Dyspnoea and clinical outcome in critically ill patients receiving noninvasive support for COVID-19 respiratory failure: *post hoc* analysis of a randomised clinical trial

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To the Editor:

In non-COVID-19 acute hypoxaemic respiratory failure, the entity of dyspnoea has been associated with severity of hypoxaemia, and represents a factor predicting noninvasive ventilation (NIV) failure, the need for endotracheal intubation and mortality [1].

In COVID-19 respiratory failure, the concept of "silent hypoxaemia" has been described: this is a condition of hypoxaemia without concomitant dyspnoea and/or signs of respiratory distress [2].

Whether in COVID-19 patients dyspnoea is related to outcome is unknown. We performed a *post hoc* analysis of a multicentre randomised trial (www.clinicaltrials.gov identifier number NCT04502576) that compared helmet NIV and high-flow nasal oxygen, aiming to assess the prevalence of dyspnoea in COVID-19 patients admitted to the intensive care unit (ICU) and to determine whether this may be related to study outcomes [3].

109 patients admitted to four ICUs and receiving noninvasive respiratory support due to COVID-19 acute hypoxaemic respiratory failure (arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2}) ratio ⩽200) were analysed. The full protocol and study procedures are described elsewhere [3].

On ICU admission, all patients were asked to rate the subjective sensation of dyspnoea from 0 to 10, with 10 representing the worst symptom, through a visual analogue scale (VAS) [4–6]. Dyspnoea was re-evaluated at 1, 6, 12, 24 and 48 h after the initiation of the assigned treatment, which was either high-flow nasal oxygen or helmet NIV. Patients with VAS dyspnoea ⩾4 were considered to have moderate-to-severe dyspnoea, while patients with VAS dyspnoea <4 were considered to have mild or no dyspnoea, as previously suggested [1].

The number of days free of advanced respiratory support (including high-flow nasal oxygen, NIV and invasive ventilation) within 28 days after enrolment; the proportion of patients who required endotracheal intubation within 28 days from study enrolment; the number of days free of invasive mechanical ventilation at day 28 and 60; 28-day, 60-day, in-ICU and in-hospital mortality; and ICU and hospital length of stay were the analysed outcomes.

Data are expressed as number of events (percentage) or median (interquartile range). Ordinal quantitative variables were compared with the Mann–Whitney U-test. Comparisons between groups regarding qualitative variables was performed with the Fisher's exact or the Chi-square test, as appropriate. Correlation was assessed with Pearson's correlation. Multivariate analyses adjusting for covariates were conducted through linear or logistic regression models. Kaplan–Meier curves are displayed for results concerning intubation rate. Intergroup differences in quantitative variables distribution in the initial 48 h of treatment were assessed with ANOVA. All results with two-sided p-values ⩽0.05 were considered statistically significant. A *post hoc* calculation of power was computed for the days free of respiratory support at 28 days, adjusting for the covariates, resulting in a power of 0.70. Statistical analysis was performed with IBM SPSS Statistics 26 and GraphPad Prism 7.

In the whole population (109 patients, median age 65 years (interquartile range (IQR) 55–70 years); 21 (19%) women), median (IQR) P_{aO_2}/F_{IO_2} on ICU admission was 102 (82–125) mmHg, median respiratory

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In #COVID19 patients, presence of moderate-to-severe dyspnoea is a marker of disease severity correlated to clinical outcomes https://bit.ly/3Bp2G1b

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rate was 28 (24–32) breaths per min and median VAS dyspnoea was 4 (1–7). 52 (48%) had moderate-to-severe dyspnoea while 57 (52%) had mild or no dyspnoea.

Demographics and most relevant study results are displayed in table 1. VAS dyspnoea on ICU admission was not related to respiratory rate (r=0.16, p=0.09), P_{aO_2}/F_{IO_2} (r=−0.14, p=0.15), arterial carbon dioxide tension (P_{aCO_2}) (r<0.1, p=0.97) or P_{aO_2} (r=0.07, p=0.50).

The median (IQR) days free of respiratory support within 28 days after randomisation were 12 (0–23) in the moderate-to-severe dyspnoea group and 21 (4–25) in the mild or no dyspnoea group (p=0.01, after adjustment for P_{aO_2}/F_{IO_2} at enrolment, Simplified Acute Physiology Score (SAPS) II and use of helmet NIV or high-flow oxygen).

44 patients required endotracheal intubation within 28 days of enrolment. The rate of endotracheal intubation was higher in patients with moderate-to-severe dyspnoea than those with mild or no dyspnoea (52% *versus* 30%), with an odds ratio of 3.8 (95% CI 1.5–9.9) (p=0.006, adjusted for P_{aO_2}/F_{IO_2} at enrolment, SAPS II score and use of helmet NIV or high-flow oxygen).

After 1 h of respiratory support, only patients that had moderate-to-severe dyspnoea on arrival showed significant improvement in VAS dyspnoea (median (IQR) VAS dyspnoea at enrolment *versus* after 1 h of the allocated treatment: 6.5 (5–7) *versus* 4 (2–5) respectively; mean difference 2.3 (95% CI 1.6–3), p<0.001), while patients with mild or no dyspnoea at arrival showed no changes in VAS dyspnoea (p=0.80). Nevertheless, despite the use of the allocated interface, patients that, on enrolment, showed

TABLE 1 Characteristics at inclusion and study outcomes, according to study group

	Moderate-to-severe dyspnoea (n=52)	Mild or no dyspnoea (n=57)	Adjusted mean difference (95% CI)	OR (95% CI)	p-value
Demographics					
Age, years	61 (53–70)	65 (58–71)			0.15
Female sex	9 (17)	12 (21)			0.64
Male sex	43 (83)	45 (79)			0.64
Body mass index, kg·m^{-2}	28 (26–30)	27 (25–30)			0.37
Respiratory rate at enrolment, breaths per min	28 (24–33)	27 (23–30)			0.13
Device-related discomfort at enrolment[#]	2 (0–5)	0 (0–0)			<0.001
Arterial blood gases at enrolment					
P_{aO_2}/F_{IO_2} ratio, mmHg	97 (82–117)	110 (83–132)			0.12
P_{aO_2}, mmHg	60 (54–74)	66 (55–75)			0.71
pH	7.46 (7.45–7.49)	7.46 (7.45–7.48)			0.95
P_{aCO_2}, mmHg	34 (31–37)	34 (32–37)			0.50
Allocated treatment[¶]					
Helmet noninvasive ventilation	27 (52)	27 (47)			0.70
High-flow oxygen	25 (48)	30 (53)			0.70
Outcomes					
Respiratory support[+]-free days at 28 days	12 (0–23)	21 (4–25)	−5 (−8–−1)		0.008
Intubation within 28 days from enrolment	27 (52)	17 (30)		3.8 (1.5–9.9)	0.006
Invasive ventilation-free days at 28 days	20 (4–28)	28 (16–28)	−5 (−9–−1)		0.02
Invasive ventilation free days at 60 days	52 (11–60)	60 (48–60)	−9 (−17–−1)		0.03
28-day mortality	10 (19)	8 (14)		1.8 (0.6–5)	0.29
60-day mortality	14 (27)	11 (19)		2 (0.8–5.5)	0.16
Intensive care unit mortality	15 (29)	10 (17)		2.8 (1–7.7)	0.05
Hospital mortality[§]	16 (31)	11 (19)		2.6 (1–7)	0.05
Length of stay in the intensive care unit, days	12 (6–29)	7 (4–12)	6 (0–6)		0.05
Length of stay in the hospital, days	24 (16–41)	18 (12–29)	8 (0–15)		0.04

Data are presented as median (interquartile range) or n (%), unless otherwise stated. There were no missing data among the two groups. Mean difference and odds ratio were adjusted for Simplified Acute Physiology Score II, allocated treatment (high-flow nasal oxygen or helmet noninvasive ventilation) and arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2}) ratio on intensive care unit admission. For non-normal quantitative variables, comparison between groups was performed with Mann–Whitney test. Comparison between groups for qualitative variables were performed with the Chi-squared test or the Fisher's exact test, as appropriate in agreement with tests assumptions. All the calculations were unadjusted. P_{aCO_2}: arterial carbon dioxide tension. [#]: discomfort was assessed through visual analogue scales adapted for intensive care unit patients, ranging from 0 to 10; [¶]: advanced respiratory support interface used in the first 48 h; [+]: invasive or noninvasive mechanical ventilation, high-flow nasal oxygen; [§]: one patient was discharged from hospital but died upon readmission.

higher VAS dyspnoea remained, overall, most dyspnoeic over time (mean±SD 3.6±2.4 *versus* 1.5±1.7 respectively; mean difference 2.1 (95% CI 1.7–2.5), one-way ANOVA p<0.001).

Conversely, over the initial 48 h of treatment, patients who subsequently required endotracheal intubation had higher mean VAS dyspnoea than the those who avoided intubation through the noninvasive treatment (3.4±2.6 *versus* 2.1±2.1 respectively; mean difference 1 (95% CI 1–2), p<0.001).

Patients with moderate-to-severe dyspnoea had fewer days free of invasive ventilation at days 28 and 60, longer ICU and hospital lengths of stay, and higher in-ICU and in-hospital mortality. There was no significant difference in 28- and 60-day mortality (table 1).

In this *post hoc* analysis of a randomised clinical trial conducted in COVID-19 patients admitted to the ICU with moderate-to-severe hypoxaemic respiratory failure and receiving a trial of noninvasive respiratory support, 52 patients (48%) showed moderate-to-severe dyspnoea on ICU admission. Conversely, 57 patients (52%) had moderate-to-severe oxygenation impairment with mild or no dyspnoea, possibly representing silent hypoxaemia.

Reporting moderate-to-severe dyspnoea on ICU admission was independently associated with increased need for endotracheal intubation, fewer respiratory support-free days, fewer invasive mechanical ventilation-free days at day 28 and 60, longer ICU and hospital length of stay, and higher in-ICU and in-hospital mortality.

The perception of dyspnoea is mediated by many physiological factors, including P_{aO_2} and P_{aCO_2}. Increases in respiratory drive and dyspnoea appear only when P_{aO_2} falls below 60–70 mmHg and P_{aCO_2} is >39 mmHg [2, 7, 8]; however, P_{aO_2} is usually maintained by clinicians >60 mmHg for safety reasons and P_{aCO_2} is commonly <39 mmHg due to higher sensitivity of the respiratory centre to carbon dioxide stimulus in patients with acute respiratory failure [8]. Indeed, only five patients exhibited P_{aO_2} <60 mmHg and/or P_{aCO_2} >39 mmHg, and among them, only two were not showing signs of dyspnoea.

In our cohort, patients that showed high-to-moderate dyspnoea on enrolment had a higher risk of endotracheal intubation and higher in-ICU mortality, confirming that the self-reported sensation of dyspnoea is not related to hypoxaemia or hypercapnia *per se*, but rather to the entity of pulmonary damage and to the severity of illness.

In COVID-19-induced moderate-to-severe acute hypoxaemic respiratory failure, the presence of moderate-to-severe dyspnoea has high prevalence, independently of the degree of oxygenation impairment, similarly to non-COVID-19 moderate-to-severe respiratory failure [1].

Presence of moderate-to-severe dyspnoea might be a marker of disease severity correlated to outcomes, possibly configuring a clinical subphenotype of COVID-19 severe respiratory failure. Use of noninvasive support in COVID-19 patients is common [9–12]. While considering a trial of noninvasive respiratory support in COVID-19 patients with moderate-to-severe respiratory failure, the presence of dyspnoea, measured during conventional oxygen therapy, in conjunction with other variables such as respiratory rate and degree of hypoxia, may represent a simple alert tool to identify patients with the highest risk of endotracheal intubation.

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