High Flow Nasal Oxygen for Severe Hypoxemia: Oxygenation Response and Outcome in COVID-19 Patients

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At a Glance Commentary

Scientific Knowledge on the Subject: In order to identify patients in the initial stages of ARDS, and facilitate inclusion into clinical trials aimed at earlier treatment, several studies have suggested diagnosing ARDS in the patients not receiving mechanical ventilation. However, the oxygenation criterion of the Berlin definition states that for the diagnosis of moderate or severe ARDS, a patient must be on invasive mechanical ventilation with a PEEP $\geq$ 5 cmH_2O, when the PaO2/FiO2 is measured; while for the diagnosis of mild ARDS the patient can be receiving PEEP or CPAP $\geq$ 5 cmH_2O also delivered non-invasively. Several

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investigators have suggested that the Berlin definition oxygenation criterion should be broadened to allow inclusion of patients on HFNO, since this technique increases end-expiratory pressure equivalent to ~5 cmH2O if HFNO flow is greater than about 30 L/min. However, there is insufficient published evidence confirming the validity of this approach.

What This Study Adds to the Field: By enrolling HFNO and NIV patients with PaO_2/FiO_2 ratio ≤300 mmHg and bilateral chest infiltrates, 7.1% of HFNO patients and 4.3% of NIV lost ARDS criteria after institution of IMV. However, the mortality rate was substantially lower in all HFNO patients compared to those who were intubated. Thus, adding patients on HFNO to the definition of ARDS may allow identification of patients at an earlier stage of the natural history of the ARDS; however, this may select patients with substantially lower mortality.

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ABSTRACT

Rationale: The "Berlin definition" of acute respiratory distress syndrome (ARDS) does not allow inclusion of patients receiving high-flow nasal oxygen (HFNO). However, several articles proposed that criteria for defining ARDS should be broadened to allow inclusion of patients receiving HFNO.

Objective: To compare the proportion of patients fulfilling ARDS criteria during HFNO and soon after intubation, and 28-day mortality between patients treated exclusively with HFNO and patients transitioned from HFNO to IMV.

Methods: From previously published studies we analyzed COVID-19 patients who had PaO_2/FiO_2 ≤300 while treated with HFNO ≥40 L/min, or NIV with PEEP ≥5 cmH_2O (comparator). In patients transitioned from HFNO/NIV to invasive mechanical ventilation (IMV), we compared ARDS severity during HFNO/NIV and soon after IMV. We compared 28-day mortality in patients treated exclusively with HFNO/NIV vs. transitioned to IMV.

Measurements and main results: We analyzed 184 and 131 patients receiving HFNO or NIV, respectively. 112 HFNO, and 69 NIV patients transitioned to IMV. 104 (92.9%) HFNO patients and 66 (95.7%) NIV patients continued to have PaO_2/FiO_2 ≤300 under IMV. 28-day mortality in patients who remained on HFNO was 4.2% (3/72) while in patients transitioned from HFNO to IMV it was 28.6% (32/112) ($p<0.001$). 28-day mortality in patients who remained on NIV was 1.6% (1/62), while in patients who transitioned from NIV to IMV it was 44.9% (31/69) ($p<0.001$). Overall mortality was 19.0% (35/184) and 24.4% (32/131) for HFNO and NIV, respectively ($p=0.2479$).

Conclusions: Broadening ARDS definition to include HFNO patients with PaO_2/FiO_2 ≤300 may identify patients at earlier stages of disease but with lower mortality.

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Key words. COVID-19, ARDS, HFNO, mechanical ventilation, non-invasive ventilation

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INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a severe form of acute hypoxemic respiratory failure not resulting from congestive heart failure or fluid overload (**1**). Although the "conceptual model" of ARDS (**2**) has not changed greatly since its original description (**3**), the formal definition of ARDS has undergone multiple modifications, occasionally with some degree of controversy (**4**). The most recent update in 2012 - the so called "Berlin definition" - classified ARDS as "*mild"*, "*moderate"*, or "*severe"* when the ratio of arterial-to-inspiratory oxygen fraction (PaO_2/FiO_2) was 200–300, 100–200 and <100 mmHg, respectively (**5**). The definition required that the PaO_2/FiO_2 criteria be obtained while the patient was receiving invasive mechanical ventilation (invasive or non-invasive) with ≥5 cmH_2O of positive end-expiratory pressure (PEEP). For mild ARDS, the definition allowed the PaO_2/FiO_2 criteria to be met while the patient was breathing spontaneously with ≥5 cmH_2O of continuous positive airway pressure (CPAP) (**5**).

One major criticism of the Berlin definition is that it does not allow inclusion of patients early in the lung injury process (**6-9**) and excludes patients on high-flow nasal oxygen (HFNO) (**10**). HFNO delivers heated and humidified oxygen via the nose at flows ≤60 L/min at oxygen concentrations up to 80–100% (**11,12**) and is increasingly being used to support patients with hypoxemic respiratory failure (**13-16**). To address these concerns, a number of authors have proposed that criteria for defining ARDS should be broadened to allow inclusion of patients receiving HFNO **(10,17,18**). However, there is a paucity of empiric data to fully support this recommendation.

The present study set out to examine some of the implications of allowing patients on HFNO to be categorized as having ARDS. We analyzed data from four published studies during the COVID-19 pandemic (**19-22**) and focused on two major study outcomes. First, in

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the subset of patients who transitioned from HFNO to invasive mechanical ventilation (IMV), we compared the proportion of patients fulfilling ARDS criteria during HFNO and soon after intubation. Second, we compared 28-day mortality between patients treated exclusively with HFNO with patients who transitioned from HFNO to IMV. Patients initially treated with non-invasive ventilation (NIV) were used as a comparator group.

METHODS

This study is a secondary analysis of data from four previously published studies performed in Italy from February-December 2020, that enrolled patients with acute hypoxemic respiratory failure due to confirmed COVID-19 (**19-22**). Patients were selected if all the following inclusion criteria were met: (a) worsening respiratory symptoms due to severe COVID-19 for ≤1 week, (b) bilateral opacities consistent with ARDS on standard chest X-ray (23), (c) PaO_2/FiO_2 ≤300 mmHg, (d) patients initially treated for ≥12 continuous hours with HFNO using gas flows ≥40 L/min, or treated with NIV with PEEP ≥5 cmH_2O. Exclusion criteria were: (a) treated with IMV since the onset of respiratory failure; (b) treated with more than one mode, e.g., HFNO/NIV/CPAP at the onset of respiratory failure; (c) underwent awake prone positioning; (d) had incomplete records for the variables of interest; (e) had a "do not intubate/do not resuscitate" order. Details of enrollment criteria for each study are in the online supplement.

Study outcomes were: (a) in the subset of patients transitioned from non-invasive ventilatory support (HFNO or NIV) to IMV, we compared the proportion of patients fulfilling ARDS criteria and the proportion of patients who fulfilled the oxygenation criteria for "*mild*", "*moderate*", and "*severe*" ARDS during HFNO or NIV, and after intubation; (b) 28-day mortality in patients treated with HFNO or NIV who did not transition to IMV vs. the 28-day mortality in patients transitioned to IMV. We examined the association between changes in

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PaO_2/FiO_2 after IMV and flow rate during HFNO, or the level of PEEP during NIV. We also examined mortality and change in PaO_2/FiO_2 after initiation of IMV in patients initially treated with HFNO vs. NIV.

We recorded the first arterial blood gases collected within the initial 12 hours of treatment with HFNO or NIV. In patients who transitioned from non-invasive ventilatory support (HFNO or NIV) to IMV, blood gases were collected before intubation (i.e., the final blood gas before intubation), and 30-120 minutes after intubation. Chest radiographs were evaluated for pulmonary infiltrates consistent with ARDS (**23**). We examined changes in PaO_2/FiO_2 ratios after intubation, as well as 28-day mortality using different PaO_2/FiO_2 cut-offs (**24**).

Continuous variables were expressed as medians and inter-quartile range, categorical variables as absolute and percentage frequencies. Comparison of continuous data between samples was done using Mann-Whitney or Kruskal-Wallis test; comparison of paired continuous variables was performed with Wilcoxon signed-rank test. Comparison of categorical data was done using χ^2 or Fisher's exact test; paired categorical data was compared with McNemar test. Correlation between continuous variables was assessed with Spearman's correlation. Logistic regression was used to compare mortality in HFNO and NIV patients and to test the effects of different variables on mortality. Multivariable logistic regression analysis was used to adjust the odds of mortality in HFNO vs. NIV for relevant confounders. All statistical tests were two-sided. Significance level was set at $p<0.05$ and no imputation of missing data was necessary as there were no missing data for key variables. Analyses were done using R software version 4.0.5 and GraphPad Prism version 9.1.

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RESULTS

Among the 2385 patients with documented COVID-19 enrolled in the four studies, 184 receiving HFNO, and 131 receiving NIV had bilateral radiographic opacities consistent with ARDS, respiratory symptoms occurring/worsening <1 week from study admission, and PaO_2/FiO_2 ≤300. Remaining patients were excluded for the following reasons: respiratory symptoms for > 1 week (n=25); no bilateral opacities on chest X-ray (n=101); PaO_2/FiO_2 > 300 mmHg (n=28); treated with IMV since the onset of respiratory failure (n=971); received a combination of NIV/HFNO/CPAP at the onset of respiratory failure (n=553); received awake prone positioning (n=50); DNI/DNR order in place (n=239); incomplete records for the variables of interest (n=103) (**Figure 1**).

Table 1 presents relevant variables at study inclusion during HFNO/NIV. HFNO (flow 55 [50-60] L/min) was started 2 [1-3] days from hospital admission. NIV (pressure support level 10 [10-12] cmH_2O and PEEP 10 [10-12] cmH_2O) was started 2 [1-4] days from hospital admission. 112 (60.9%) HFNO patients, and 69 (47.6%) NIV patients were intubated and received mechanical ventilation for severe hypoxemia not responding to 1 [0-1] days and 1 [0-3] days of HFNO and NIV, respectively. Clinical and physiological variables in patients exclusively treated with HFNO or NIV and in patients transitioned from HFNO/NIV to IMV are reported in **Tables S1A and S1B** (*supplement*). Ventilatory settings post-intubation are reported in **Table S2** (*supplement*).

In patients who transitioned from HFNO to IMV, median PaO_2/FiO_2 increased from 100 [86-115] during HFNO to 152 [115-201] mmHg after initiation of IMV (p<0.0001) (**Figure 2**, *top*); 91 (81.3%) patients had an increase in PaO_2/FiO_2 and 21 (18.7%) had a decrease after IMV. In the subset who transitioned from NIV to IMV, median PaO_2/FiO_2 increased from 116 [91-154] to 137 [100-196] mmHg after initiation of IMV (p=0.0013)

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(**Figure 2**, *bottom*); 45 (65.2%) patients had an increase in PaO_2/FiO_2 and 24 (34.8%) had a decrease after IMV. Shortly after intubation, 92.9% (104/112) of patients who had PaO_2/FiO_2 ≤300 mmHg while on HFNO, and 95.7% (66/69) on NIV continued to have PaO_2/FiO_2 ≤300. The proportion of HFNO patients that lost ARDS criteria after intubation [7.1% (8/112)] was not different from the proportion of NIV patients that lost ARDS criteria after intubation [4.3% (3/69), p=0.5363].

Figure 3, *top* and **Figure S2**, *top* show severity categories during HFNO and shortly after institution of IMV. Three patients with "*mild"* ARDS pre-intubation continued to have "*mild"* ARDS after IMV. For "*moderate"* ARDS, ~10% lost ARDS criteria (PaO_2/FiO_2 >300 mmHg), ~20% had "*mild"* ARDS, ~60% had no change in severity, and ~10% had "*severe*" ARDS after IMV. For "*severe*" ARDS, ~20% maintained the same severity after IMV and ~60% had "*moderate*" ARDS; remaining patients lost PaO_2/FiO_2 criteria for ARDS or were classified as "*mild*" ARDS. In HFNO patients, ARDS severity decreased significantly after intubation (Wilcoxon's test=7.39, p<0.001). **Figure 3**, *bottom,* and **Figure S2**, *bottom* present patients classified by ARDS severity during NIV and shortly after institution of IMV. Among the 69 NIV patients, 66 patients (95.7%) continued to have PaO_2/FiO_2 ≤300 mmHg after intubation. There were only 4 patients with "*mild*" ARDS; of these, 2 remained "*mild*", and 2 had "*moderate*" ARDS after intubation. For "*moderate*" ARDS after IMV, ~60% maintained the same severity, ~5% lost criteria, ~20% had "*mild*" ARDS, and ~15% had "*severe*" ARDS. For NIV patients classified as "*severe*" ARDS, following intubation ~50% remained severe, ~30% had "*moderate*" ARDS, ~10% had "*mild*" ARDS and ~10% lost ARDS criteria. In NIV patients, ARDS severity decreased significantly after intubation (Wilcoxon's test=4.22, p=0.001).

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Figure 4 shows 28-day mortality in patients initially treated with HFNO (*left*) and NIV (*right*). Mortality in patients in patients treated with HFNO who were not intubated was 4.2% (3/72) while in patients transitioned from HFNO to IMV mortality was 28.6% (32/112) (p<0.001). Mortality in patients treated with NIV but not intubated was 1.6% (1/62) while in patients who transitioned from NIV to IMV mortality was 44.9% (31/69) (p<0.001). Overall mortality in patients initially treated with HFNO and NIV was 19.0% (35/184) and 24.4% (32/131), respectively (p=0.2479). **Table S3** (*supplement)* presents the comparison of mortality between HFNO and NIV patients using logistic regression, and multiple logistic regression analysis. Mortality was similar in the two groups in univariate analysis (HFNO vs. NIV OR=0.727, 95% CI 0.422-1.250) and after adjusting for covariates (OR=0.603, 95% CI 0.320-1.137).

The relationship between ARDS severity and mortality differed depending on whether patients were receiving HFNO or IMV is reported in **Table 2**. Patients treated with HFNO and classified after intubation as having severe ARDS had almost double the 28-day mortality of patients who had a PaO_2/FiO_2 ≤100 before intubation (~46.7% vs. ~26.7%, McNemar's test=31.3, p<0.001). This was not the case for patients with severe ARDS initially treated with NIV (McNemar's test=0.063, p=0.804).

Table 3 compares the 28-mortality between patients transitioned and not transitioned to IMV using different PaO_2/FiO_2 cutoff values. There was a significant difference between the two groups at each cutoff, except for PaO_2/FiO_2 ≤100. The percentage of patients who lost ARDS oxygenation criteria after IMV according to different PaO_2/FiO_2 cutoff values is presented in **Table S4** (*supplement)*.

The relationship between gas flow during HFNO and changes in PaO_2/FiO_2 following IMV was not significant (Spearman's rho=0.044, p=0.6520). Higher PEEP levels during NIV

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were associated with greater increases in PaO_2/FiO_2 following IMV (rho=0.361, p=0.004) (**Figure S1**, *supplement*). Changes in PaO_2/FiO_2 following IMV were unrelated to PEEP (during IMV) in patients treated initially with HFNO or with NIV (rho=0.097, p=0.33, and rho=0.03, p=0.8150, for HFNO and NIV groups, respectively) (**Figure S1** (*supplement)*).

DISCUSSION

In the present study we provide data to help address how, in COVID-19 patients with bilateral infiltrates consistent with ARDS treated with HFNO, the assessment of severity of hypoxemia based on PaO_2/FiO_2 may change after transition from HFNO to IMV. Our data provide some support that the hypoxemia criterion of ARDS based on PaO_2/FiO_2 can be applied to patients on HFNO in that only 7.1% of patients treated with HFNO lost ARDS criteria immediately after intubation. However, our data also show that ARDS severity categories changed substantially after intubation, and 28-day mortality in patients treated exclusively with HFNO was significantly lower than in patients who transitioned from HFNO to IMV (4.2% vs. 28.6%; p<0.001). Thus, allowing patients initially treated with HFNO to be categorized as having ARDS could lead to identification of patients with different outcomes than patients diagnosed while on invasive ventilation. This may have great implications for clinical trials.

To identify patients in the initial stages of acute lung injury, several studies have proposed to allow the diagnosis of ARDS in patients not receiving invasive mechanical ventilation (**6**). Coudroy and coworkers found that most patients with bilateral pulmonary infiltrates and $PaO_2/FiO_2 \leq 300$ mmHg under conventional oxygen therapy, still fulfilled ARDS criteria after NIV was initiated, with an overall mortality rate of 31% (**7**). Kangelaris and coworkers reported that mortality in patients meeting ARDS criteria (other than intubation)

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had a hospital mortality similar to ARDS patients that were intubated early (26 vs. 30 %, respectively) (**8**).

The Berlin definition states that patients being managed with non-invasive respiratory support can be diagnosed as having mild ARDS if their airway pressure is ≥5 cmH_2O ventilation and $300 \geq PaO_2/FiO_2 > 200$ mmHg (**5**). However, the definition is somewhat ambiguous with respect to other severity categories since there is no explicit guidance given. As such, Hernu and coworkers (**25**) interpreted the Berlin definition as not being able to classify patients on non-invasive support as having ARDS if their PaO_2/FiO_2 ratio was <200 mmHg (**5**). However, Bellani and coworkers (**26**) and Zhao and coworkers (**27**) categorized patients treated with non-invasive support using all levels of ARDS severity based on the PaO_2/FiO_2 ratio categories for invasively ventilated patients. For the purposes of this study, we compared the change in ARDS severity before-after intubation of our two cohorts (patients on HFNO and NIV) with the NIV patients reported by Bellani and coworkers (**26**) (Table S5, *supplement*). We found that our patients on NIV for COVID-19 ARDS behaved similarly to "conventional" ARDS patients after intubation (**26**).

There are several physiological mechanisms by which HFNO may improve outcomes: decreased dead space by washout of carbon dioxide, increased secretion clearance, decreased nasal resistance, decreased entrainment of ambient air and generating positive airway pressure similar to CPAP (**11,28**). Groves and colleagues demonstrated that in healthy subjects, HFNO flow rates of 40-60 L/min could pressurize the airways up to 5-7 cmH_2O (**29**). Papazian and colleagues reported values of end-expiratory pressure ≥5 cmH_2O with flow rates of 60 L/min (**12**). Parke and coworkers found that for every 10 L/min increase in flow, there was a ~0.7 cmH_2O increase in generated pressure (**30**). This increase in end-expiratory pressure during HFNO provides the physiological rationale underpinning the proposal that patients on HFNO

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with flows ≥30 L/min should be considered to have ARDS if they fulfill all Berlin criteria except PEEP ≥5 cmH_2O (**10**). Indeed, our data demonstrate that 93% of patients who fulfilled (non-intubation) ARDS criteria on HFNO at 40-60 L/min also fulfilled these criteria following intubation and ventilation.

In our study, the percentage of HFNO patients that lost ARDS criteria after intubation was similar to the percentage of NIV patients that lost ARDS criteria (7.1% versus 4.3%, p=0.5363). However, applying these criteria in HFNO patients may require the adoption of a different "conceptual model" of ARDS that includes much less severely ill patients since (*a*) many patients had a change in severity after transition from HFNO to IMV; for example, only 20% of patients with PaO_2/FiO_2 <100 during HFNO were classified as having "*severe*" ARDS after IMV; (*b*) mortality rate based on ARDS severity changed substantially depending on whether categorization was based on PaO_2/FiO_2 during HFNO or during IMV, and *(c)* mortality rate was substantially lower in HFNO patients who were not intubated compared to patients who were intubated. Of course, the latter observation is expected given that less sick patients would not need to be intubated, a finding that has been previously reported in COVID-19 patients (**31**). However, in the context of a clinical trial that enrolled patients based on PaO_2/FiO_2 while on HFNO or while on IMV, this could lead to recruitment of patients with substantially different mortality rates.

Although a comparison between HFNO and NIV was not the primary focus of our study, we examined the basic pathophysiological mechanisms underlying variations in PaO_2/FiO_2 after institution of IMV. We hypothesized that the higher the HFNO flow, the lower would be the difference in PaO_2/FiO_2 after intubation. Our findings did not confirm this hypothesis. This could be due to the fact that our sample was limited to a relatively narrow range of flow rates (40-60 L/min), and thus the "effective" PEEP on HFNO would have been

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similar at all the HFNO flow rates; or could be due to variability in PEEP, and hence in PaO_2, after intubation which was set "clinically". We did observe a positive association between PEEP on NIV and difference in PaO_2/FiO_2; this observation is perhaps counter intuitive. It is possible that PEEP level on NIV is more a marker of severity of respiratory failure and more severe patients may benefit more from the transition to IMV. Another possible explanation is that higher PEEP levels during NIV may be associated with higher leaks, making this mode of ventilation less effective compared to IMV.

Strengths of our study include its multicenter design and the fact that it selected patients who were exclusively treated with HFNO, (**19-22**) and were intubated without a NIV trial (**32**). However, there are several important limitations that should be taken into account in interpreting our results. *First*, there may be issues in generalizing our results. We included only patients with COVID-19 ARDS, and this could represent a problem in generalizing to ARDS from other causes. As well, all patients included in the comparison of PaO_2/FiO_2 before and after intubation transitioned to IMV because of respiratory worsening. As such, these patients represent the most severe patients. In addition, our sample may have intrinsic heterogeneity since it is a post-hoc analysis of data collected for observational (**20-22**) or interventional (**19**) studies. Some of the patients were treated outside ICUs (**20,21**) and patients in the trial by Grieco and coworkers were randomized to HFNO or NIV prior to requiring higher levels of respiratory support (**19**). This could have modified timing for intubation and/or mortality. However, our dataset (n=315 out of 2,385) only selected patients from the previous four studies for whom clinicians were committed to full support (**Figure 1**). Consistently, in Tonetti and coworkers' study, 28-day mortality of patients receiving non-invasive ventilatory support outside the ICU was not substantially different from the 28-day mortality observed in patients treated in the ICU (52.1 vs. 47.3 %; p=0.01) (**21**). *Second*, HFNO flow rates were in a relatively narrow range between 40 and 60 L/min and thus we cannot directly address whether patients

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treated with lower flow rates would have similar PaO_2/FiO_2 ratios pre- and post-intubation (**Figure 3**). *Third*, we had a relatively small sample size despite starting with a relatively large cohort. This meant we had very few patients with mild ARDS prior to intubation, so we cannot draw any definitive conclusion on this severity group. However, based on the moderate and severe patient data (~60 mmHg increases in PaO_2/FiO_2 after intubation), it is tempting to speculate that many patients diagnosed as mild ARDS on HFNO would not meet oxygenation criteria for ARDS after intubation.

In conclusion, our data suggest that categorizing hypoxemic patients with bilateral infiltrates who are treated with HFNO as having ARDS may permit identification of patients at an earlier stage of the natural history of acute lung injury both in the context of clinical trials and clinical management. However, this may select patients with lower mortality, and thus have important implications in terms of recruitment of patients into clinical trials.

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Table 1. Baseline characteristics of the patients included in the study.

	HFNO (n= 184)	**NIV (n=131)**	**p-value**
Male gender (n (%))	144 (78.3)	99 (75.6)	0.5755
Age (years)	63 (54-71)	67 (59-73)	0.0122
Weight (kg)	80 (74-90)	80 (75-90)	0.7456
Height (cm)	174 (168-179)	172 (170-177)	0.8128
BMI (kg/m^2)	27.4 (24.7-30.9)	27.5 (25.5-29.8)	0.8938
SOFA score	3 (2-4)	2 (2-3)	0.0009
Time from hospital admission to HFNO/NIV start (days)	2 (1-3)	2 (1-4)	0.4604
HFNO Flow (l/min)	55 (50-60)	--	--
NIV PEEP (cmH_2O)	--	10 (10-12)	--
NIV Pressure Support (cmH_2O)	--	10 (10-12)	--
PaO_2 (mmHg)	79 (68-89)	79 (69-92)	0.1728
FiO_2 (%)	60 (60-60)	60 (50-70)	0.8422
PaO_2/FiO_2 ratio (mmHg)	128 (107-163)	147 (121-178)	0.0021
$PaCO_2$	35 (33-37)	35 (31-39)	0.8265
pH (units)	7.46 (7.44-7.48)	7.45 (7.43-7.48)	0.1320

Data are median (interquartile range). Definitions of abbreviations. BMI: body mass index; SOFA: sequential organ failure assessment; HFNO: high flow nasal oxygen; NIV: non-invasive ventilation; PaO_2: partial pressure of arterial oxygen; FiO_2: inspiratory oxygen fraction; $PaCO_2$: partial pressure of arterial carbon dioxide.

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Table 2. 28-day mortality according to severity before and after IMV

A. 28-day mortality in the HFNO group				
	Mild	Moderate	Severe	p-value
Severity based on blood gas during first 12 hours on HFNO	7.7% (1/13)	19.3% (27/140)	22.6% (7/31)	0.327
Severity based on last HFNO blood gas prior to IMV	0.0% (0/3)	32.7% (16/49)	26.7% (16/60)	0.768
Severity based on first blood gas on IMV	25.0% (5/20)	29.0% (20/69)	46.7% (7/15)	0.202

B. 28-day mortality in the NIV group				
	Mild	Moderate	Severe	p-value
Severity based on blood gas during first 12 hours on NIV	10.5% (2/19)	21.2% (21/92)	45.0% (9/20)	0.012
Severity based on last NIV blood gas prior to IMV	25.0% (1/4)	48.8% (21/43)	40.9% (9/22)	0.887
Severity based on first blood gas on IMV	46.2% (6/13)	48.6% (17/35)	38.9% (7/18)	0.634

Definitions of abbreviations. HFNO: high flow nasal oxygen; IMV: invasive mechanical ventilation; NIV: non-invasive ventilation.

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Table 3. 28-day mortality according to different PaO_2/FiO_2 cut-offs

	Exclusively treated with HFNO	Transitioned from HFNO to IMV	P for Fisher's exact test	Exclusively treated with NIV	Transitioned from NIV to IMV	P for Fisher's exact test
Blood gas within first 12 hours of HFNO or NIV						
$PaO_2/FiO_2 \leq 300$	3/72 (4.2%)	32/112 (28.6%)	<0.0001	1/62 (1.6%)	31/69 (44.9%)	<0.0001
$PaO_2/FiO_2 \leq 250$	3/71 (4.2%)	31/111 (27.9%)	<0.0001	1/59 (1.7%)	31/65 (47.7%)	<0.0001
$PaO_2/FiO_2 \leq 200$	3/64 (4.7%)	31/107 (29.0%)	<0.0001	1/53 (1.9%)	29/59 (49.2%)	<0.0001
$PaO_2/FiO_2 \leq 150$	2/41 (4.9%)	26/84 (31.0%)	0.001	1/31 (3.2%)	20/40 (50.0%)	<0.0001
$PaO_2/FiO_2 \leq 100$	0/4 (0.0%)	7/27 (25.9%)	0.55	0/4 (0.0%)	9/16 (56.3%)	0.0941

Definitions of abbreviations. IMV: invasive mechanical ventilation; HFNO: high flow nasal oxygen; NIV: non-invasive ventilation; PaO_2: partial pressure of arterial oxygen; FiO_2: inspiratory oxygen fraction.

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FIGURE LEGENDS

Figure 1. Flow-chart of the study. Definition of abbreviations. HFNO: high flow nasal oxygen; NIV: non-invasive ventilation; IMV: invasive mechanical ventilation; PaO_2: partial pressure of arterial oxygen; FiO_2: inspiratory oxygen fraction; ARF: acute respiratory failure; DNI/DNR: "do not intubate/do not resuscitate" order.

Figure 2. Values of PaO_2/FiO_2 ratio before and after intubation in patients treated with HFNO (*top*) and with NIV (*bottom*). Horizontal solid lines indicate median values of PaO_2/FiO_2. Horizontal dotted line indicates the cut off value of PaO_2/FiO_2 ($\leq$300) below which patients are classified as having ARDS. Definition of abbreviations. HFNO: high flow nasal oxygen; NIV: non-invasive ventilation; PaO_2: partial pressure of arterial oxygen; FiO_2: inspiratory oxygen fraction. **** $p<0.0001$; ** $p=0.0013$.

Figure 3. Percentage distribution in the different severity classes before and after institution of IMV for HFNO patients (*top*) and NIV patients (*bottom*). See text for more details.

Figure 4. Mortality at 28-day in the HFNO (*left*) and NIV (*right*) groups. Mortality in patients in patients treated with HFNO who were not intubated was 4.2% (3/72) while in patients transitioned from HFNO to IMV mortality was 28.6% (32/112) ($p<0.001$). Mortality in patients treated with NIV but not intubated was 1.6% (1/62) while in patients who transitioned from NIV to IMV mortality was 44.9% (31/69) ($p<0.001$). Overall mortality in patients initially treated with HFNO and NIV was 19.0% (35/184) and 24.4% (32/131), respectively ($p=0.2479$).

AJRCCM Articles in Press. Published December 03, 2021 as 10.1164/rccm.202109-2163OC

REFERENCES

1. Thompson BT, Chambers RC, Liu KD. Acute Respiratory Distress Syndrome. *N Engl J Med* 2017; 377: 562-572.

2. Rubenfeld GD. Epidemiology of acute lung injury. *Crit Care Med* 2003; 31: S276-284.

3. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet* 1967; 2: 319-323.

4. Villar J, Blanco J, Kacmarek RM. Acute respiratory distress syndrome definition: do we need a change? *Curr Opin Crit Care* 2011; 17: 13-17.

5. Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012; 307: 2526-2533.

6. Levitt JE, Bedi H, Calfee CS, Gould MK, Matthay MA. Identification of early acute lung injury at initial evaluation in an acute care setting prior to the onset of respiratory failure. *Chest* 2009; 135: 936-943.

7. Coudroy R, Frat JP, Boissier F, Contou D, Robert R, Thille AW. Early Identification of Acute Respiratory Distress Syndrome in the Absence of Positive Pressure Ventilation: Implications for Revision of the Berlin Criteria for Acute Respiratory Distress Syndrome. *Crit Care Med* 2018; 46: 540-546.

8. Kangelaris KN, Ware LB, Wang CY, Janz DR, Zhuo H, Matthay MA, Calfee CS. Timing of Intubation and Clinical Outcomes in Adults With Acute Respiratory Distress Syndrome. *Crit Care Med* 2016; 44: 120-129.

AJRCCM Articles in Press. Published December 03, 2021 as 10.1164/rccm.202109-2163OC

9. Ranieri VM, Rubenfeld GD, Thompson BT. Defining ARDS: do we need a mandatory waiting period? *Intensive Care Med* 2013; 39: 775-778.

10. Matthay MA, Thompson BT, Ware LB. The Berlin definition of acute respiratory distress syndrome: should patients receiving high-flow nasal oxygen be included? *Lancet Respir Med* 2021;9(8):933-936.

11. Rochwerg B, Einav S, Chaudhuri D, Mancebo J, Mauri T, Helviz Y, Goligher EC, Jaber S, Ricard JD, Rittayamai N, Roca O, Antonelli M, Maggiore SM, Demoule A, Hodgson CL, Mercat A, Wilcox ME, Granton D, Wang D, Azoulay E, Ouanes-Besbes L, Cinnella G, Rauseo M, Carvalho C, Dessap-Mekontso A, Fraser J, Frat JP, Gomersall C, Grasselli G, Hernandez G, Jog S, Pesenti A, Riviello ED, Slutsky AS, Stapleton RD, Talmor D, Thille AW, Brochard L, Burns KEA. The role for high flow nasal cannula as a respiratory support strategy in adults: a clinical practice guideline. *Intensive Care Med* 2020; 46: 2226-2237.

12. Papazian L, Corley A, Hess D, Fraser JF, Frat JP, Guitton C, Jaber S, Maggiore SM, Nava S, Rello J, Ricard JD, Stephan F, Trisolini R, Azoulay E. Use of high-flow nasal cannula oxygenation in ICU adults: a narrative review. *Intensive Care Med* 2016; 42: 1336-1349.

13. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, Prat G, Boulain T, Morawiec E, Cottereau A, Devaquet J, Nseir S, Razazi K, Mira JP, Argaud L, Chakarian JC, Ricard JD, Wittebole X, Chevalier S, Herbland A, Fartoukh M, Constantin JM, Tonnelier JM, Pierrot M, Mathonnet A, Beduneau G, Deletage-Metreau C, Richard JC, Brochard L, Robert R, Group FS, Network R. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015; 372: 2185-2196.

AJRCCM Articles in Press. Published December 03, 2021 as 10.1164/rccm.202109-2163OC

14. Hernandez G, Vaquero C, Gonzalez P, Subira C, Frutos-Vivar F, Rialp G, Laborda C, Colinas L, Cuena R, Fernandez R. Effect of Postextubation High-Flow Nasal Cannula vs Conventional Oxygen Therapy on Reintubation in Low-Risk Patients: A Randomized Clinical Trial. *JAMA* 2016; 315: 1354-1361.

15. Demoule A, Vieillard Baron A, Darmon M, Beurton A, Geri G, Voiriot G, Dupont T, Zafrani L, Girodias L, Labbe V, Dres M, Fartoukh M, Azoulay E. High-Flow Nasal Cannula in Critically III Patients with Severe COVID-19. *Am J Respir Crit Care Med* 2020; 202: 1039-1042.

16. Mellado-Artigas R, Ferreyro BL, Angriman F, Hernandez-Sanz M, Arruti E, Torres A, Villar J, Brochard L, Ferrando C, Network C-SI. High-flow nasal oxygen in patients with COVID-19-associated acute respiratory failure. *Crit Care* 2021; 25: 58.

17. Chertoff J. High-Flow Oxygen, Positive End-Expiratory Pressure, and the Berlin Definition of Acute Respiratory Distress Syndrome: Are They Mutually Exclusive? *Am J Respir Crit Care Med* 2017; 196: 396-397.

18. Riviello ED, Kiviri W, Twagirumugabe T, Mueller A, Banner-Goodspeed VM, Officer L, Novack V, Mutumwinka M, Talmor DS, Fowler RA. Hospital Incidence and Outcomes of the Acute Respiratory Distress Syndrome Using the Kigali Modification of the Berlin Definition. *Am J Respir Crit Care Med* 2016; 193: 52-59.

19. Grieco DL, Menga LS, Cesarano M, Rosa T, Spadaro S, Bitondo MM, Montomoli J, Falo G, Tonetti T, Cutuli SL, Pintaudi G, Tanzarella ES, Piervincenzi E, Bongiovanni F, Dell'Anna AM, Delle Cese L, Berardi C, Carelli S, Bocci MG, Montini L, Bello G, Natalini D, De Pascale G, Velardo M, Volta CA, Ranieri VM, Conti G, Maggiore SM, Antonelli M, Group C-IGS. Effect of Helmet Noninvasive Ventilation vs High-Flow

AJRCCM Articles in Press. Published December 03, 2021 as 10.1164/rccm.202109-2163OC

Nasal Oxygen on Days Free of Respiratory Support in Patients With COVID-19 and Moderate to Severe Hypoxemic Respiratory Failure: The HENIVOT Randomized Clinical Trial. *JAMA* 2021; 325: 1731-1743.

20. Franco C, Facciolongo N, Tonelli R, Dongilli R, Vianello A, Pisani L, Scala R, Malerba M, Carlucci A, Negri EA, Spoladore G, Arcaro G, Tillio PA, Lastoria C, Schifino G, Tabbi L, Guidelli L, Guaraldi G, Ranieri VM, Clini E, Nava S. Feasibility and clinical impact of out-of-ICU noninvasive respiratory support in patients with COVID-19-related pneumonia. *Eur Respir J* 2020; 56.

21. Tonetti T, Grasselli G, Zanella A, Pizzilli G, Fumagalli R, Piva S, Lorini L, Iotti G, Foti G, Colombo S, Vivona L, Rossi S, Girardis M, Agnoletti V, Campagna A, Gordini G, Navalesi P, Boscolo A, Graziano A, Valeri I, Vianello A, Cereda D, Filippini C, Cecconi M, Locatelli F, Bartoletti M, Giannella M, Viale P, Antonelli M, Nava S, Pesenti A, Ranieri VM, Network C-NII. Use of critical care resources during the first 2 weeks (February 24-March 8, 2020) of the Covid-19 outbreak in Italy. *Ann Intensive Care* 2020; 10: 133.

22. Boscolo A, Sella N, Lorenzoni G, Pettenuzzo T, Pasin L, Pretto C, Tocco M, Tamburini E, De Cassai A, Rosi P, Polati E, Donadello K, Gottin L, De Rosa S, Baratto F, Toffoletto F, Ranieri VM, Gregori D, Navalesi P, Network C-VI. Static compliance and driving pressure are associated with ICU mortality in intubated COVID-19 ARDS. *Crit Care* 2021; 25: 263.

23. Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, Brochard L, Brower R, Esteban A, Gattinoni L, Rhodes A, Slutsky AS, Vincent JL, Rubenfeld GD, Thompson BT, Ranieri VM. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med* 2012; 38: 1573-1582.

AJRCCM Articles in Press. Published December 03, 2021 as 10.1164/rccm.202109-2163OC

24. Maiolo G, Collino F, Vasques F, Rapetti F, Tonetti T, Romitti F, Cressoni M, Chiumello D, Moerer O, Herrmann P, Friede T, Quintel M, Gattinoni L. Reclassifying Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med* 2018; 197: 1586-1595.

25. Hernu R, Wallet F, Thiolliere F, Martin O, Richard JC, Schmitt Z, Wallon G, Delannoy B, Rimmele T, Demaret C, Magnin C, Vallin H, Lepape A, Baboi L, Argaud L, Piriou V, Allaouchiche B, Aubrun F, Bastien O, Lehot JJ, Ayzac L, Guerin C. An attempt to validate the modification of the American-European consensus definition of acute lung injury/acute respiratory distress syndrome by the Berlin definition in a university hospital. *Intensive Care Med* 2013; 39: 2161-2170.

26. Bellani G, Laffey JG, Pham T, Madotto F, Fan E, Brochard L, Esteban A, Gattinoni L, Bumbasirevic V, Piquilloud L, van Haren F, Larsson A, McAuley DF, Bauer PR, Arabi YM, Ranieri M, Antonelli M, Rubenfeld GD, Thompson BT, Wrigge H, Slutsky AS, Pesenti A, Investigators LS, Group ET. Noninvasive Ventilation of Patients with Acute Respiratory Distress Syndrome. Insights from the LUNG SAFE Study. *Am J Respir Crit Care Med* 2017; 195: 67-77.

27. Zhao X, Huang W, Li J, Liu Y, Wan M, Xue G, Zhu S, Guo H, Xia Q, Tang W. Noninvasive Positive-Pressure Ventilation in Acute Respiratory Distress Syndrome in Patients With Acute Pancreatitis: A Retrospective Cohort Study. *Pancreas* 2016; 45: 58-63.

28. Goligher EC, Slutsky AS. Not Just Oxygen? Mechanisms of Benefit from High-Flow Nasal Cannula in Hypoxemic Respiratory Failure. *Am J Respir Crit Care Med* 2017; 195: 1128-1131.

AJRCCM Articles in Press. Published December 03, 2021 as 10.1164/rccm.202109-2163OC

29. Groves N, Tobin A. High flow nasal oxygen generates positive airway pressure in adult volunteers. *Aust Crit Care* 2007; 20: 126-131.

30. Parke RL, Eccleston ML, McGuinness SP. The effects of flow on airway pressure during nasal high-flow oxygen therapy. *Respir Care* 2011; 56: 1151-1155.

31. Calligaro GL, Lalla U, Audley G, Gina P, Miller MG, Mendelson M, Dlamini S, Wasserman S, Meintjes G, Peter J, Levin D, Dave JA, Ntusi N, Meier S, Little F, Moodley DL, Louw EH, Nortje A, Parker A, Taljaard JJ, Allwood BW, Dheda K, Koegelenberg CFN. The utility of high-flow nasal oxygen for severe COVID-19 pneumonia in a resource-constrained setting: A multi-centre prospective observational study. *EClinicalMedicine* 2020; 28: 100570.

32. Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342: 1301-1308.

AJRCCM Articles in Press. Published December 03, 2021 as 10.1164/rccm.202109-2163OC

Figure 1

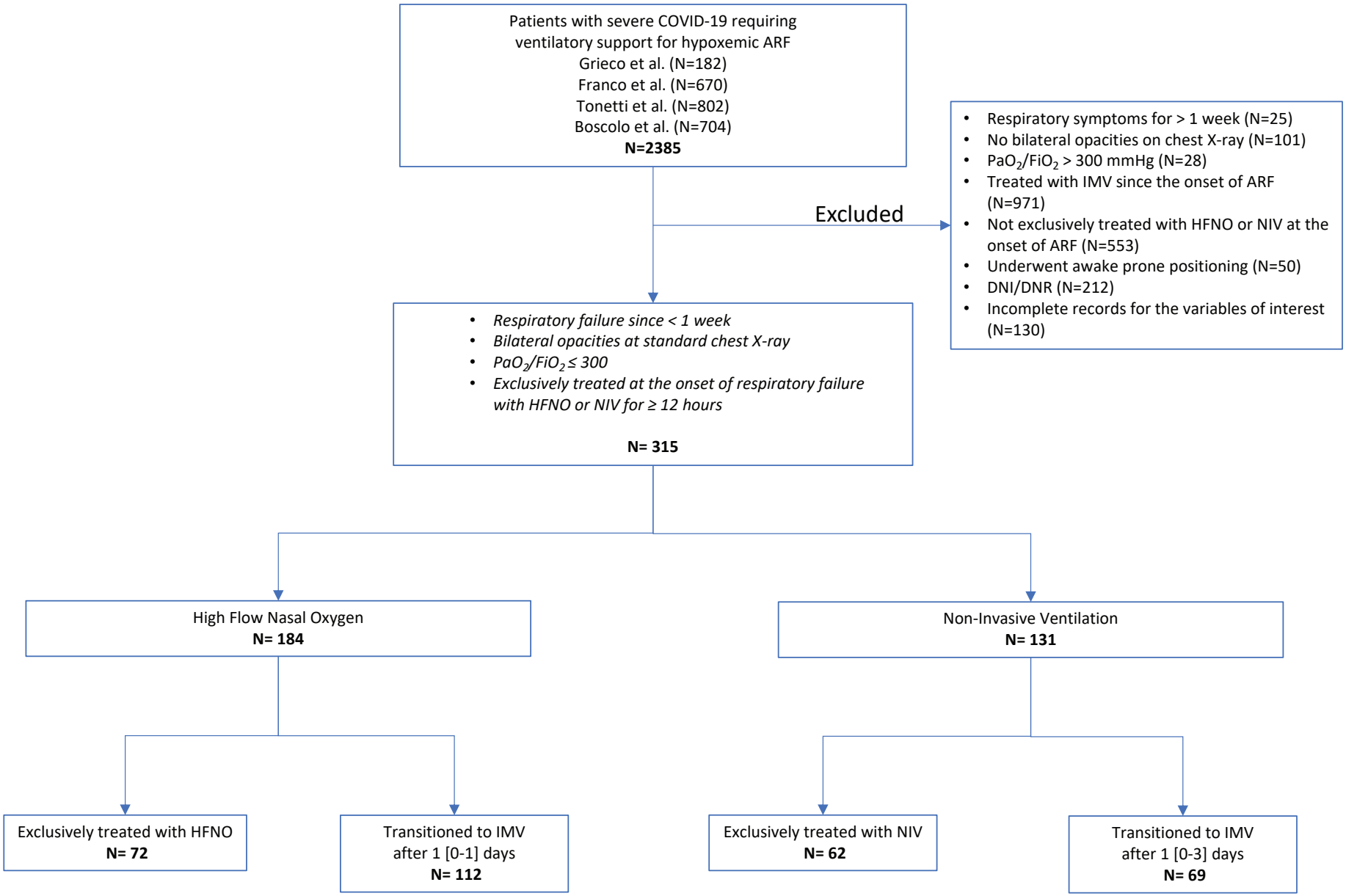

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Figure 2

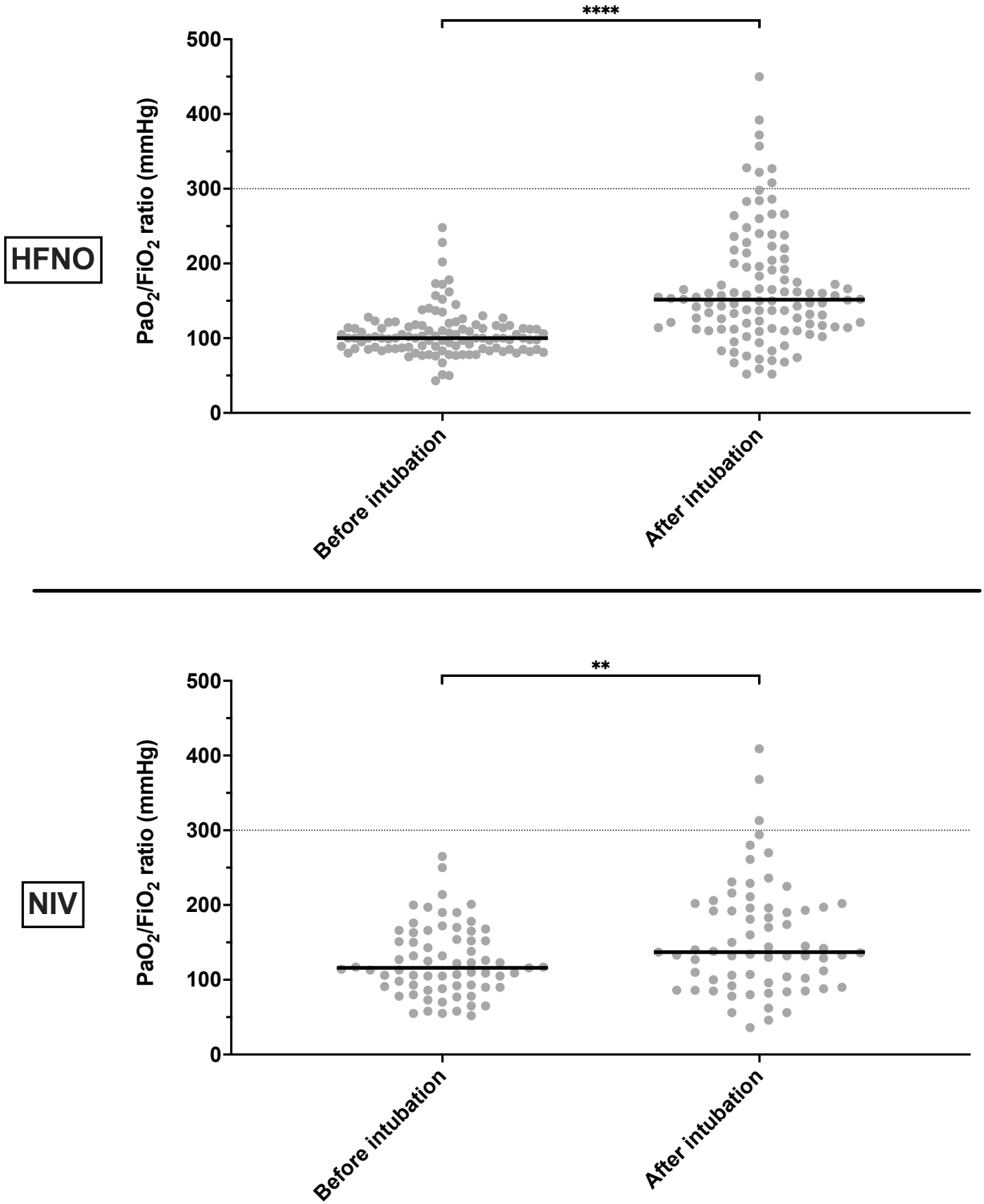

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Figure 3

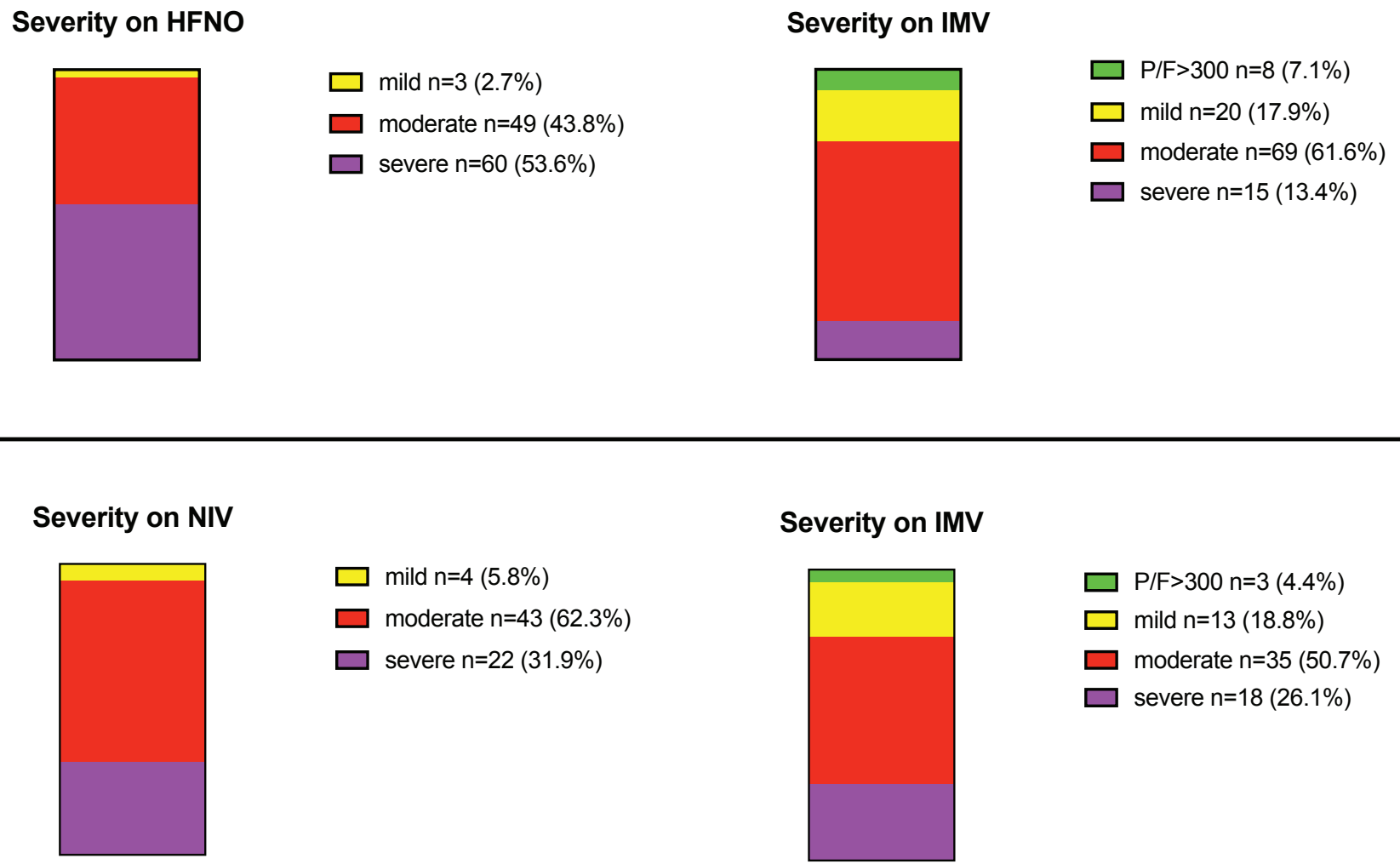

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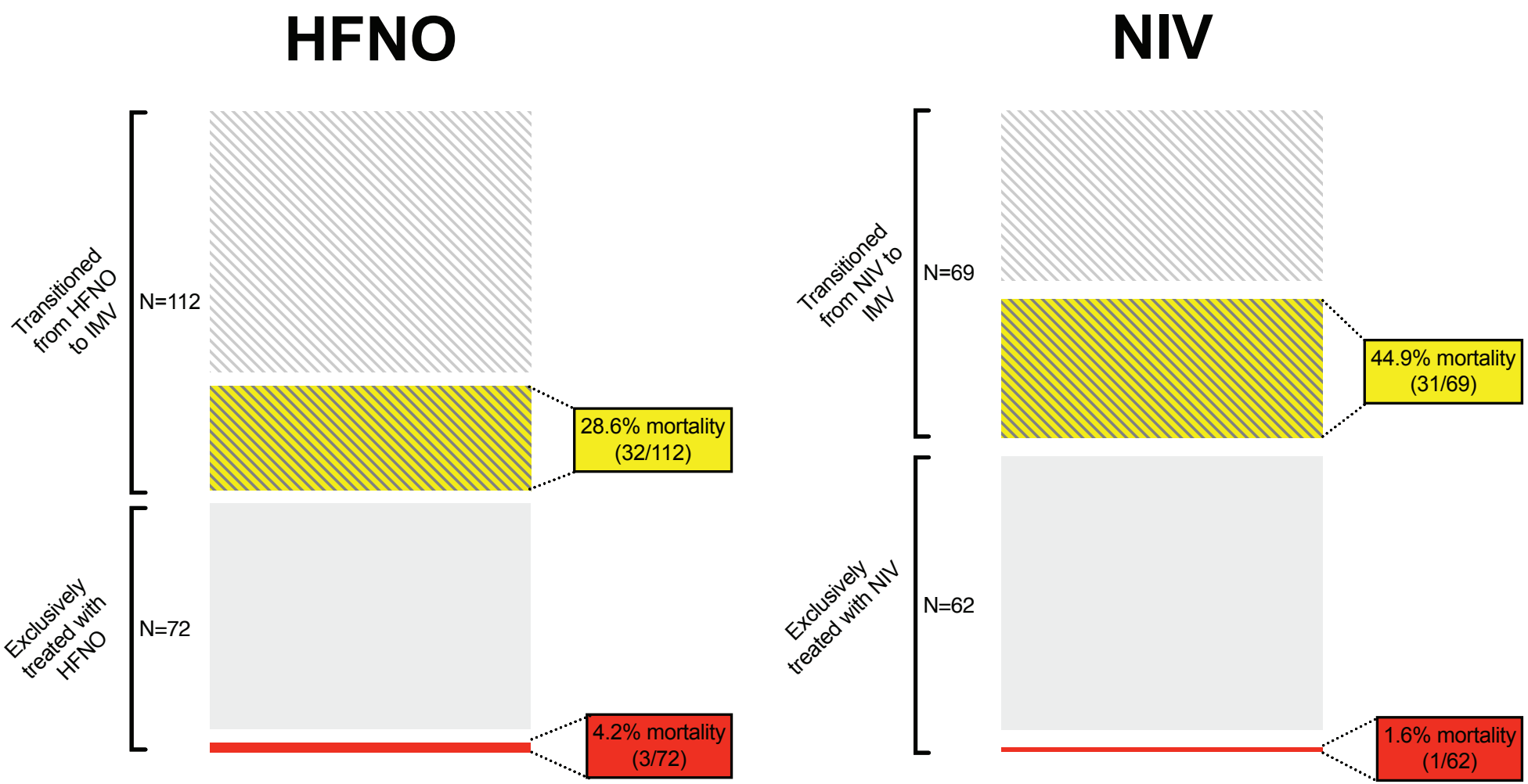
Figure 4



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High Flow Nasal Oxygen for Severe Hypoxemia: Oxygenation Response and Outcome in COVID-19 Patients

V. Marco Ranieri, Tommaso Tonetti, Paolo Navalesi, Stefano Nava, Massimo Antonelli, Antonio Pesenti, Giacomo Grasselli, Domenico Luca Grieco, Luca Salvatore Menga, Lara Pisani, Annalisa Boscolo, Nicolò Sella, Laura Pasin, Chiara Mega, Giacinto Pizzilli, Alessio Dell'Olio, Roberto Dongilli, Paola Rucci, Arthur S. Slutsky

ONLINE SUPPLEMENT

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SUPPLEMENTARY METHODS

Criteria for patients' eligibility in the four studies used to create the current investigation database.

- Grieco DL et al.[1]: eligibility inclusion criteria were assessed within the first 24 hours from intensive care unit admission, while patients were receiving oxygen through a Venturi mask, and enrolled if all of the following were met: PaO_2/FIO_2 equal to or below 200, $PaCO_2$ equal to or lower than 45 mm Hg, absence of history of chronic respiratory failure or moderate to severe cardiac insufficiency (New York Heart Association class >II or left ventricular ejection fraction <50%), confirmed molecular diagnosis of COVID-19, and written informed consent. Prospective multi-center randomized trial that enrolled 182 patients in 4 ICUs in Italy to compare NIV to HFNO

- Franco C et al.[2]: patients were included if they matched the last two of four categories of the severity score for triage developed by the Italian Respiratory joint Societies: SaO_2 <94%, RR >20 breaths·min^{-1} but poor response to oxygen 10–15 L·min^{-1} and requiring CPAP/NIV with high FiO_2; SaO_2 <94%, RR >20 breaths·min^{-1} but poor response to oxygen 10–15 L·min^{-1}, CPAP/NIV with high FiO_2 or presenting respiratory distress with PaO_2/FiO_2 <200 and requiring endotracheal intubation. Multi-center

[1] Grieco DL, Menga LS, Cesarano M, et al. Effect of Helmet Noninvasive Ventilation vs High-Flow Nasal Oxygen on Days Free of Respiratory Support in Patients With COVID-19 and Moderate to Severe Hypoxemic Respiratory Failure: The HENIVOT Randomized Clinical Trial. *JAMA*. 2021;325(17):1731-1743. doi:10.1001/jama.2021.4682.

[2] Franco C, Facciolongo N, Tonelli R, et al. Feasibility and clinical impact of out-of-ICU noninvasive respiratory support in patients with COVID-19-related pneumonia. *Eur Respir J*. 2020;56(5):2002130. doi:10.1183/13993003.02130-2020.

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observational studies performed in medical wards, emergency departments and ICUs on the Emilia-Romagna ICU network that included 670 patients.

- Tonetti T et al.[3]: the study enrolled consecutive critically ill patients with confirmed Covid-19 that underwent evaluation by a senior intensivist. Multi-center observational study performed in the medical wards, emergency departments and ICUs of the Regione Veneto, Regione Lombardia and Regione Emilia-Romagna, all in Italy that included 802 patients (542 in the ICU and 260 outside the ICU).

- Boscolo A et al.[4]: patients were included if they showed confirmed SARS-CoV-2 infection and fulfilled the Berlin criteria of ARDS criteria (all in the ICU). Multi-center observational study performed in the ICUs of the Regione-Veneto, Italy that included 704 consecutive adult patients (Figure 1 in reference 4)

[3] Tonetti T, Grasselli G, Zanella A, et al. Use of critical care resources during the first 2 weeks (February 24-March 8, 2020) of the Covid-19 outbreak in Italy. *Ann Intensive Care*. 2020;10(1):133. doi:10.1186/s13613-020-00750-z.

[4] Boscolo A, Pasin L, Sella N, et al. Outcomes of COVID-19 patients intubated after failure of non-invasive ventilation: a multicenter observational study. *Sci Rep*. 2021;11(1):17730. doi: 10.1038/s41598-021-96762-1.

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SUPPLEMENTARY TABLES

Table S1A. Clinical and physiological variables (measured within 12 hours of HFNO institution) in patients exclusively treated with HFNO and in patients who were transitioned from HFNO to IMV

	Exclusively treated with HFNO (n=72)	Transitioned from HFNO to IMV (n=112)	p-value
Demographics			
Male gender (n (%))	56 (77.8)	88 (78.6)	0.8986
Age (years)	60 (49-69)	65 (56-72)	0.0276
Weight (kg)	80 (75-88)	80 (73-91)	0.5196
Height (cm)	172 (168-176)	175 (168-180)	0.4232
BMI (kg/m^2)	27.0 (24.8-29.4)	27.7 (24.7-30.9)	0.6724
SOFA score	2 (2-3)	4 (3-5)	<0.0001
Variables at HFNO start			
Time from hospital admission to HFNO start (days)	3 (2-5)	1 (0-2)	<0.0001
Flow (l/min)	60 (55-60)	50 (40-60)	<0.0001
PaO_2 (mmHg)	84 (73-92)	76 (61-88)	0.0006
FiO_2 (%)	60 (50-60)	60 (60-70)	<0.0001
PaO_2/FiO_2 ratio (mmHg)	141 (121-169)	119 (102-150)	0.0002
$PaCO_2$	35 (33-37)	34 (33-36)	0.4569
pH (units)	7.46 (7.44-7.47)	7.46 (7.45-7.49)	0.1875
ARDS criteria (n (%)) Mild Moderate Severe	72 (100) 8 (11.1) 60 (83.3) 4 (5.6)	112 (100) 5 (4.5) 80 (71.4) 27 (24.1)	0.0019

Data are reported as median (interquartile range) or n (%). Definitions of abbreviations. IMV: invasive mechanical ventilation; BMI: body mass index; HFNO: high flow nasal oxygen; PaO_2: partial pressure of arterial oxygen; FiO2: inspiratory oxygen fraction; $PaCO_2$: partial pressure of arterial carbon dioxide; ARDS: Acute Respiratory Distress Syndrome.

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Table S1B. Clinical and physiological variables (measured within 12 hours of NIV institution) in patients exclusively treated with NIV and in patients who were transitioned from NIV to IMV

	Exclusively treated with NIV (n=62)	Transitioned from NIV to IMV (n=69)	p-value
Demographics			
Male gender (n (%))	46 (74.2)	53 (76.8)	0.7277
Age (years)	65 (56-73)	68 (62-73)	0.0489
Weight (kg)	80 (75-90)	80 (79-90)	0.5779
Height (cm)	174 (165-180)	170 (170-175)	0.6461
BMI (kg/m^2)	26.3 (25.4-30.1)	27.7 (26.0-29.5)	0.5032
SOFA score	2 (2-3)	3 (2-3)	0.3156
Variables at NIV start			
Time from hospital admission to NIV start (days)	2 (1-4)	2 (0-3)	0.1915
PEEP (cmH_2O)	10 (10-12)	10 (10-12)	0.8661
Inspiratory Pressure (cmH_2O)	10 (10-12)	12 (10-12)	0.1562
PaO_2 (mmHg)	86 (74-94)	77 (63-91)	0.0307
FiO_2 (%)	60 (50-60)	70 (60-80)	<0.0001
PaO_2/FiO_2 ratio (mmHg)	151 (135-181)	136 (104-176)	0.0240
$PaCO_2$	35 (32-39)	33 (29-39)	0.0818
pH (units)	7.45 (7.43-7.48)	7.46 (7.42-7.48)	0.9092
ARDS criteria (n (%)) Mild Moderate Severe	62 (100) 9 (14.5) 49 (79.0) 4 (6.5)	69 (100) 10 (14.5) 43 (62.3) 16 (23.2)	0.0261

Data are reported as median (interquartile range) or n (%). Definitions of abbreviations. IMV: invasive mechanical ventilation; BMI: body mass index; NIV: non-invasive ventilation; PEEP: positive-end expiratory pressure; PaO_2: partial pressure of arterial oxygen; FiO_2: inspiratory oxygen fraction; $PaCO_2$: partial pressure of arterial carbon dioxide; ARDS: Acute Respiratory Distress Syndrome.

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Table S2. Respiratory variables on IMV in the patients that were transitioned from HFNO or NIV to IMV.

	HFNO (n=112)	**NIV (n=69)**	**p-value**
Time from HFNO or NIV to IMV (days)	1 (0-1)	1 (0-3)	0.0513
PaO_2 (mmHg)	95 (76-118)	86 (69-104)	0.0443
FiO_2 (%)	60 (60-75)	65 (50-80)	0.7597
PaO_2/FiO_2 ratio (mmHg)	152 (115-201)	137 (100-196)	0.2391
$PaCO_2$ (mmHg)	44 (39-50)	45 (40-56)	0.1179
pH (units)	7.39 (7.33-7.41)	7.35 (7.30-7.43)	0.6256
Respiratory rate (bpm)	20 (16-25)	24 (18-26)	0.0420
Tidal volume (mL/Kg PBW)	6.4 (5.8-7.1)	6.4 (5.7-6.8)	0.2242
PEEP (cmH_2O)	12 (10-14)	12 (10-15)	0.9384
Plateau pressure (cmH_2O)	22 (20-26)	23 (21-26)	0.4045
Driving Pressure (cmH_2O)	10 (9-13)	11 (9-13)	0.3699
Static compliance (mL/cmH_2O)	43 (36-49)	40 (34-47)	0.2151

Data are reported as median (interquartile range). Definitions of abbreviations. IMV: invasive mechanical ventilation; HFNO: high flow nasal oxygen; NIV: non-invasive ventilation; PaO_2: partial pressure of arterial oxygen; FiO_2: inspiratory oxygen fraction; $PaCO_2$: partial pressure of arterial carbon dioxide.

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Table S3. Multiple logistic regression analysis for 28-day mortality

	OR	95% CI for OR		p
		lower	Upper	
HFNO vs. NIV	0.603	0.320	1.137	0.118
Need for IMV	15.653	5.407	45.313	<0.001
Sex (female vs. male)	0.899	0.429	1.882	0.777
Age	1.059	1.025	1.096	0.001
PaO_2/FiO_2 ratio during first 12 hours of HFNO or NIV	0.994	0.987	1.001	0.086
Constant	0.002			<0.001

Definitions of abbreviations. IMV: invasive mechanical ventilation; HFNO: high flow nasal oxygen; NIV: non-invasive ventilation; PaO_2: partial pressure of arterial oxygen; FiO_2: inspiratory oxygen fraction.

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Table S4. Number (percentage) of patients losing ARDS criteria after transitioning from non-invasive ventilatory support (HFNO or NIV) to IMV, at different PaO_2/FiO_2 cut-offs.		
	Transitioned from HFNO to IMV	Transitioned from NIV to IMV
Blood gas before intubation (mmHg)		
$PaO_2/FiO_2 \leq 300$	8/112 (7.1%)	3/69 (4.3%)
$PaO_2/FiO_2 \leq 250$	8/112 (7.1%)	3/68 (4.4%)
$PaO_2/FiO_2 \leq 200$	8/109 (7.3%)	3/65 (4.6%)
$PaO_2/FiO_2 \leq 150$	8/103 (7.8%)	3/48 (6.3%)
$PaO_2/FiO_2 \leq 100$	4/60 (6.7%)	2/22 (9.1%)
"Losing criteria for ARDS" indicates a PaO_2/FiO_2 ratio >300 mmHg after institution of IMV.		

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Table S5. ARDS category after intubation			
	NIV LUNG-SAFE (N=113) [5]	NIV present study (N=69)	HFNO present study (N=112)
Better, n (%)	40 (35.4)	21 (30.4)	62 (55.4) *
Same, n (%)	55 (48.7)	39 (56.5)	45 (40.2)
Worse, n (%)	18 (15.9)	9 (13.0)	5 (4.5) †

Note: category "unknown" was excluded from the analysis.

Overall χ^2-test comparing NIV with LUNG-SAFE: $\chi^2=1.07$, $p=0.587$
Overall χ^2-test comparing HFNO with LUNG-SAFE: $\chi^2=13.09$, $p<0.001$

* post-hoc comparison: $p<0.01$ vs LUNG-SAFE
† post-hoc comparison: $p<0.05$ vs LUNG-SAFE

Definition of abbreviations: NIV: non-invasive ventilation; HFNO: high flow nasal oxygen.

[5] Bellani G, Laffey JG, Pham T, et al. Noninvasive Ventilation of Patients with Acute Respiratory Distress Syndrome. Insights from the LUNG SAFE Study. *Am J Respir Crit Care Med*. 2017;195(1):67-77. doi:10.1164/rccm.201606-1306OC.

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SUPPLEMENTARY FIGURES

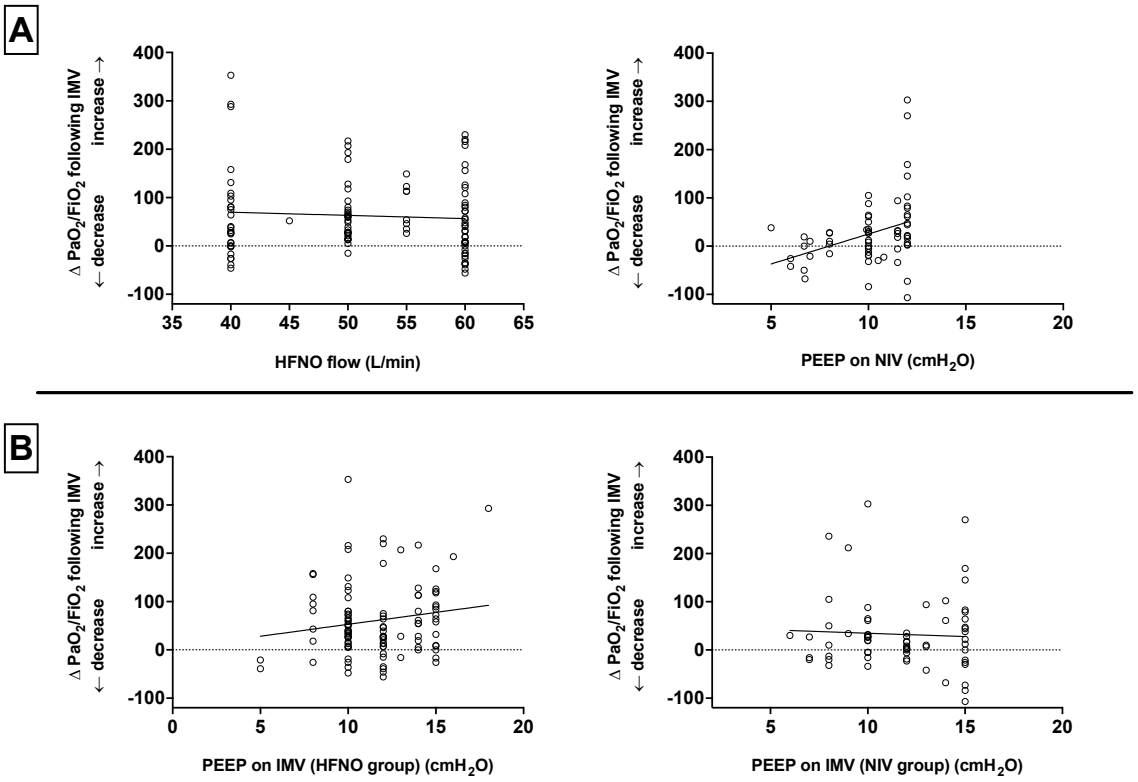

Figure S1. Panel A: Relationship between absolute changes in PaO_2/FiO_2 ratio following institution of IMV (post- minus pre-intubation values) versus the level of HFNO gas flow before intubation (left); and versus PEEP levels while on NIV (right). **Panel B:** Relationship between absolute changes in PaO_2/FiO_2 ratio (post- minus pre-intubation values) vs PEEP while on IMV in the HFNO group (left); and in the NIV group (right).

Definitions of abbreviations. HFNO: high flow nasal oxygen; NIV: non-invasive ventilation; PEEP: positive end-expiratory pressure; PaO_2: partial pressure of arterial oxygen; FiO_2: inspiratory oxygen fraction.

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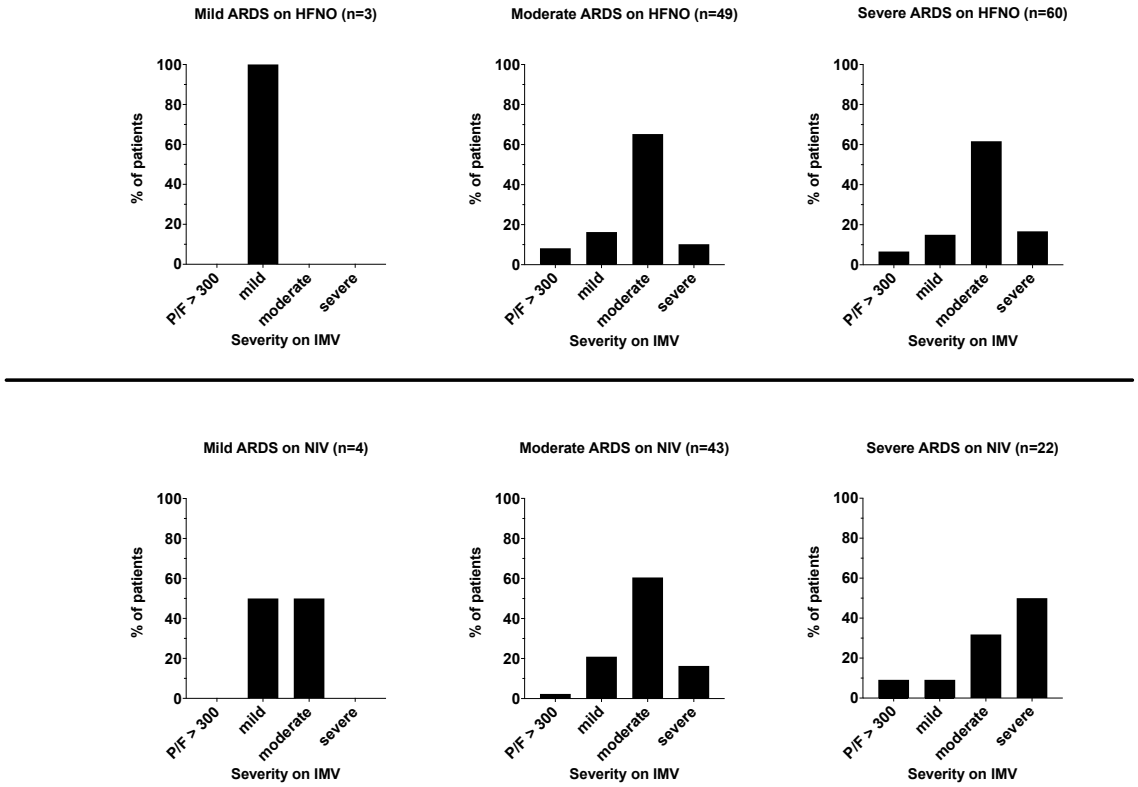

Figure S2. Number of patients that were classified as having mild, moderate and severe ARDS during HFNO (*top*) and NIV (*bottom*) that maintained severity category shortly institution of IMV. Definition of abbreviations. HFNO: high flow nasal oxygen; NIV: non-invasive ventilation; PaO_2: partial pressure of arterial oxygen; FiO_2: inspiratory oxygen fraction.

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