a higher intubation rate in patients with dyspnea.

Our research has several limitations. First, this is a retrospective study based on medical records acquired during a medical emergency with overwhelmed resources, therefore data reliability could be reasonably questioned. However, this study provides valuable information on a large cohort of patients, with a specific focus on dyspnea and strong clinical outcomes, including a matched analysis and a fixed and reasonable follow-up time for all of them. Second, the presence of dyspnea was reported only at admission and not during the overall hospitalization; even if systematically evaluated in the emergency department, it was not graded or evaluated by a specific questionnaire. We would like to stress that data were collected in a condition of overwhelmed medical resources, therefore scoring dyspnea would have been time consuming without a clear added value. Similarly, describing dyspnea evolution during the overall hospitalization was not always straightforward, also because the high rate of internal and external patient transfers. Finally, we matched patients for severity, arbitrarily choosing criteria to be included (*i.e.* radiological impairment and

PaO_2/FiO_2 ratio), nevertheless, this assumption has a clinical rationale. PaO_2/FiO_2 ratio is the most used index to assess gas exchange in critically ill patients, and physicians rely on it to define and characterize the respiratory impairment severity, furthermore it is a criterion to define ARDS [6], while chest X-ray, especially through scoring system of lung abnormalities, has been used to predict patients at high risk of mortality [42-44].

Conclusions

In conclusion, the lack of dyspnea is common in patients suffering from COVID-19 pneumonia, since up to a third of them could be asymptomatic on admission. Dyspnea *per se* correlates with pneumonia severity, and prognosis. However, dyspnea loses its predictive relevance once other findings to evaluate pneumonia severity are available such as PaO_2/FiO_2 and imaging. Silent hypoxemic patients are less likely to receive CPAP during the first 24 hours and ETI during the hospitalization, in spite of a comparable mortality to the dyspneic ones.

Declarations

Ethics approval and consent to participate

This retrospective, observational study was approved by the local Ethics Committee (Comitato Etico di Bergamo, Italy. N°37/2020). According to the approved protocol, verbal consent was obtained when feasible. We avoided written consent in the light of the urgent need to treat critical patients, and to avoid paper contamination. The accepting physician was responsible for verbal consent collection, it was documented by signing a declaration form.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are available in Papa Giovanni XXIII Hospital digital repository. The datasets generated and/or analysed during the current study are not publicly available due to individual privacy policy but are available from the corresponding author on reasonable request.

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There was no funding for this study.

Competing interests

The authors declare that they have no competing interests.

Conflict of interest

Fabiano Di Marco received financial activities outside this work, Fabiano Di Marco reports grants or consulting fees from Boehringer Ingelheim, GSK, Chiesi, Zambon, Novartis, Guidotti/Malesci, AZ, Menarini,

Mundipharma, TEVA, Almirall, Levante Pharma and Sanofi. All other authors have no conflicts of interest to declare.

Authors' contributions

Luca Novelli, Federico Raimondi and Fabiano Di Marco conceived the idea and designed the research. Luca Novelli, Federico Raimondi, Chiara Galimberti, Roberta Biza, Roberta Trapasso, Marisa Anelli, Mariangela Amoroso, Chiara Allegri, Gianluca Imeri, Carterina Conti collected clinical records data. Arianna Ghirardi analysed study data and developed statistical models and design of methodology. Fabiano Di Marco and Stefano Fagiuoli were the responsible for the research activity, management and coordination. Luca Novelli, Federico Raimondi, Fabiano Di Marco, and Arianna Ghirardi created and wrote the initial draft. All the authors critically analysed data and revised the draft. Luca Novelli, Federico Raimondi and Fabiano Di Marco prepared the final version of manuscript. All authors read and approved the final version of the manuscript.

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We would like to acknowledge all the members of HPG23 Covid-19 Study Group listed in Supplementary file 4.

Supplementary file 1: Definitions

Supplementary file 2: Supplementary Table 1

Supplementary file 3: Supplementary Table 2

Supplementary file 4: Members of HPG23 COVID-19 Study Group

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Table 1. Demographic and clinical characteristics by the presence of dyspnea at admission

	Unmatched					Matched				
	N not missing	Total N=1,316	No dyspnea N=469	Dyspnea N=847	P-value	N not missing	Total N=508	No dyspnea N=254	Dyspnea N=254	P-value
Male gender – *n. (%)*	1,316	939 (71.4)	**314 (67.0)**	**625 (73.8)**	**0.009**	508	370 (72.8)	177 (69.7)	193 (76.0)	0.11
Age, *y – mean (SD)*	1,316	66.3 (13.4)	66.6 (14.3)	66.2 (12.8)	0.63	508	66.1 (12.6)	66.6 (13.1)	65.5 (12.2)	0.32
BMI – *median [IQR]*	938	26.5 [24.5-29.7]	**25.9 [23.8-29.0]**	**27.1 [24.7-30.2]**	**<0.001**	370	26.2 [24.5-29.4]	26.0 [24.6-29.4]	26.6 [24.5-29.6]	0.47
Obesity – n. (%)	952	233 (24.5)	**72 (20.7)**	**161 (26.7)**	**0.039**	375	87 (23.2)	44 (22.9)	43 (23.5)	0.89
Smoking history – *n. (%)*										
Current/former/never smoker	1,168	47 (4.0)/**246 (21.1)**/875 (74.9)	19 (4.7)/**79 (19.5)**/307 (75.8)	28 (3.7)/**167 (21.9)**//568 (74.4)	0.48	441	17 (3.9)/105 (23.8)/319 (72.3)	10 (4.5)/51 (23.2)/159 (72.3)	7 (3.2)/54 (24.4)/160 (72.4)	0.73
Comorbidities – *n. (%)*										
Hypertension	1,305	680 (52.1)	241 (52.3)	439 (52.0)	0.93	507	258 (50.9)	128 (50.6)	130 (51.2)	0.89
Diabetes	1,303	248 (19.0)	76 (16.5)	172 (20.4)	0.083	505	95 (18.8)	45 (17.8)	50 (19.8)	0.55
Chronic Kidney Failure	1,302	97 (7.5)	41 (8.9)	56 (6.7)	0.14	506	34 (6.7)	20 (7.9)	14 (5.5)	0.29
COPD	1,304	81 (6.2)	28 (6.1)	53 (6.3)	0.88	506	35 (6.9)	20 (7.9)	15 (5.9)	0.38
Long-term oxygen therapy	1,304	23 (1.8)	**3 (0.7)**	**20 (2.4)**	**0.024**	506	8 (1.6)	3 (1.2)	5 (2.0)	0.48
Active solid neoplasm	1,302	47 (3.6)	17 (3.7)	30 (3.6)	0.89	506	18 (3.6)	9 (3.6)	9 (3.6)	1.00
Active hematologic malignancy	1,303	48 (3.7)	15 (3.3)	33 (3.9)	0.55	506	21 (4.2)	8 (3.2)	13 (5.1)	0.27
Cerebrovascular disease	1,298	70 (5.4)	23 (5.0)	47 (5.6)	0.64	504	20 (4.0)	8 (3.2)	12 (4.8)	0.35
Previous Myocardial Infarction	1,302	118 (9.1)	41 (8.9)	77 (9.1)	0.89	506	43 (8.5)	22 (8.7)	21 (8.3)	0.87
Chronic heart failure	1,303	55 (4.2)	25 (5.4)	30 (3.6)	0.11	505	23 (4.6)	11 (4.4)	12 (4.7)	0.84
CAD	1,276	137 (10.7)	47 (10.3)	90 (11.0)	0.71	495	54 (10.9)	27 (10.9)	27 (10.9)	0.99
Atrial fibrillation	1,280	120 (9.4)	**56 (12.3)**	**64 (7.8)**	**0.008**	496	43 (8.7)	28 (11.2)	15 (6.1)	0.041
Vasculopathy	1,304	111 (8.5)	36 (7.8)	75 (8.9)	0.50	506	37 (7.3)	16 (6.3)	21 (8.3)	0.39
Rheumatic pathology	1,302	67 (5.1)	29 (6.3)	38 (4.5)	0.16	505	37 (7.3)	23 (9.1)	14 (5.5)	0.12

Demographic and clinical characteristics of all admitted patients. P values obtained by χ^2 test (or Fisher's Exact test when appropriate) for categorical variables and t-test (or Wilcoxon-Mann-Whitney test when appropriate) for continuous variables. No dyspnea and dyspnea as referred by patients at presentation. Unmatched and matched data refer to the severity (i.e. PaO_2/FiO_2 and chest imaging). In bold font data with P value <0.05.
Abbreviations: y, years; n, number; BMI, Body Mass Index (Body weight and height as referred by patient); Obesity defined as BMI >30 kg/m^2; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; SD, Standard Deviation; IQR, interquartile range in brackets.

Table 2. Symptoms at presentation by the presence of dyspnea at admission

	Unmatched					Matched				
	N not missing	Total N=1,316	No dyspnea N=469	Dyspnea N=847	P-value	N not missing	Total N=508	No dyspnea N=254	Dyspnea N=254	P-value
Symptoms – *n. (%)*										
Fever	1,315	1,176 (89.4)	411 (87.6)	765 (90.4)	0.11	508	471 (92.7)	237 (93.3)	234 (92.1)	0.61
Cough	1,315	589 (44.8)	202 (43.1)	387 (45.7)	0.35	508	259 (51.0)	125 (49.2)	134 (52.8)	0.42
Anorexia	1,314	109 (8.3)	**58 (12.4)**	**51 (6.0)**	**<0.001**	508	**48 (9.4)**	**34 (13.4)**	**14 (5.5)**	**0.002**
Asthenia	1,315	347 (26.4)	**154 (32.8)**	**193 (22.8)**	**<0.001**	508	**144 (28.3)**	**90 (35.4)**	**54 (21.3)**	**<0.001**
Myalgia	1,315	80 (6.1)	32 (6.8)	48 (5.7)	0.40	508	25 (4.9)	14 (5.5)	11 (4.3)	0.54
Sore throat	1,314	27 (2.1)	9 (1.9)	18 (2.1)	1.00	508	10 (2.0)	4 (1.6)	6 (2.4)	0.75
Dizziness	1,314	64 (4.9)	**39 (8.3)**	**25 (3.0)**	**<0.001**	508	**21 (4.1)**	**17 (6.7)**	**4 (1.6)**	**0.004**
Abdominal pain	1,315	34 (2.6)	17 (3.6)	17 (2.0)	0.077	508	9 (1.8)	6 (2.4)	3 (1.2)	0.31
Diarrhoea	1314	121 (9.2)	50 (10.7)	71 (8.4)	0.17	507	52 (10.3)	29 (11.5)	23 (9.1)	0.37
Nausea	1,313	66 (5.0)	28 (6.0)	38 (4.5)	0.23	507	20 (3.9)	14 (5.5)	6 (2.4)	0.067
Vomiting	1,315	63 (4.8)	**32 (6.8)**	**31 (3.7)**	**0.010**	508	**26 (5.1)**	**18 (7.1)**	**8 (3.1)**	**0.044**
Chest pain	1,315	40 (3.0)	11 (2.3)	29 (3.4)	0.27	508	**11 (2.2)**	**2 (0.8)**	**9 (3.5)**	**0.033**
Hypo/anosmia	1,289	17 (1.3)	8 (1.7)	9 (1.1)	0.34	498	7 (1.4)	5 (2.0)	2 (0.8)	0.26
Hypo/agenusia	1,290	28 (2.2)	14 (3.0)	14 (1.7)	0.12	498	13 (2.6)	8 (3.2)	5 (2.0)	0.41

Symptoms as referred by patient at presentation. P values obtained by χ^2 test (or Fisher's Exact test when appropriate) for categorical variables. Unmatched and matched data refer to the severity (i.e. PaO_2/FiO_2 and chest imaging) In bold font data with P value <0.05. Abbreviations: n, numbers.

Table 3. Severity at presentation, radiological impairment and outcomes by the presence of dyspnea at admission

		Unmatched				Matched				
	N not missing	Total N=1,316	No dyspnea N=469	Dyspnea N=847	p-value	N not Missing	Total N=508	No dyspnea N=254	Dyspnea N=254	p-value
HR, *bpm – median [IQR]*	1,167	85 [75-95]	**82 [73-92]**	**85 [76-95]**	**0.003**	466	85 [75-94]	83 [73-92]	86 [75-96]	0.073
SBP, *mmHg – median [IQR]*	1,154	127 [115-140]	126 [112-140]	128 [115-140]	0.29	461	126 [115-140]	125 [115-140]	127 [115-140]	0.66
RR, *breaths/min – median [IQR]*	767	24 [19-28]	**21 [17-26]**	**24 [20-30]**	**<0.001**	316	24 [18-28]	22 [18-28]	24 [20-30]	0.055
pH *– median [IQR]*	857	7.48 [7.45-7.50]	7.48 [7.45-7.50]	7.48 [7.44-7.50]	0.52	475	7.48 [7.45-7.50]	7.48 [7.45-7.50]	7.48 [7.45-7.50]	0.23
PaO_2/FiO_2 *– median [IQR]*	908	194 [108-271]	**242 [141-295]**	**174 [99-256]**	**<0.001**	508	229 [135-286]	229 [135-286]	229 [135-286]	m.v.
<200 – n. (%)	908	466 (51.3)	**109 (38.5)**	**357 (57.1)**	**<0.001**	508	208 (40.9)	103 (40.6)	105 (41.3)	m.v.
$PaCO_2$, *mmHg – median [IQR]*	896	32 [29-35]	32 [30-35]	32 [28-35]	0.31	494	32 [29-35]	32 [29-35]	31 [28-35]	0.32
HCO_3^-, *mmol/L – median [IQR]*	311	24 [22-26]	24 [22-25]	24 [21-26]	0.86	176	24 [22-26]	24 [22-25]	24 [22-26]	0.63
Lac, *mmol/L – median [IQR]*	454	1.40 [1.09-1.79]	**1.30 [1.00-1.59]**	**1.44 [1.14-1.90]**	**0.001**	**253**	**1.32 [1.08-1.69]**	**1.29 [1.00-1.56]**	**1.38 [1.16-1.81]**	**0.026**
Oxygen and ventilatory support during first 24 h *– n. (%)*										
Low flow oxygen cannula	1,194	315 (26.4)	**144 (34.9)**	**171 (21.9)**	**<0.001**	487	147 (30.2)	83 (33.9)	64 (26.4)	0.074
Venturi mask	1,194	97 (8.1)	31 (7.5)	66 (8.5)	0.57	487	48 (9.9)	24 (9.8)	24 (9.9)	0.96
Non-rebreather mask	1,194	317 (26.5)	113 (27.4)	204 (26.1)	0.64	487	145 (29.8)	80 (32.7)	65 (26.9)	0.16
CPAP	1,194	321 (26.9)	**49 (11.9)**	**272 (34.8)**	**<0.001**	487	**121 (24.8)**	**42 (17.1)**	**79 (32.6)**	**<0.001**
NIV	1,194	34 (2.8)	**4 (1.0)**	**30 (3.8)**	**0.005**	487	7 (1.4)	1 (0.4)	6 (2.5)	0.067
ETI	1,194	17 (1.4)	5 (1.2)	12 (1.5)	0.65	487	3 (0.6)	2 (0.8)	1 (0.4)	1.00
FiO_2, % *– median [IQR]*	1,136	60 [35-70]	**40 [30-70]**	**60 [40-70]**	**<0.001**	471	60 [35-70]	60 [35-70]	60 [36-70]	0.15
PEEP, *cmH_2O – median [IQR]*	347	15 [12-16]	15 [12-16]	15 [12-15]	0.33	126	15 [12-15]	15 [13.3-16]	14.5 [12-15]	0.083
Chest X-Ray abnormalities – n. (%)	1,292	1,176 (91.0)	**382 (84.1)**	**794 (94.7)**	**<0.001**	508	474 (93.3)	237 (93.3)	237 (93.3)	m.v.
Unilateral	1,292	160 (12.4)	67 (14.8)	93 (11.1)	0.057	508	62 (12.2)	31 (12.2)	31 (12.2)	m.v.
Bilateral	1,292	1,016 (78.6)	**315 (69.4)**	**701 (83.7)**	**<0.001**	508	412 (81.1)	206 (81.1)	206 (81.1)	m.v.
Ventilatory support and intensity of care during hospitalization *– n. (%)*										
CPAP	1,316	513 (39.0)	**131 (27.9)**	**382 (45.1)**	**<0.001**	508	215 (42.3)	98 (38.6)	117 (46.1)	0.088
NIV	1,316	104 (7.9)	**22 (4.7)**	**82 (9.7)**	**0.001**	508	38 (7.5)	14 (5.5)	24 (9.4)	0.092
ICU	1,316	189 (14.4)	**44 (9.4)**	**145 (17.1)**	**<0.001**	508	71 (14.0)	29 (11.4)	42 (16.5)	0.096
Semi intensive care unit	1,316	88 (6.7)	**20 (4.3)**	**68 (8.0)**	**0.009**	508	31 (6.1)	15 (5.9)	16 (6.3)	0.85
ETI	1,316	200 (15.2)	**42 (9.0)**	**158 (18.7)**	**<0.001**	508	**71 (14.0)**	**26 (10.2)**	**45 (17.7)**	**0.015**
Overall 28-day mortality	1,316	354 (26.9)	**106 (22.6)**	**248 (29.3)**	**0.009**	508	122 (24.0)	55 (21.7)	67 (26.4)	0.21

No dyspnea and dyspnea as referred by patients at presentation. Unmatched and matched data refer to the severity (i.e. PaO_2/FiO_2 and chest imaging). In bold font data with P value <0.05. Abbreviations: HR, heart rate; bpm, beat per minute; RR, respiratory rate; SBP, systolic blood pressure; Emergency Room (ER) admission arterial blood gas analysis performed in room air shown as pH, FiO_2, inspired oxygen ratio; PaO_2, arterial partial pressure of oxygen; SaO_2, oxygen arterial saturation; $PaCO_2$, arterial partial pressure of carbon dioxide; HCO_3, Bicarbonate and Lac, lactate concentration; Oxygen and ventilatory support in the first 24 hours by the ER presentation intended as the highest between low flow oxygen nasal cannula (≤5 L/min of oxygen), Venturi mask (FiO_2 ranging from 31 to 60%), non-rebreather mask (reservoir) 15 L/min of oxygen, CPAP, continuous positive airway pressure with helmet, NIV, noninvasive ventilation and ETI, endotracheal intubation; PEEP, positive end expiratory pressure; ICU, intensive care unit; SD, Standard Deviation; IQR, interquartile range in brackets

Figure 1. 28-day overall mortality – all patients.

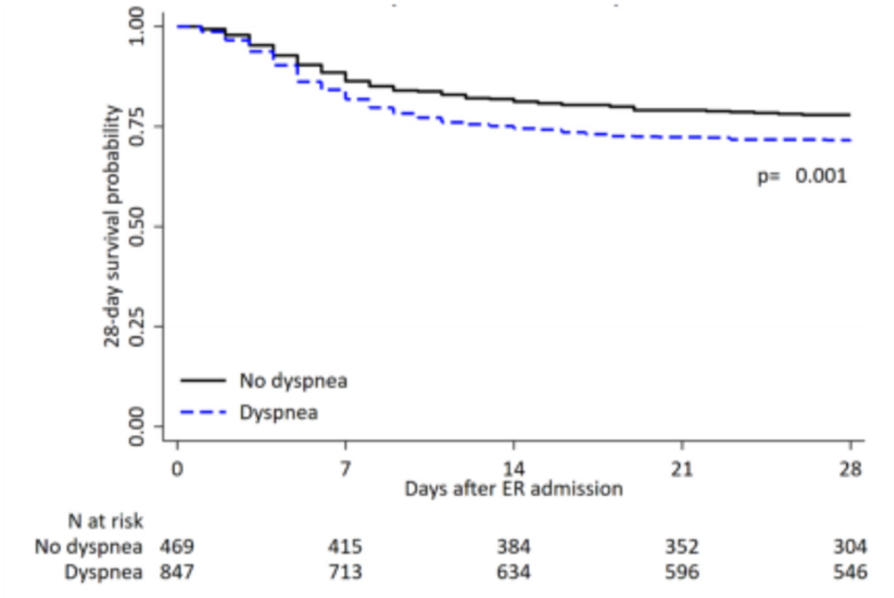

Figure 1. Kaplan–Meier 28-day mortality since hospitalization by the presence of dyspnea at admission in the overall population (N= 1316). Comparison by the log-rank test.

Figure 2. 28-day mortality – severity matched analysis.

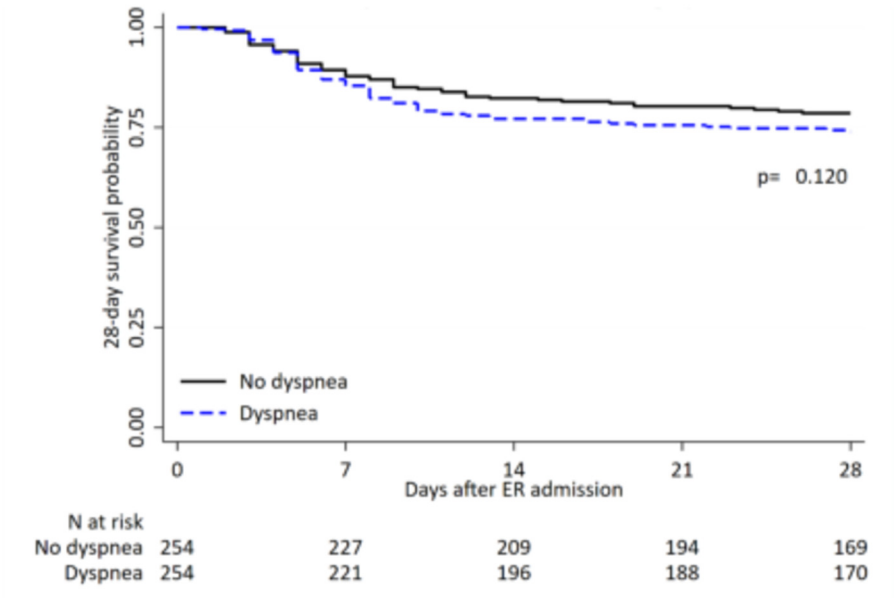

Figure 2. Kaplan–Meier 28-day mortality since hospitalization by the presence of dyspnea at admission in patients matched for disease severity (*i.e.* PaO_2/FiO_2 and imaging, N= 508). Comparison by the log-rank test.

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