CORRESPONDENCE

Phenotypes of Patients with COVID-19 Who Have a Positive Clinical Response to Helmet Noninvasive Ventilation

To the Editor:

Recently, we published the results of a randomized trial (HENIVOT) comparing helmet noninvasive ventilation followed by high-flow nasal oxygen versus high-flow nasal oxygen alone in patients with coronavirus disease (COVID-19) and moderate to severe respiratory failure ($Pa_{O_2}/FI_{O_2} < 200$ mm Hg and $Pa_{CO_2} \geqslant 45$ mm Hg). Results showed no significant intergroup difference in the primary outcome (28-day respiratory support-free days), but lower intubation rate and increased 28-day invasive ventilation-free days in the helmet group (1). The accompanying editorial addressed the relevant issue of personalizing treatments by identifying subphenotypes of patients who may best benefit from each technique (2).

We performed *post hoc* analyses to establish whether any bedside available parameter before randomization (Pa_{O_2}/FI_{O_2}, Pa_{CO_2}, respiratory rate, visual analog scale [VAS] dyspnea, Pa_{O_2}/[FI_{O_2} × respiratory rate], Sp_{O_2}/[FI_{O_2} × respiratory rate] (3), Pa_{O_2}/[FI_{O_2} × VAS dyspnea]) could help identify subgroups of patients who could most benefit from the interventions of the trial.

The parameters that were found to identify subgroups of patients with different response to treatments were presence of hypocapnia and Pa_{O_2}/(FI_{O_2} × VAS dyspnea) < 30 before randomization. In these *post hoc* analyses, we report study outcomes in the two groups after classifying patients according to *1*) whether they were normo- or hypocapnic; and *2*) whether their Pa_{O_2}/(FI_{O_2} × VAS dyspnea) was less than 30 or at 30 or more.

Methods

A total of 109 patients admitted to four ICUs in Italy with COVID-19 and moderate to severe hypoxemic respiratory failure ($Pa_{O_2}/FI_{O_2} \leqslant 200$) were randomized to receive 48-hour continuous treatment with helmet noninvasive ventilation (positive end-expiratory pressure 10–12 cm H_2O and pressure support 10–12 cm H_2O) eventually followed by high-flow nasal oxygen, or high-flow nasal oxygen alone (flow, 60 L/min). Full details of study protocol are provided elsewhere (clinicaltrials.gov NCT04502576) (1). The study was approved by the ethics committee of all centers.

In these *post hoc* analyses, intergroup differences in study outcomes were analyzed in the subgroups of patients exhibiting *1*) Pa_{CO_2} less than 35mm Hg or 35mm Hg or more; and *2*) Pa_{O_2}/(FI_{O_2} × VAS dyspnea) < 30 or ⩾30 (median of the cohort). Pa_{O_2}/FI_{O_2}, Pa_{CO_2}, and VAS dyspnea were measured while patients were receiving Venturimask oxygen before randomization. VAS dyspnea was assessed by visual analog scale, ranging from 0 to 10, with 10 representing the worst symptom (4, 5). For patients with VAS dyspnea = 0, Pa_{O_2}/(FI_{O_2} × VAS dyspnea) was considered equal to Pa_{O_2}/FI_{O_2}.

The number of days free of respiratory support (high-flow nasal oxygen, noninvasive, and invasive ventilation) within 28 days after enrollment was the primary endpoint. The rate of endotracheal intubation within 28 days, the number of days free of invasive mechanical ventilation at Days 28 and 60, in-ICU and in-hospital mortality, mortality at Days 28 and 60, and ICU and hospital length of stay were secondary outcomes.

Data are expressed as number of events (percentage) or median (interquartile range [IQR]). Ordinal quantitative variables were compared with the Mann-Whitney *U* test, after the nonnormal distribution was determined with the Shapiro-Wilk test. Comparisons between groups regarding qualitative variables were performed with the Fisher's exact or the chi-square test, as appropriate. Multivariate analyses adjusting for simplified acute physiology score II, sequential organ failure assessment, Pa_{O_2}/FI_{O_2} at inclusion, and site of enrollment and time of randomization as random effects were conducted through linear or logistic regression models. Kaplan-Meier curves are displayed for results concerning intubation. All results with two-sided $P \leqslant 0.05$ are considered statistically significant. Statistical analysis was performed with IBM SPSS 26.

Results

Demographic study endpoints are displayed in Table 1. Kaplan-Meier tables are displayed in Figure 1.

Pa_{CO_2} before treatment start. Among 109 analyzed patients, 59 patients had Pa_{CO_2} of less than 35 mm Hg and 50 had Pa_{CO_2} of 35 mm Hg or more.

In patients with Pa_{CO_2} of less than 35 mm Hg, the median (IQR) days free of respiratory support within 28 days after randomization were 21 (11–25) in the helmet group and 14 (0–21) in the high-flow group, a difference that was not significant before or after adjustment for covariates ($P = 0.07$).

The rate of endotracheal intubation was significantly lower in the helmet group than in the high-flow group: 18% versus 61%, with an absolute risk reduction of −43% (95% confidence interval [CI], −61% to −19%) and an adjusted odds ratio of 0.10 (95% CI, 0.22 to 0.42; $P = 0.002$) (Figure 1C).

In-ICU mortality was significantly lower in the helmet group than in the high-flow group: 11% versus 39%, with an absolute risk reduction of −28% (95% CI, −47% to −6%) and an adjusted odds ratio of 0.15 (95% CI, 0.03 to 0.69; $P = 0.015$).

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Author Contributions: D.L.G. and M.A. conceived the study. All authors contributed to data acquisition. L.S.M. conducted statistical analysis. D.L.G. interpreted the data and wrote the first draft of the manuscript. S.M.M. and M.A. critically revised the manuscript. M.A. organized the study as an overall supervisor. All authors reviewed the final draft of the manuscript and agreed on submitting it to the *Journal*.

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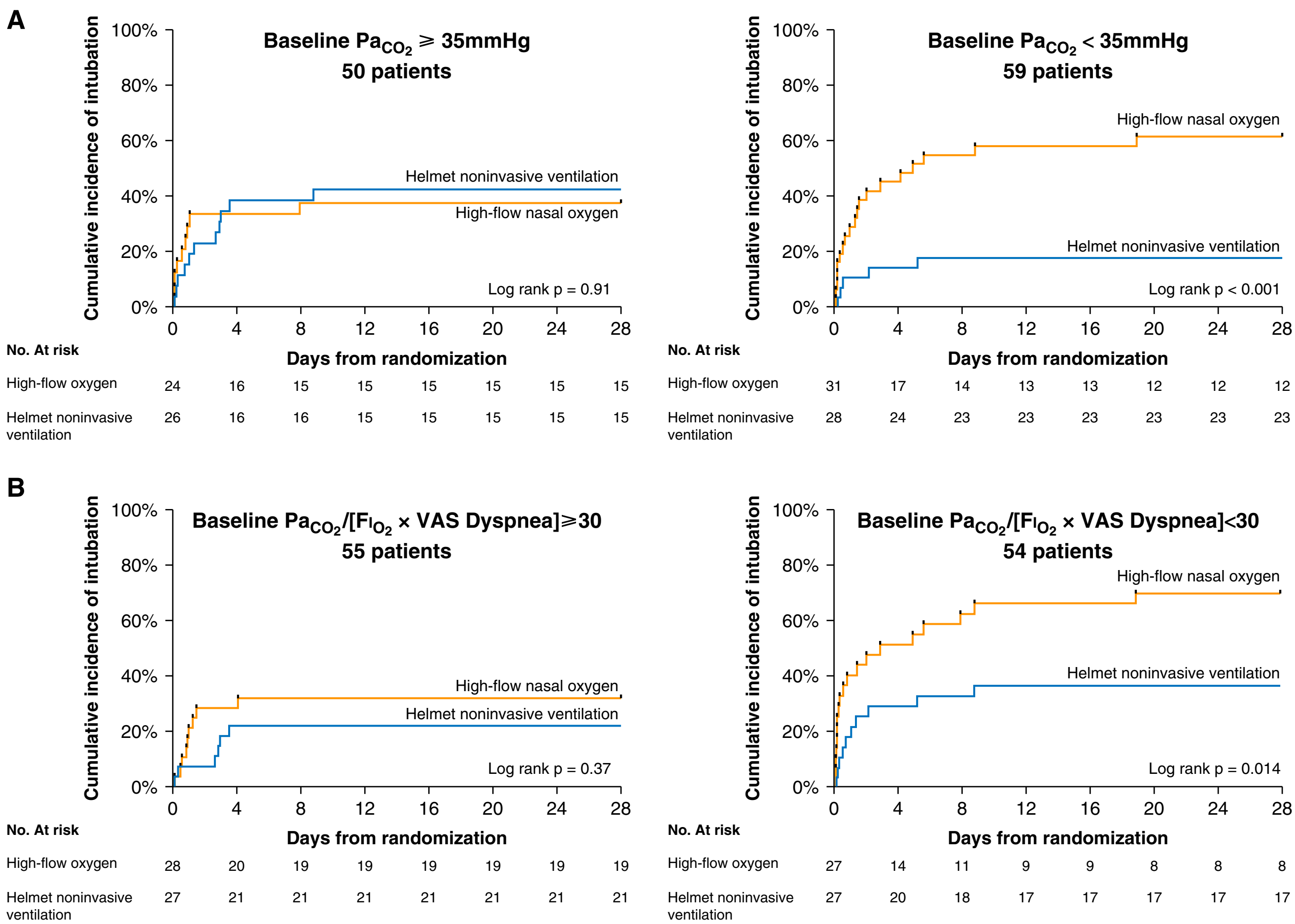

Figure 1. (*A*) Kaplan-Meier plots of the cumulative incidence of intubation from randomization to Day 28 in the subgroup of patients with Pa_{CO_2} of less than 35 mm Hg (n = 59 patients) and 35 mm Hg or more (n = 50 patients) at study enrollment. The hazard ratio for endotracheal intubation in the helmet noninvasive ventilation group in patients with Pa_{CO_2} of less than 35 mm Hg was 0.25 (95% CI, 0.11–0.57). The hazard ratio for endotracheal intubation in the helmet noninvasive ventilation group in patients with Pa_{CO_2} of at least 35 mm Hg was 1.05 (95% CI, 0.44–2.53). (*B*) Kaplan-Meier plots of the cumulative incidence of intubation from randomization to Day 28 in the subgroup of patients with Pa_{O_2}/(Fi_{O_2} × dyspnea) lower (n = 54 patients) and equal to or higher than (n = 55 patients) 30 at study enrollment. The hazard ratio for endotracheal intubation in the helmet noninvasive ventilation group in patients with Pa_{O_2}/(Fi_{O_2} × VAS dyspnea) < 30 was 0.39 (95% CI, 0.19–0.82). The hazard ratio for endotracheal intubation in the helmet noninvasive ventilation group in patients with Pa_{O_2}/(Fi_{O_2} × VAS dyspnea) ≥ 30 was 0.63 (95% CI, 0.23–1.73). CI = confidence interval; VAS = visual analog scale.

In patients with Pa_{CO_2} of 35 mm Hg or less, there were no significant differences between the helmet and the high-flow group for any analyzed outcome.

Pa_{O_2}/(Fi_{O_2} × VAS dyspnea) before treatment start. Among 109 analyzed patients, 55 patients had Pa_{O_2}/(Fi_{O_2} × VAS dyspnea) ≥ 30 and 54 had Pa_{O_2}/(Fi_{O_2} × VAS dyspnea) ≤ 30.

In patients with Pa_{O_2}/(Fi_{O_2} × VAS dyspnea] < 30, the median (IQR) days free of respiratory support within 28 days after randomization was 13 (0–24) in the helmet group and 1 (0–19) in the high-flow group, a difference that was not statistically significant (P = 0.29). At the adjusted analysis, the number of days free of respiratory support at 28 days was significantly higher in the helmet group, with an adjusted mean difference of 5 (95% CI, 0–10; P = 0.04).

The rate of endotracheal intubation was significantly lower in the helmet group than in the high-flow group: 37% versus 70%, with an absolute risk reduction of 33% (95% CI, −7% to 54%) and an adjusted odds ratio of 0.11 (95% CI, 0.02 to 0.55; P = 0.008) (Figure 1B).

In patients with Pa_{O_2}/(Fi_{O_2} × VAS dyspnea) ≥ 30, there were no significant differences between the helmet and the high-flow group for any analyzed outcome.

Discussion

The results of these *post hoc* analyses of the HENIVOT trial indicate that the beneficial effects of helmet noninvasive ventilation over high-flow nasal oxygen in patients with COVID-19 with moderate to severe hypoxemia are magnified and limited to the subgroup of patients with Pa_{O_2}/(Fi_{O_2} × VAS dyspnea) < 30 and/or Pa_{CO_2} of less than 35mm Hg before treatment start.

Pa_{O_2}/Fi_{O_2} and VAS dyspnea are markers of disease severity (5); hypocapnia may reflect dysregulation of brain homeostasis toward a lower level of Pa_{CO_2}, resulting in increased inspiratory effort, high V_T, and tachypnea (6).

Table 1. Characteristics at Inclusion and Study Outcomes, according to Study Group*

	Pa_{CO_2} < 35mm Hg (*n* = 59)					Pa_{CO_2} ⩾ 35 mm Hg (*n* = 50)				
	Helmet Noninvasive Ventilation (*n* = 28)	**High-Flow Nasal Oxygen (*n* = 31)**	**Absolute or Mean Difference (95% CI)**	**OR (95% CI)**	***P* Value**	**Helmet Noninvasive Ventilation (*n* = 26)**	**High-Flow Nasal Oxygen (*n* = 24)**	**Absolute or Mean Difference (95% CI)**	**OR (95% CI)**	***P* Value**
Characteristics at study inclusion										
Age, yr	66 (53 to 73)	64 (55 to 71)	−1 (−8 to 4)	—	0.93	66 (60 to 72)	61 (53 to 68)	8 (1 to 14)	—	0.056
Sex, F, *n* (%)	4 (14)	5 (16)	−2 (−20 to 18)	0.87 (0.21 to 3.6)	>0.99	18 (69)	20 (83)	−14 (−36 to 10)	2.22 (0.57 to 8.65)	0.33
Sex, M, *n* (%)	24 (86)	26 (84)	2 (−18 to 20)	1.15 (0.28 to 4.81)	>0.99	8 (31)	4 (17)	14 (−10 to 36)	0.45 (0.12 to 1.75)	0.33
Body mass index[†]	26 (26 to 29)	27 (23 to 32)	0 (−1 to 1)	—	0.97	28 (26 to 31)	30 (23 to 33)	−2 (−5 to 1)	—	0.18
Respiratory rate at enrollment, breaths/min	28 (24 to 35)	26 (23 to 32)	1 (−3 to 5)	—	0.61	30 (24 to 31)	28 (23 to 31)	1 (−2 to 3)	—	0.69
Device-related discomfort at enrollment[‡]	1 (0 to 3)	0 (0 to 1)	1 (0 to 2)	—	0.13	0 (0 to 5)	0 (0 to 2)	0 (−1 to 2)	—	0.96
VAS dyspnea at enrollment[‡]	3 (2 to 6)	4 (0 to 6)	1 (−1 to 2)	—	0.41	4 (1 to 7)	3 (1 to 7)	2 (−1 to 2)	—	0.98
VAS dyspnea change after 1 h of treatment[‡]	1 (0 to 3)	0 (−1 to 1)	2 (0 to 3)	—	0.006	1 (0 to 3)	0 (−1 to 3)	1 (−1 to 2)	—	0.10
Arterial blood gases at enrollment										
Pa_{O_2}/F_{IO_2} ratio, mm Hg	103 (84 to 126)	93 (80 to 122)	10 (−4 to 17)	—	0.30	106 (82 to 126)	109 (84 to 130)	−4 (−21 to 13)	—	0.68
Pa_{CO_2}, mm Hg	31 (28 to 33)	32 (30 to 34)	−1 (−3 to 0)	—	0.046	37 (36 to 39)	37 (36 to 40)	0 (−1 to 2)	—	0.85
SAPS II	32 (25 to 35)	29 (24 to 37)	0 (−4 to 3)	—	0.98	32 (28 to 37)	24 (28 to 32)	4 (0 to 9)	—	0.024
Outcomes										
Respiratory support–free days	21 (11 to 25)	14 (0 to 21)	5 (0 to 11)	—	0.07	16 (0 to 24)	20 (1 to 23)	−2 (−8 to 4)	—	0.80
Intubation within 28 d from enrollment	5 (18)	19 (61)	−43 (−61 to −19)	0.14 (0.04 to 0.46)	0.001	11 (42)	9 (38)	9 (−17 to 33)	1.22 (0.39 to 3.80)	0.78
28-d invasive ventilation-free days	28 (28 to 28)	19 (3 to 28)	8 (2 to 14)	—	0.003	28 (4 to 28)	28 (9 to 28)	−2 (−8 to 5)	—	0.81
60-d invasive ventilation-free days	60 (60 to 60)	50 (5 to 60)	17 (5 to 30)	—	0.002	60 (8 to 60)	60 (33 to 60)	−8 (−20 to 5)	—	0.36
28-d mortality	3 (11)	8 (26)	−15 (−34 to 5)	0.34 (0.08 to 1.46)	0.19	5 (19)	2 (8)	11 (−10 to 30)	2.62 (0.46 to 15)	0.42
60-d mortality	5 (18)	10 (32)	−14 (−35 to 8)	0.46 (0.13 to 1.55)	0.24	8 (31)	2 (8)	22 (0 to 43)	4.89 (0.92 to 25.97)	0.78
In-ICU mortality	3 (11)	12 (39)	−28 (−47 to −6)	0.19 (0.05 to 0.77)	0.018	8 (31)	2 (8)	22 (0 to 43)	4.89 (0.92 to 25.97)	0.78
In-hospital mortality[§]	5 (18)	12 (39)	−21 (−41 to 2)	0.34 (0.10 to 1.15)	0.092	8 (31)	2 (8)	22 (0 to 43)	4.89 (0.92 to 25.97)	0.78
Duration of stay in the ICU, d	8 (4 to 17)	12 (6 to 23)	−9 (−18 to 0)	—	0.12	9 (4 to 22)	8 (5 to 17)	−3 (−13 to 8)	—	0.88
Duration of stay in the hospital, d	22 (14 to 33)	23 (13 to 47)	−8 (−20 to 3)	—	0.37	20 (13 to 28)	18 (13 to 32)	−4 (−15 to 6)	—	0.91

(*Continues*)

Table 1. (*Continued*)

	$Pa_{O_2}/(FI_{O_2} \times$ VAS Dyspnea) ≥ 30 (*n* = 55)					$Pa_{O_2}/(FI_{O_2} \times$ VAS Dyspnea) < 30 (*n* = 54)				
	Helmet Noninvasive Ventilation (*n* = 27)	High-Flow Nasal Oxygen (*n* = 28)	Absolute or Mean Difference (95% CI)	OR (95% CI)	*P* Value	Helmet Noninvasive Ventilation (*n* = 27)	High-Flow Nasal Oxygen (*n* = 27)	Absolute or Mean Difference (95% CI)	OR (95% CI)	*P* Value
Characteristics at study inclusion										
Age, yr	65 (59 to 72)	64 (57 to 69)	3 (−3 to 9)	—	0.36	67 (53 to 73)	59 (53 to 70)	2 (−4 to 8)	—	0.44
Sex, F, *n* (%)	5 (18)	6 (21)	−3 (−24 to 18)	0.83 (0.22 to 3.14)	>0.99	7 (26)	3 (11)	15 (−6 to 35)	2.8 (0.6 to 12.2)	0.29
Sex, M, *n* (%)	22 (82)	22 (79)	3 (−18 to 24)	1.2 (0.32 to 4.52)	>0.99	20 (74)	24 (89)	−15 (−35 to 6)	0.36 (0.08 to 1.56)	0.29
Body mass index†	26 (26 to 29)	28 (25 to 31)	−1.2 (−3.8 to 1.3)	—	0.62	28 (26 to 30)	28 (27 to 32)	−0.5 (−2.5 to 1.5)	—	0.72
Respiratory rate at enrollment, breaths/min	29 (24 to 31)	25 (22 to 29)	2 (0 to 5)	—	0.11	28 (24 to 32)	30 (25 to 34)	−1 (−5 to 3)	—	0.42
Device-related discomfort at enrollment‡	0 (0 to 2)	0 (0 to 0)	0 (0 to 1)	—	0.67	2 (0 to 5)	1 (0 to 5)	0 (−1 to 2)	—	0.47
VAS dyspnea at enrollment‡	2 (0 to 3)	1 (0 to 2)	0 (0 to 1)	—	0.37	7 (5 to 7)	6 (4 to 7)	1 (0 to 1)	—	0.15
VAS dyspnea change after 1 h of treatment‡	0 (0 to 2)	0 (−2 to 0)	1 (0 to 2)	—	0.005	2 (1 to 4)	1 (0 to 3)	1 (0 to 3)	—	0.04
Arterial blood gases at enrollment										
Pa_{O_2}/FI_{O_2} ratio, mm Hg	114 (83 to 133)	115 (92 to 136)	1 (−17 to 19)	—	0.98	97 (82 to 115)	90 (72 to 115)	7 (−6 to 20)	—	0.34
Pa_{CO_2}, mm Hg	34 (31 to 37)	34 (32 to 38)	−1 (−3 to 1)	—	0.51	34 (31 to 38)	34 (32 to 37)	0 (−2 to 2)	—	0.93
SAPS II	32 (27 to 35)	29 (24 to 36)	1 (−3 to 5)	—	0.56	32 (29 to 35)	29 (24 to 32)	2 (−2 to 6)	—	0.10
Outcomes										
Respiratory support-free days	22 (13 to 25)	21 (10 to 23)	1 (5 to 6)	—	0.49	13 (0 to 24)	1 (0 to 19)	3 (−2 to 9)	—	0.29
Intubation within 28 d from enrollment	6 (22)	9 (32)	−10 (−32 to 13)	0.6 (0.18 to 2.01)	0.55	10 (37)	19 (70)	−33 (−54 to −7)	0.25 (0.08 to 0.77)	0.03
28-d invasive ventilation-free days	28 (28 to 28)	28 (18 to 28)	1 (−5 to 6)	—	0.46	28 (5 to 28)	9 (2 to 28)	6 (0 to 13)	—	0.04
60-d invasive ventilation-free days	60 (60 to 60)	60 (50 to 60)	2 (−10 to 13)	—	0.45	60 (9 to 60)	30 (9 to 60)	10 (−3 to 23)	—	0.09
28-d mortality	3 (11)	4 (14)	−3 (−22 to 16)	0.75 (0.15 to 3-72)	>0.99	5 (18)	6 (22)	−4 (−25 to 18)	0.80 (0.21 to 3)	>0.99
60-d mortality	5 (19)	5 (18)	1 (−20 to 21)	1.05 (0.27 to 4.12)	>0.99	8 (30)	7 (26)	4 (−20 to 26)	1.2 (0.36 to 4)	>0.99
In-ICU mortality	4 (15)	5 (18)	−3 (−23 to 17)	0.8 (0.19 to 3.36)	>0.99	7 (26)	9 (33)	−7 (−30 to 16)	0.7 (0.22 to 2.27)	0.76
In-hospital mortality§	4 (15)	5 (18)	−3 (−23 to 17)	0.8 (0.19 to 3.36)	>0.99	9 (33)	9 (33)	0 (−24 to 24)	1 (0.32 to 3.1)	>0.99
Duration of stay in the ICU, d	5 (3 to 10)	8 (5 to 11)	−1 (−8 to 6)	—	0.21	13 (6 to 26)	14 (5 to 57)	−11 (−23 to 0)	—	0.42
Duration of stay in the hospital, d	17 (11 to 26)	19 (13 to 30)	−1 (−9 to 6)	—	0.50	24 (16 to 36)	23 (14 to 70)	−12 (−26 to 1)	—	0.50

Definition of abbreviations: CI = confidence interval; OR = odds ratio; SAPS II = Simplified Acute Physiology Score II; VAS = visual analog scale.

There were no missing data among the two groups. For calculations, Pa_{O_2} was expressed in mm Hg and FI_{O_2} as fraction of the unity (0.21–1). For nonnormal quantitative variables, comparison between groups was performed with Mann-Whitney test. Comparisons between groups for qualitative variables were performed with the chi-square test or the Fisher's exact test, as appropriate in agreement with test's assumptions. Mean differences and odds ratios are unadjusted. For adjusted results, *see* the main text. Respiratory support: invasive or noninvasive mechanical ventilation, high-flow nasal cannula.

*Values are displayed as median (interquartile range) if not otherwise specified.

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

‡Dyspnea and discomfort were assessed through visual analog scales adapted for patients in the ICU ranging from 0 to 10.

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

Results from this *post hoc* analysis are consistent with data indicating that the physiologic benefit of helmet noninvasive ventilation over high-flow nasal oxygen is prominent among patients with more severe oxygenation impairment and intense inspiratory effort (7).

These results may aid bedside patient phenotyping for clinical decision making and personalizing treatments. High-flow nasal oxygen is a simple, easy-to-use tool applied worldwide (8). Conversely, helmet noninvasive ventilation is a less diffuse technique (9) and requires a mechanical ventilator and personnel expertise, whose shortage in the context of the COVID-19 pandemic may limit the number of patients who may have access to this kind of support. $Pa_{O_2}/(FI_{O_2} \times$ VAS dyspnea) and Pa_{CO_2} are bedside-available parameters that may help identify patients in whom helmet noninvasive ventilation as applied in the HENIVOT trial may improve clinical outcome (7, 10).

Our study has limitations: The *post hoc* nature of these analyses and the small sample make the results hypothesis generating, warranting further confirmatory investigations; the thresholds proposed should be taken cautiously; and VAS dyspnea is mainly used to compare dyspnea within a subject before and after a stimulus is applied, but it has been recently used to compare subjects undergoing noninvasive support (4, 5). We believe that its application in the present investigation is legitimate.

In patients with COVID-19 and moderate to severe hypoxemic respiratory failure, these analyses suggest that high-flow oxygen is as effective as helmet noninvasive ventilation in patients who show $Pa_{O_2}/(FI_{O_2} \times$ VAS dyspnea) $\geqslant 30$ and/or Pa_{CO_2} of 35 mm Hg or more under conventional oxygen, whereas helmet noninvasive ventilation as applied in the HENIVOT trial may improve clinical outcome among subjects exhibiting $Pa_{O_2}/(FI_{O_2} \times$ VAS dyspnea) < 30 and/or Pa_{CO_2} of less than 35 mm Hg. ■

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Construct Validity of Pa_{O_2}/F_{IO_2} Ratios in Defining Acute Respiratory Distress Syndrome

To the Editor:

Acute respiratory distress syndrome (ARDS) is a clinical syndrome of inflammatory lung injury characterized by increased alveolar permeability, severe hypoxemia, and reduced lung compliance (1, 2). The Pa_{O_2}/F_{IO_2} (P/F) ratio plays a key role in defining ARDS, although it may vary with F_{IO_2} and positive end-expiratory pressure (PEEP) (3, 4). According to the Berlin definition of ARDS, the criteria for hypoxemia are a P/F ratio ⩽300 mm Hg with a PEEP of ⩾5 cm H_2O (2). However, the rationale for choosing 300 mm Hg as the P/F cutoff remains obscure. In the absence of an available gold standard to determine the cutoff of P/F ratios for differentiating patients with and without ARDS, evaluating the construct validity of P/F ratios may provide new insights into this issue. Construct validity refers to a concept that cannot be directly observed, but its characteristics can be measured by other indicators (5). In this study, we evaluated the construct validity of P/F ratios in defining ARDS to explore whether there was a threshold to identify hypoxemic events matching the characteristics of ARDS. We hypothesized that a poor respiratory outcome (death or ventilator dependence) and low respiratory compliance (<40 ml/cm H_2O) due to widespread lung injury would be the key features of ARDS compared with non-ARDS respiratory failure (2).

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Methods

In this retrospective multi-ICU study, we identified adult patients who received invasive mechanical ventilation (MV) for >24 hours and had arterial blood gas analysis on the first day of MV from October 2014 to July 2020 at the National Taiwan University Hospital in Taiwan. Patient demographics, P/F ratios and ventilator settings on the first MV day, respiratory compliance, and outcomes at ICU discharge were collected. For measurement of respiratory compliance, patients were put on the volume control mode with constant flow. Measurements of respiratory mechanics were only performed in patients who had been adequately sedated or had no spontaneous breathing. The static compliance of the total respiratory system was calculated by dividing the inflation volume by the difference between the end-inspiratory plateau pressure and the PEEP set by the ventilator. Stata software version 15 was used for statistical analysis.

The need for written informed consent was waived by the Research Ethics Committee of the National Taiwan University Hospital (No. 202009066RINC) because this was a retrospective study and procedures were adopted to protect and anonymize personal patient information.

The primary analysis was to evaluate the relationship between P/F ratios and the composite outcome of death and MV dependence at ICU discharge using logistic regression. The secondary analysis evaluated the relationship between P/F ratios and ICU mortality using logistic regression, and the relationship between P/F ratios and static respiratory compliance using linear regression. Respiratory compliance was standardized to predicted body weight to account for the influence of body size on

Table 1. Characteristics of the Study Cohort (*N* = 4,060)

Characteristic	Value
Age, yr, median (IQR)	67 (56–78)
Sex, F, *n* (%)	1,512 (37.2)
APACHE II, median (IQR)	19 (13–24)
Height, cm, median (IQR)	163 (156–168)
Weight, kg, median (IQR)	60 (51–69)
Causes of respiratory failure, *n* (%)	
Respiratory	1,938 (47.7)
Shock or acidemia	1,001 (24.7)
Postoperative	628 (15.5)
Other	493 (12.1)
Respiratory parameters, median (IQR)	
F_{IO_2}	0.5 (0.4–0.7)
Pa_{O_2}, mm Hg	115 (85–165)
Pa_{O_2}/F_{IO_2} ratio, mm Hg	232 (141–354)
PEEP, cm H_2O	6 (5–8)
pH	7.42 (7.37–7.46)
Pa_{CO_2}, mm Hg	32 (28–38)
HCO_3^-, mmol/L	21 (18–24)
Static respiratory compliance, ml/cm H_2O	35 (27–46)
Distribution of Pa_{O_2}/F_{IO_2} ratios, *n* (%)	
<100 mm Hg	496 (12.2)
100 to <200 mm Hg	1,202 (29.6)
200 to <300 mm Hg	916 (22.6)
300 to <400 mm Hg	695 (17.1)
400 to <500 mm Hg	440 (10.8)
⩾500 mm Hg	311 (7.7)

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; IQR = interquartile range; PEEP = positive end-expiratory pressure.