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Early View

Research letter

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Please cite this article as: Menga LS, Grieco DL, Rosà T, *et al*. Dyspnea and clinical outcome in critically ill patients receiving noninvasive support for COVID-19 respiratory failure: post-hoc analysis of a randomized clinical trial. *ERJ Open Res* 2021; in press (https://doi.org/10.1183/23120541.00418-2021).

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

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Author contribution

LSM, DLG and MA conceived the study. All authors contributed to data acquisition. TR conducted statistical analysis. LSM and TR interpreted the data and wrote the first draft of the manuscript. DLG and MA critically revised the manuscript. MA organized the study as an overall supervisor. All the authors reviewed the final draft of the manuscript and agreed on submitting it to the European Respiratory Journal Open Research.

Conflict of interests

DLG has received payments for travel expenses by Maquet, Getinge and Air Liquide. MA has received payments for Board participation from Maquet, Air Liquide and Chiesi. DLG and MA disclose a research grant by General Electric Healthcare.

Funding

The study was funded by a research grant (2017 MSD award) by the Italian Society of Anesthesia, Analgesia and Intensive Care Medicine (SIAARTI). The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Outside of the submitted work, Dr. Grieco is supported by a research grant by the European Society of Intensive Care Medicine (ESICM).

Dear editor

In non-COVID 19 acute hypoxemic respiratory failure, the entity of dyspnea has been associated with severity of hypoxemia, 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 hypoxemia" has been described: this is a condition of hypoxemia without concomitant dyspnea and/or signs of respiratory distress [2]. Whether in COVID-19 patients dyspnea is related to outcome is unknown. We performed a post-hoc analysis of a multicenter randomized trial (NCT04502576) that compared helmet noninvasive ventilation and high-flow nasal oxygen, aiming to assess the prevalence of dyspnea in COVID-19 patients admitted to the intensive care unit (ICU) and to determine whether this may be related to study outcomes [3].

Materials and Methods

One-hundred nine patients admitted to four ICUs and receiving noninvasive respiratory support due to COVID-19 acute hypoxemic respiratory failure ($PaO_2/FiO_2 \leq 200$) were analyzed. The full protocol and study procedures are described elsewhere [3].

At ICU admission, all patients were asked to rate the subjective sensation of dyspnea from 0 to 10, with 10 representing the worst symptom, through a visual analog scale [4–6]. Dyspnea was re-evaluated at 1, 6, 12, 24 and 48 hours after the initiation of the assigned treatment, which was either high-flow nasal oxygen or helmet NIV.

Patients with VAS dyspnea≥4 were considered having moderate-to-severe dyspnea group, while patients with VAS dyspnea<4 were considered having mild-or-no dyspnea, as previously suggested [1].

The number of days free of advanced respiratory support (including high-flow nasal oxygen, non-invasive and invasive ventilation) within 28 days after enrollment, the proportion of patients who required endotracheal intubation within 28 days from study enrollment, the number of days free of invasive mechanical ventilation at day 28 and 60, 28-day, 60-day, in-ICU and in-hospital mortality, ICU and hospital length of stay were the analyzed 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. Inter-group differences in quantitative variables distribution in the initial 48 hours of treatment were assessed with analysis of variance. All results with 2-sided $p \leq 0.05$ are 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 Statistic 26 and GraphPad Prism 7.

Results

In the whole population (109 patients, median age 65 years [IQR 55-70]; 21 (19%) women), median PaO_2/FiO_2 [IQR] at ICU admission was 102 [82-125], median respiratory rate was 28 [24-32] breaths per minute, and median VAS dyspnea was 4 [1-7]. Fifty-two (48%) had moderate-to-severe dyspnea, while 57 (52%) had mild-or-no dyspnea.

Demographics and most relevant study results are displayed in Table 1. VAS Dyspnea at ICU admission was not related to respiratory rate (r=0.16, p=0.09), PaO_2/FiO_2 (r=-0.14, p=0.15), $PaCO_2$ (r<0.1, p=0.97) nor PaO_2 (r=0.07, p=0.50).

The median [IQR] days free of respiratory support within 28 days after randomization were 12 [0-23] in the moderate-to-severe dyspnea group and 21 [4-25] in the mild-or-no dyspnea group (p = 0.01, after adjustment for PaO_2/FiO_2 at enrollment, SAPS II and use of helmet NIV or high flow oxygen).

Forty-four patients required endotracheal intubation within 28 days from enrollment. The rate of endotracheal intubation was higher in patients with moderate-to-severe dyspnea than those with mild-or-no dyspnea [52% vs 30%], with an odds ratio of 3.8 (95% CI: 1.5 to 9.9) (p=0.006) adjusted for PaO_2/FiO_2 at enrollment, SAPSII, use of helmet noninvasive ventilation or high-flow oxygen.

After one hour of respiratory support, only patients that had moderate-to-severe dyspnea at arrival showed significant improvement in VAS dyspnea (median VAS dyspnea [IQR] at enrollment vs median VAS dyspnea [IQR] after 1 hour of the allocated treatment: 6.5 [5 - 7] vs 4 [2 - 5] respectively, mean difference 2.3 [95% CI, 1.6 to 3], p value < 0.001) , while patients with mild or no dyspnea at arrival showed no changes in VAS dyspnea (p value = 0.80). Nevertheless, despite the use of the allocated interface, patients that at enrollment showed higher VAS dyspnea remained overall most dyspneic over time (mean (SD)) 3.6 (2.4) vs 1.5 (1.7) respectively, mean difference 2.1 [95% CI, 1.7 to 2.5], one-Way ANOVA p value < 0.001).

Conversely, over the initial 48 hours of treatment, patients who subsequently required endotracheal intubation had higher mean VAS dyspnea than the those who avoided intubation through the noninvasive treatment [mean (SD) 3.4 (2.6) vs 2.1 (2.1) respectively, mean difference 1 [95% CI, 1 to 2] p<0.001].

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

Discussion

In this post-hoc analysis of a randomized clinical trial conducted in COVID-19 patients admitted to the ICU with moderate-to-severe hypoxemic respiratory failure and receiving a trial of noninvasive respiratory support, 52 patients (48%) showed moderate-to-severe dyspnea at ICU admission. Conversely, 57 patients (52%) had moderate-to-severe oxygenation impairment with mild or no dyspnea, possibly configuring the 'silent hypoxemia' condition.

Reporting moderate-to-severe dyspnea at ICU admission was independently associated with increased need for endotracheal intubation, less respiratory support-free days, less 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 dyspnea is mediated by many physiological factors, including PaO_2 and $PaCO_2$. Increases in respiratory drive and dyspnea appear only when PaO_2 falls below 60-70 mmHg and $PaCO_2$ is more than 39 mmHg [2, 7, 8]; however, PaO_2 is usually maintained by clinicians above 60 mmHg for safety reasons, and $PaCO_2$ is commonly below 39 mmHg due to higher sensitivity of respiratory center to CO_2 stimulus in

patients with acute respiratory failure [8]. Indeed, only 5 patients exhibited PaO_2 below 60 mmHg and/or $PaCO_2$ above 39 mmHg, and among them only 2 were not showing signs of dyspnea.

In our cohort, patients that showed high-to-moderate dyspnea at enrollment had higher risk of endotracheal intubation and higher in-ICU mortality, confirming that the self-reported sensation of dyspnea is not related to hypoxemia 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 hypoxemic respiratory failure the presence of moderate-to-severe dyspnea has high prevalence, independently from the degree of oxygenation impairment, similarly to non-COVID 19 moderate-to-severe respiratory failure [1].

Presence of moderate-to-severe dyspnea might be a marker of disease severity correlated to outcomes, possibly configuring a clinical sub-phenotype 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 dyspnea, 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.

Acknowledgements

Members of the COVID-ICU Gemelli study group (Collaborative Authors)

Gian Marco Anzellotti, Giuseppe Bello, Maria M. Bitondo, Maria Grazia Bocci, Filippo Bongiovanni, Simone Carelli, Laura Cascarano, Giorgio Conti, Paolo De Santis, Antonio M. Dell'Anna, Mariangela Di Muro, Miriana Durante, Giulia Falò, Nicoletta Filetici, Veronica Gennenzi, Antonio Gullì, Gianmarco Lombardi, Alessio Maccaglia, Riccardo Maviglia, Alessandro Mele, Giovanna Mercurio, Teresa Michi, Tony C. Morena, Luca Montini, Jonathan Montomoli, Martina Murdolo, Daniele Natalini, Mariano Alberto Pennisi, Edoardo Piervincenzi, Stefania Postorino, Francesca Pozzana, Martina Savino, Roberta Scarascia, Angela Scavone, Donatella Settanni, Serena Silva, Savino Spadaro, V. Marco Ranieri, Tommaso Tonetti, Joel Vargas, Matteo Velardo, Carlo Alberto Volta, Carmelina Zaccone.

We are grateful to all intensive care unit physicians, residents, nurses, and personnel from the participating centers, whose sacrifice, efforts, devotion to patients, and passion have made possible this timely report.

Table 1. Characteristics at inclusion and study outcomes, according to Study Group.*				
	Moderate-to-severe dyspnea (n=52)	**Mild-or-no dyspnea (n=57)**	**Adjusted mean difference or odds ratio (95% CI)**	**P**
Demographics				
Age – years	61 [53 - 70]	65 [58-71]		0.15
Female sex – no. (%)	9 (17)	12 (21)		0.64
Male sex – no. (%)	43 (83)	45 (79)		0.64
Body Mass index§	28 [26 - 30]	27 [25 - 30]		0.37
Respiratory rate at enrolment, breaths per minute	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				
PaO2/FiO2 ratio - mmHg	97 [82 - 117]	110 [83 - 132]		0.12
PaO2 - mmHg	60 [54 - 74]	66 [55 - 75]		0.71
pH	7.46 [7.45 – 7.49]	7.46 [7.45 – 7.48]		0.95
PaCO2 – 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 to -1]	0.008
Intubation within 28 days from enrolment	27 (52)	17 (30)	3.8 (1.5 to 9.9)	0.006
28-day invasive ventilation free days	20 [4 - 28]	28 [16 - 28]	-5 [-9 to -1]	0.02
60-day invasive ventilation free days	52 [11 - 60]	60 [48 - 60]	-9 [-17 to -1]	0.03
28-day mortality	10 (19)	8 (14)	1.8 (0.6 to 5)	0.29
60-day mortality	14 (27)	11 (19)	2 (0.8 to 5.5)	0.16

Intensive care unit mortality	15 (29)	10 (17)	2.8 (1 to 7.7)	0.05
Hospital mortality †	16 (31)	11 (19)	2.6 (1 to 7)	0.05
Length of stay in the intensive care unit, days	12 [6 - 29]	7 [4 - 12]	6 [0 to 6]	0.05
Length of stay in the hospital, days	24 [16 - 41]	18 [12 - 29]	8 [0 to 15]	0.04

There were no missing data among the two groups.

*Values are displayed as median [interquartile range], if not otherwise specified.

** Mean difference and odds ratio were adjusted for SAPS II, Allocated treatment (high flow nasal oxygen or Helmet NIV) and PaO2/FiO2 at ICU admission.

FiO2 denotes fraction of inspired oxygen.

PaCO2 partial pressure of arterial carbon dioxide, and PaO2 partial pressure of arterial oxygen.

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§§ Discomfort was assessed through visual analog scales adapted for intensive care unit patients ranging from 0 to 10

§§§ Allocated treatment refers to the advanced respiratory support interface used in the first 48 hours.

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.

Respiratory support: invasive or noninvasive mechanical ventilation, high-flow nasal oxygen.

† One patient was discharged from hospital but died upon readmission.

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