Supplemental Online Content

Grieco DL, Menga LS, Cesarano M, et al; COVID-ICU Gemelli Study Group. 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. Published March 25, 2021. *JAMA*. doi:10.1001/jama.2021.4682

This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix. Exclusion criteria

- Pregnancy;
- Body mass index>40;
- Exacerbation of asthma or chronic obstructive pulmonary disease;
- Known hypercapnia ($PaCO_2$>45 mmHg) with or without respiratory acidosis;
- More than 2 organ failures, including the lung.
- Documented pneumothorax;
- Clinical diagnosis of Cardiogenic pulmonary oedema;
- Haemodynamic instability (Systolic blood pressure<90 mmHg or mean arterial pressure<65mmHg) and/or lactic acidosis (lactate>5 mmol/L) and/or clinically diagnosed Shock requiring administration of vasoactive agents (norepinephrine>0.1 mcg/Kg/min);
- Metabolic Acidosis (ph <7.30 with normal- or hypo-carbia);
- Chronic kidney failure requiring dialysis before ICU admission;
- Chronic hypoxemic respiratory failure requiring long-term oxygen therapy;
- Altered neurological status that requires immediate intubation and/or making the patient uncooperative;
- Urgent need for endotracheal intubation, according to the decision of the attending physician;
- Do not intubate order;
- Decision of withdrawal of life-sustaining therapy;
- Thoracic or abdominal surgery in the previous 7 days;
- Any condition that makes the patient very likely to require endotracheal intubation due to a reason different from respiratory failure;
- Recent head surgery or anatomy that prevent the application of helmet or Optiflow to patient's face.

Patients that have already received NIV continuously for more than 12 hours before the screening visit were excluded.

eTable 1. Primary and secondary outcomes, according to Study Group in the pre-specified secondary analysis including all patients who did not show major protocol deviations.					
Outcome	Helmet Noninvasive Ventilation (n=53)	High-flow nasal oxygen (n=54)	Absolute difference (CI)	Odds Ratio (CI)	p-value
Primary outcome					
Respiratory support free days	20 [1-25]	19 [0 - 22]	2 (-2 to 6)		0.25
Secondary outcomes					
Intubation within 28 days from enrolment	15 (28)	27 (50)	- 22 (-38 to -3)	0.39 (0.18 to 0.88)	0.029
Intubation within 28 days from enrolment, after the adjudication of the external committee	14 (26)	27 (50)	- 24 (-40 to -5)	0.36 (0.16 to 0.81)	0.017
28-day invasive ventilation free days	28 [15 - 28]	26 [4 - 28]	4 (0 to 8)		0.034
60-day invasive ventilation free days	60 [47 - 60]	58 [19 - 60]	6 (-3 to 15)		0.06
28-day mortality	7 (13)	9 (17)	-3 (-17 to 10)	0.76 (0.26 to 2.22)	0.79
60-day mortality	12 (23)	11 (20)	2 (-13 to 18)	1.14 (0.45 to 2.88)	0.82
In-intensive care unit mortality	10 (19)	13 (24)	-5 (-21 to 10)	0.73 (0.29 to 1.86)	0.64
In-hospital mortality †	12 (23)	13 (24)	-1 (-18 to 15)	0.92 (0.38 to 2.26)	> 0.99
Duration of stay in the intensive care unit, days	9 [4 – 17]	10 [5 - 23]	-6 (-13 to 1)		0.26
Duration of stay in the hospital, days	21 [14-30]	22 [13 - 45]	-7 (-15 to 1)		0.53
Safety endpoints					
Hours to intubation	32 [8 - 72]	19 [4 - 49]	0 (-54 to 54)		0.28
Emergency intubation	0 (0)	0 (0)			> 0.99
Causes of endotracheal intubation – no. of patients (%)					
Hypoxemia (lack of improvement)	14 (26)	26 (48)	-22 (-38 to -3)	0.39 (0.17 to 0.87)	0.028
Signs of respiratory muscles fatigue	12 (23)	24 (44)	-22 (-38 to -4)	0.37 (0.16 to 0.85)	0.024
Intolerance to treatment	10 (19)	5 (9)	10 (-4 to 23)	2.28 (0.72 to 7.19)	0.17
SpO_2 below 90% for more than 5 minutes	9 (17)	22 (41)	-24 (-39 to -7)	0.30 (0.12 to 0.73)	0.01
Worsening or unbearable dyspnea	8 (15)	24 (44)	-29 (-44 to -12)	0.22 (0.09 to 0.56)	0.001
Altered mental status	1 (2)	1 (2)	0 (-8 to 8)	1.02 (0.06 to 17)	> 0.99
Shock	1 (2)	1 (2)	0 (-8 to 8)	1.02 (0.06 to 17)	> 0.99
Hypercapnia	1 (2)	0 (0)	2 (-5 to 10)		0.49
Inability to clear secretions	1 (2)	0 (0)	2 (-5 to 10)		0.49
Adverse events					
Intensive care unit-acquired infections §	16 (30)	22 (41)	- 11 (-28 to 7)	0.63 (0.28 to 1.40)	0.31
Ventilator-associated pneumonia	14 (26)	18 (33)	- 7 (-24 to 10)	0.72 (0.31 to 1.65)	0.53
Septic shock	11 (21)	19 (35)	- 14 (-30 to 3)	0.48 (0.20 to 1.15)	0.13
Tracheostomy	4 (7)	11 (20)	- 13 (-26 to 1)	0.32 (0.09 to 1.08)	0.09
Acute kidney injury requiring renal replacement therapy	3 (6)	8 (15)	- 9 (-22 to 3)	0.35 (0.09 to 1.38)	0.20

Barotrauma §	2 (4)	7 (13)	- 9 (-21 to 2)	0.26 (0.05 to 1.33)	0.16
Pneumothorax	2 (4)	4 (7)	- 4 (-14 to 6)	0.49 (0.09 to 2.8)	0.78
Subcutaneous emphysema	0 (0)	5 (9)	- 9 (-20 to -1)		0.06
Upper limber vein thrombosis	1 (2)	0 (0)	2 (-5 to 10)		0.49
Extracorporeal membrane oxygenation	0 (0)	3 (6)	- 6 (-15 to 2)		0.24
Liver failure	0 (0)	2 (4)	- 4 (-13 to 4)		0.49

There were no missing data among the two groups.

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

Physiological outcomes (PaO_2/FiO_2, $PaCO_2$, Respiratory rate, Discomfort related to the device and Dyspnoea) at 1-6-12-24-48-72 hours after randomization are reported in Figure 4.

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

† One patient was discharged from hospital but died upon readmission

§ Subcategories may not tally with the category total.

What is reported are number of patients with the event rather than number of events.

eTable 2. Physiological outcomes, according to Study Group in the overall population.

Outcome	Helmet Noninvasive Ventilation (n=53)	High-flow nasal oxygen (n=54)	Mean difference (CI)	p-value
Mean PaO_2/FiO_2 in the first 48 hours after enrolment, PaO_2/FiO_2 ratio	188 (73)	138 (46)	50 (39 to 61)	< 0.001
Mean $PaCO_2$ in the first 48 hours after enrolment, $PaCO_2$ – mmHg	36 (5)	35 (4)	1 (0 to 2)	0.008
Mean Respiratory rate in the first 48 hours after enrolment - breaths per minute	24 (5)	24 (5)	0 (-1 to 1)	0.82
Mean Dyspnea in the first 48 hours after enrolment - Visual Analogue Scale	1.9 (2)	2.5 (2.2)	-0.5 (-1 to -0.2)	0.003
Mean Device-related discomfort in the first 48 hours after enrolment - Visual Analogue Scale	3.7 (3.1)	1.8 (2.4)	1.9 (1.4 to 2.5)	< 0.001

Comparisons between groups were performed with a one-way ANOVA; being the missing data due to endotracheal intubation, they were not accounted in the analysis.

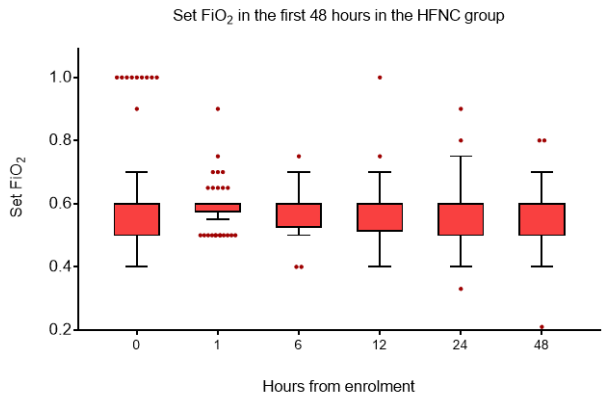
eFigure 1.
In the upper panel, the main setting of Helmet noninvasive ventilation (Helmet NIV) in the first 48 hours are shown.
In the lower panel the setting of high-flow nasal cannula (HFNC) in the first 48 hours are shown. After intubation patients were excluded from the analysis. Box plots are shown where the middle line represents the median observed value, boxes represent the interquartile range, whiskers extend to the most extreme observed values with 1.5*IQR of the nearer quartile, and dots represent observed values outside that range.

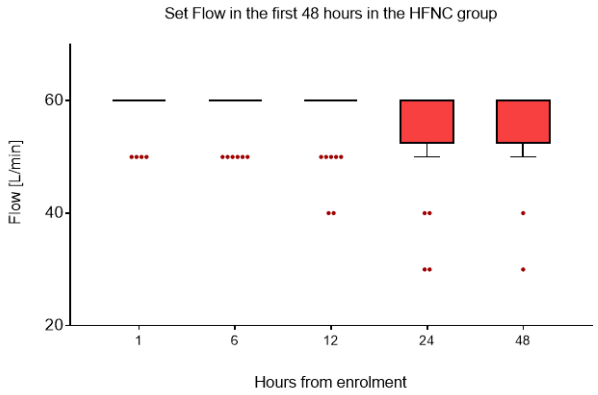
eFigure 2.
Kaplan–Meier Plots of the Cumulative Incidence of Intubation from Randomization to day 28 cohort of prespecified secondary analysis, conducted after the exclusion of 2 patients that showed major protocol deviations.

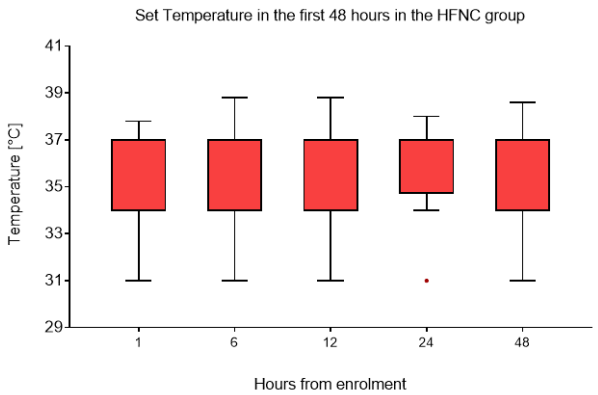
eFigure 3.
Patients' management after randomization up to 28 days. Each bar represents an individual patient.

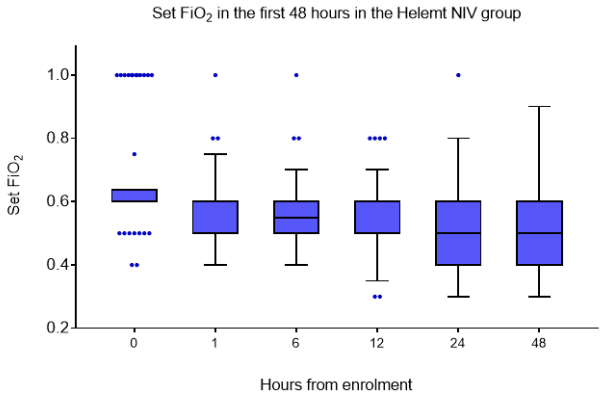
eFigure 4.
Richmond Agitation-Sedation Scale in the overall population in the first 48 hours. After endotracheal intubation patients were excluded from the analysis.
Richmond Agitation-Sedation Scale is a 10-point scale, with four levels of anxiety or agitation: 0 denoting a calm and alert state, +4 representing a very combative, violent patient, and – 5 representing an unarousable patient.

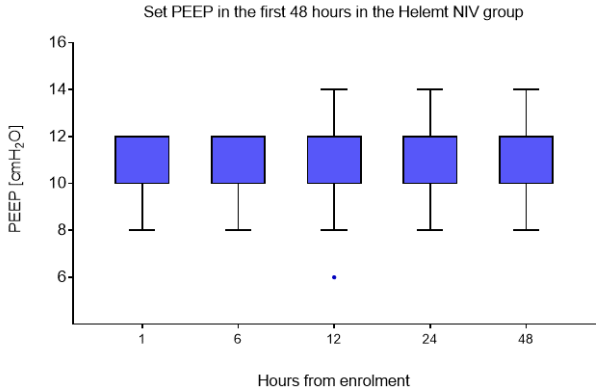
E- Figure 1



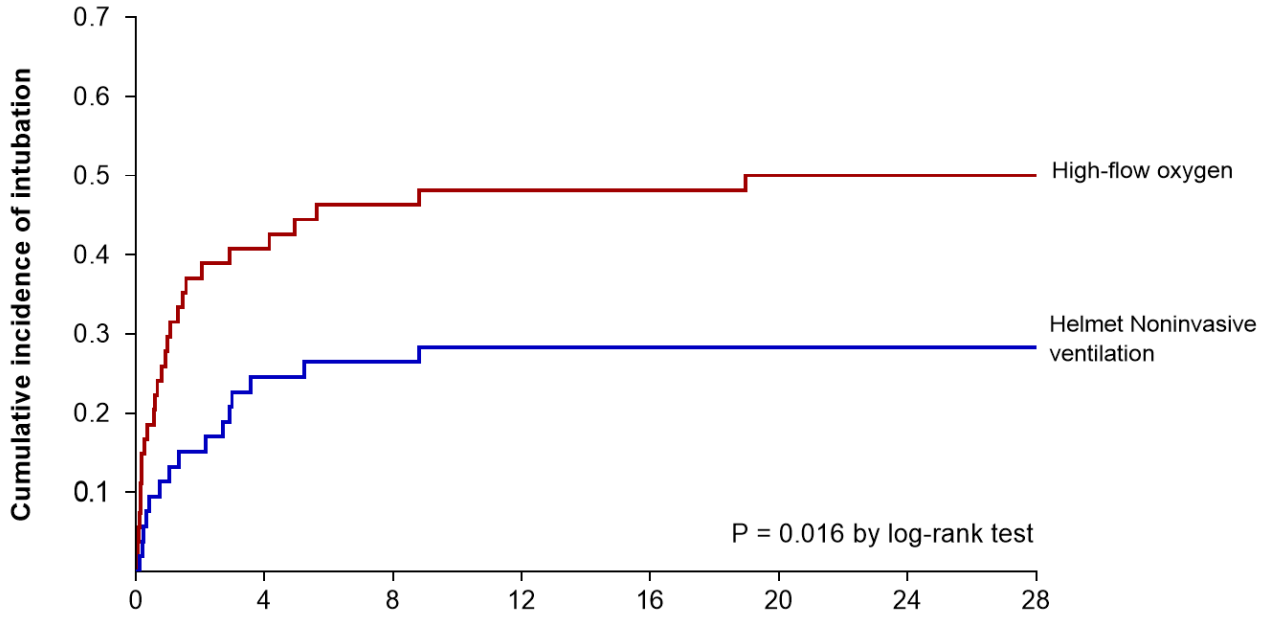








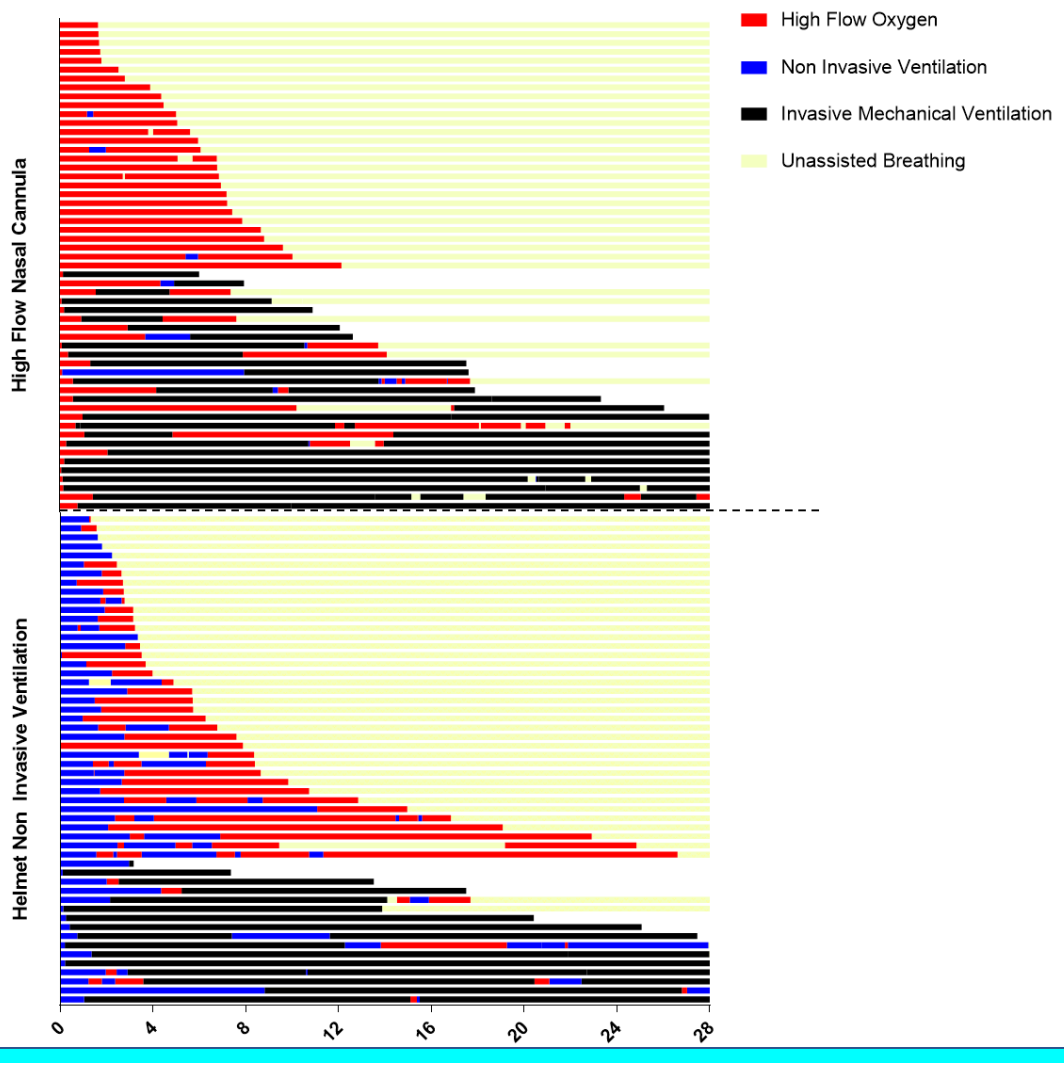
E- Figure 2 – Secondary analysis



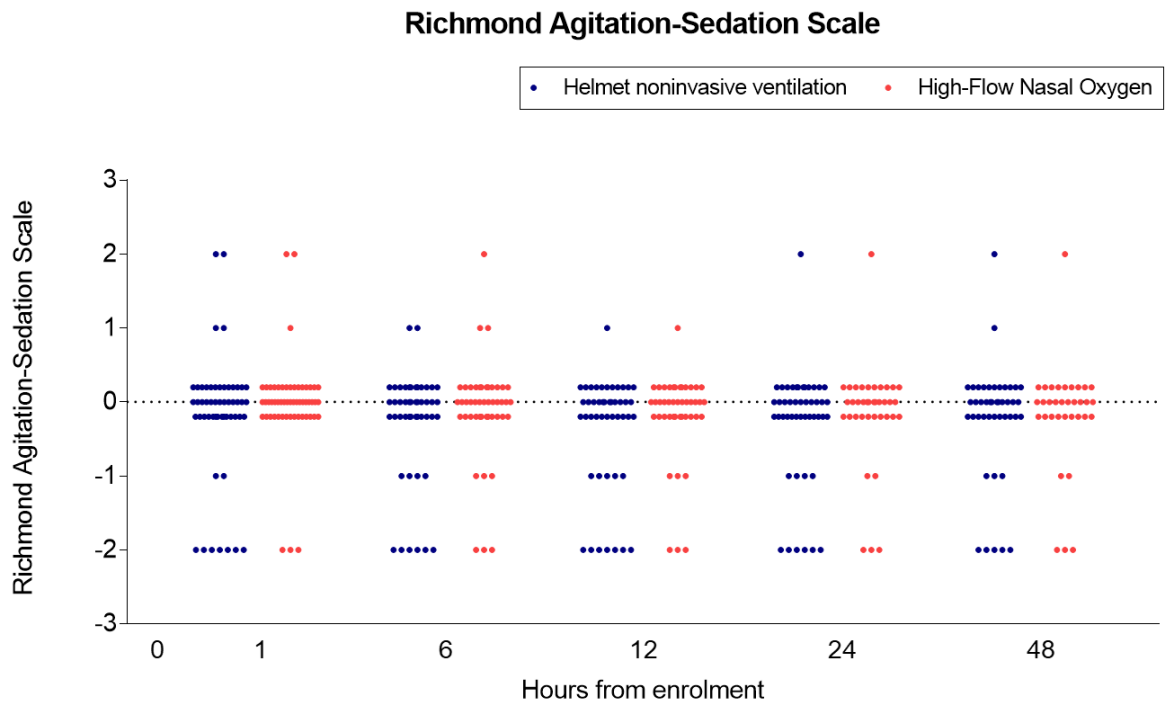
No. At risk

High-flow oxygen	54	34	30	28	28	27	27	27
Helmet noninvasive ventilation	53	41	39	38	38	38	38	38

E- Figure 3



E- Figure 4



High Flow Nasal Cannula	55	55	46	44	38	34
Helmet NIV	54	53	48	47	44	44