Critical Care

Awake prone positioning does not reduce the risk of intubation in COVID-19 treated with High-Flow Nasal Oxygen therapy. A multicenter, adjusted cohort study

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KEY POINTS

Question: Does awake prone positioning (awake-PP) reduce the risk of intubation in COVID-19 critically ill patients with acute respiratory failure (ARF) treated with high-flow nasal oxygen therapy (HFNO)?

Findings: In this prospective, multicentre, matched study of 199 COVID-19 ICU patients with ARF treated with HFNO, 82 patients were intubated independent of awake-PP (22, 40%) or not (60, 41%). After adjusting for severity, patients receiving awake-PP combined with HFNO did not have a reduction of intubation [RR 1.002 (95%CI: 0.531–1.890), p=0.99], but were intubated later compared with those treated with HFNO alone [4.1 vs 2.0 days, p=0.054]. However, 28- day mortality [RR 2.411 (95%CI: 0.556 – 10.442), p=0.23] was not affected.

Meaning: In ARF caused by COVID-19, the combined use of HNFO and awake-PP did not reduce the need for endotracheal intubation. Although awake-PP delayed intubation and invasive mechanical ventilation, did not cause an increase in 28-day mortality.

ABSTRACT

Importance. Awake prone positioning (awake-PP) in non-intubated coronavirus disease 2019 (COVID-19) patients could avoid endotracheal intubation, reduce the use of critical care resources, and improve survival.

Objective. To examine whether the combination of high-flow nasal oxygen therapy (HFNO) with awake-PP prevents the need for intubation when compared to HFNO alone.

Design, setting, and participants. Prospective, multicentre, adjusted cohort study in consecutive patients with acute respiratory failure (ARF) caused COVID-19 receiving respiratory support with HFNO.

Intervention. HFNO with or without awake-PP.

Main outcomes and Measures. Logistic models were fitted to predict treatment at baseline using the following variables: age, sex, obesity, non-respiratory sequential organ failure assessment score, APACHE-II, C-reactive protein, days from symptoms onset to HFNO initiation, respiratory rate, peripheral oxyhemoglobin saturation. We compared data on demographics, vital signs, laboratory markers, need for invasive mechanical ventilation, days to intubation, ICU length of stay, and ICU mortality between HFNO patients with and without awake-PP.

Results. From 12 March to 9 June 2020, a total of 1076 patients with COVID-19 ARF were admitted, and 199 patients were eligible for analysis: 55 (27.6%) were proned during HFNO; 60 (41%) and 22 (40%) patients from the HFNO and HFNO+awake-PP groups were intubated. The use of awake-PP as an adjunctive therapy to HFNO did not reduce the risk of intubation [RR 0.87 (95%CI: 0.53–1.43), p=0.60]. HFNO+awake-PP demonstrated a delay in intubation compared to HFNO alone [median 1 (interquartile range, IQR 1.0-2.5) vs 2 IQR 1.0-3.0] days, (p=0.055), but awake-PP did not affect 28-day mortality [RR 1.04 (95%CI: 0.40–2.72), p=0.92].

Conclusion and Clinical relevance. In patients with COVID-19 ARF treated with HFNO, the use of awake-PP did not reduce the need for intubation or affect mortality.

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4 tables, 2 figures

INTRODUCTION

A high number of patients with coronavirus disease 19 (COVID-19) develop severe bilateral viral pneumonia. Many COVID-19 patients evolve to acute respiratory distress syndrome (ARDS), characterized by a profound hypoxemia and an associated high mortality rate.[2] High-flow nasal oxygen therapy (HFNO) is effective in decreasing the need for endotracheal intubation in patients with acute hypoxemic respiratory failure (ARF).[3] However, the lack of proven benefits in COVID-19 patients together with the concerns of increased risk of aerosolization, led to recommending early intubation and invasive mechanical ventilation (MV) at the beginning of the pandemic. Due to the high infection rate of COVID-19, this resulted in a rapid exhaustion of ICU resources worldwide[4].

However, MV is associated with important risks including ventilator-associated pneumonia, ICU-acquired weakness, delirium and cognitive impairment. The recognition that the potential benefits of HFNO of preventing intubation and sparing critical ICU resources could outweigh its risks, soon led to guidelines and expert recommendations advocating its use during the pandemic.[5-7] Nevertheless, when choosing HFNO to support COVID-19-related ARF, two considerations should be made. First, HFNO may be insufficient to correct the hypoxemia secondary to intrapulmonary shunt and ventilation-perfusion (V/Q) mismatch. Second, it may delay intubation and invasive MV, which may worsen patients´ outcome, as suggested in ARDS patients.[8] Vigorous breathing efforts in hypoxemic ARF patients promoting further lung injury (a process known as patient self-inflicted lung injury, P-SILI) may worse outcome.[9] In this context, the use of awake prone positioning (awake-PP) during spontaneous breathing in non-intubated patients, could contribute to a reduction of the risk of P-SILI by promoting a more homogeneous distribution of ventilation while improving oxygenation and V/Q matching.[10]

Several studies have shown that the combination of awake-PP and HFNO or non-invasive ventilation (NIV) is feasible in patients with severe COVID-19 pneumonia, resulting in an increase in oxygenation or a decrease in the respiratory rate and/or dyspnea.[11-16] However, to date, it has not been established whether the combination of HFNO plus awake-PP could prevent the need for invasive MV in COVID-19 patients with ARF, and decrease the need of ICU resources. We performed this large multicenter adjusted cohort study to investigate those issues.

METHODS

Study design

This is a prospective, multicenter, adjusted cohort study of consecutive patients with COVID-19 ARDS admitted in 36 hospitals from Spain and Andorra (see Supplementary file). The study was approved by the referral Ethics Committee (Hospital de Cruces, Vizcaya, Spain) and all participating centers. The need for written informed consent was considered by each participating center. This study followed the "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)" guidelines for observational cohort studies.[17]

Study population and data collection

Data from patients´ electronic medical records were reviewed and collected by physicians trained in critical care according to a previously standardized common protocol. Each investigator had a personal username/password, and entered data into a specifically pre-designed online data acquisition system (CoVid19.ubikare.io) endorsed and validated by the Spanish Society of Anesthesiology and Critical Care (SEDAR). Patient confidentiality was protected by assigning a de-identified patient code. All consecutive COVID-19 patients included in the dataset from March 12th to June 9th, 2020 were enrolled if they fulfilled the following criteria: 1) age $\geq$18 years, 2) confirmed SARS-CoV-2 infection from a respiratory tract sample using PCR-based tests, 3) no previous invasive MV or NIV use before starting HFNO, and 4) peripheral oxyhemoglobin saturation (SpO_2) <93% with a non-rebreather face mask at 15 L/min. Patients with non-confirmed SARS-CoV-2 infection according to WHO guidance, and patients with no data on ventilation strategies were excluded.

Recorded data included demographics [age, gender, body mass index (BMI)], comorbidities, previous pharmacological treatments, disease chronology [time from onset of symptoms and from hospital admission to initiation of respiratory support, ICU length of stay (LOS)], symptoms at ICU admission, vital signs [temperature, mean arterial pressure (MAP), heart rate], laboratory parameters (blood test, coagulation, biochemical), non-respiratory Sequential Organ Failure Assessment (non-respiratory SOFA) and APACHE II scores, patients requiring invasive MV, patients discharged from ICU, and patients who had died or were still under ICU care on June 28, 2020.

We defined baseline as the first day on HFNO, and collected a full set of data on that day. Site investigators collected what they considered the representative data of each day from admission to ICU discharge. We also collected the "worst" values during the study period (maximum or minimum, depending on the variable). In the case report form, prone position was only considered if the duration was greater >16h/day regardless of the number of sessions. Before data were analyzed, two independent investigators and a statistician screened for erroneous data against standardized ranges and contacted local investigators with any queries. Only validated or corrected data were entered into the database. For the purpose of this analysis, patients were classified into two groups: 1) patients who received HFNO +awake-PP, and 2) patients who only received HFNO.

Statistical analysis

As this is an observational study, and no harm is inflicted and no benefit associated with being in the study we aimed to recruit as many patients as possible, with no pre-defined sample size. Descriptive variables are expressed as percentage, mean and standard deviation (SD), or median and interquartile range (IQR), as appropriate for each variable. We used the Student t-test or Mann-Whitney test for numerical variables, and Chi squared test or Fisher exact test for categorical variables, to compare variables across groups. We used inverse probability of treatment weighted to account for baseline differences between HFNO and HFNO+awake-PP groups. We fitted logistic models to predict treatment at baseline using the following variables as predictors of treatment: age, sex, obesity, non-respiratory SOFA score, APACHE II, C-reactive protein (CRP), days from symptoms onset to HFNO initiation, respiratory rate, SpO_2, and type of hospital (4 groups depending on the number of enrolled patients). Weights were calculated following the methodology described elsewhere and a weighted population (adjusted sample) was built subsequently.[18] To assess the relationship among the exposure awake-PP and the probability of being intubated and mortality at day-28 time to event curves were plotted using the Kaplan-Meier method and analyzed with log-rank test and multivariate Cox regression analysis. For Kaplan-Meier analyses, patients with complementary outcome were right-censored at the longest recorded length of stay. We also stratified patients by PaO_2/FiO_2 bellow or above 100. Missing data were not computed. Analyses were performed on a complete case analysis basis. All

tests were two-sided, and a P-value <0.05 was considered statistically significant. All analyses were performed with STATA version 16.

RESULTS

Between March 12th and June 9th, 2020, 1076 critically ill patients admitted in 36 ICUs in Spain and Andorra were included in the database. HFNO was used in 400 patients during their ICU stay, but in 199 patients HFNO was the first therapeutic option (Figure 1). From those 199 patients, 55 (27.6%) were proned during HFNO. The median time from symptoms onset and from hospital admission to HFNO and HFNO+awake-PP start were 7 vs 7 days and 10 vs 11 days, respectively (table 1).

Patients´ demographics, symptoms at ICU admission, baseline vital signs, arterial blood gases and laboratory findings according to HFNO or HFNO+awake-PP are shown in table 1, both in the original and adjusted samples. There were no differences in the time form symptoms onset to hospital admission or onset of HFNO (Table 1). No substantial imbalances in patients´ demographics, vital signs, arterial blood gases and laboratory findings at baseline were observed (Table 1). In both samples, PaO_2/FiO_2 was significantly higher in the HFNO+awake-PP group.

Table 2 shows the worst patients´ findings during the ICU course while under HFNO treatment in the original and adjusted samples. There were no clinically substantial differences except for IL-6 and procalcitonin levels, both being higher in HFNO patients. Mean values of SpO_2, RR and ROX index over time in the adjusted sample are reported in eFigures 1 to 3. Differences of the adjusted sample at baseline and during ICU stay while treated with HFNO -between intubated and non-intubated patients- are shown in eTables 1 to 4 and eFigures 1 to 3.

From 199 patients, 82 (41%) patients required intubation and invasive MV: 60 (41%) and 22 (40%) in the HFNO and HFNO+awake-PP groups, respectively (Table 3). The use of awake-PP as adjunctive therapy to HFNO did not reduce the risk of being intubated neither in the original nor in the adjusted samples [hazard ratio (RR) 0.87 (95%CI: 0.538-1.435), p=0.60] and [RR 1.002 (95%CI: 0.531–1.890), p=0.99] (Table 4).–HNFO+awake-PP did also not reduce the risk of being intubated in the subgroups of patients with PaO_2/FiO_2 greater or less than 100 (eFigure 4). Time from HFNO to intubation was longer in the HFNO+awake-PP in the original (1.0 vs 2.0 days, p=0.055) and adjusted (4.1 vs 2.0 days, p=0.054) samples, although differences did not reach statistical significance. As of June 27, 2020, 147 (73%) patients were discharged from the ICU with no differences between HFNO,

105 (86%) patients and HFNO+awake-PP 41 (83%) patients (Table 3). ICU length of stay did not vary among HFNO and HFNO+awake-PP (7.5 vs 8.0, p=0.27).

The 28-day mortality risk was not influenced by the use of awake-PP [RR 2.411 (95%CI: 0.556 – 10.442), p=0.23)] (Table 4 and Figure 2). Neither did it influence the subgroups of patients with PaO_2/FiO_2 greater or less than 100 (eFigure 5).

DISCUSSION

In this prospective multicenter adjusted study in 199 patients with COVID-19 ARF treated with HFNO, the synergistic use of awake-PP did not reduce the risk of intubation. Our findings also suggest that awake-PP could have a potentially negative impact as it was associated with a delay in intubation although did not affect 28-day mortality. Our analysis does not support the widespread use of awake-PP in all COVID-19 patients with ARF treated with HFNO. However, given the observational nature of our study, these results should be interpreted with caution and by no means considered definitive.

Published studies on the management of ARF in COVID-19 patients have shown that the vast majority need invasive MV with prolonged times on the ventilator.[19,20] Alternatives to invasive respiratory support such as HFNO, a simple technique with few side effects, have been widely used during the pandemic to manage severe hypoxemia, despite initial concerns about the possibility of increased risk of virus transmission. Other adjunctive techniques, such as awake-PP, have been widely used in combination with oxygen therapy, NIV or HFNO to correct hypoxemia and avoid the need for intubation and invasive MV.[11-16] The benefits of prone positioning in ARDS patients have been well established. By rearrangement of the vertical transpulmonary pressure gradients, prone positioning favors lung recruitment improving V/Q mismatch by decreasing shunt.[21,22] In addition, the resulting more homogeneous distribution of ventilation could decrease the risk of ventilator-induced lung injury, a mechanism directly related to the mortality reduction in mechanically ventilated ARDS patients.[23] However, the experience with awake-PP in ARDS patients treated with HFNO is limited. The only previously published study included 20 patients of which 9 patients (45%) required intubation; for the 11 non-intubated patients, 8 received HFNO+awake PP, and six of them needed escalation to NIV.[24]

Data on the use of awake-PP in COVID-19 patients is limited to small, single-center studies or case series with contradictory results. Elharrar et al.[11] examined the effects of awake-PP in 24 patients receiving oxygen therapy. Oxygenation improved in about one fourth of patients, and deteriorated again after turning the patient to supine. No information regarding the need for intubation was provided.[11] Thompson et al.[12] in a similar population of 25 patients managed with conventional oxygen therapy found a heterogeneous response to awake-PP with improvements in SpO_2 ranging from 1% to 37%, but 12 patients (48%) patients required intubation. Better results were found by Ng et al.[13] who applied daily

awake-PP sessions of 5 hours in 10 non-ICU patients with only one needing intubation. Similar results were reported by Sartini et al.[14] in 15 non-ICU patients supported with NIV in whom awake-PP was used as a rescue therapy, resulting in an improvement of oxygenation and respiratory rate, and only one patient required intubation. In the study by Xu et al.[15] intubation was needed in 5 (50%) out of 10 patients managed with HFNO plus early awake-PP 16h/day during three consecutive days. Finally, Coppo et al.[16] performed a feasibility and physiological study including 56 patients in which awake prone lasting >3h improved oxygenation but not dyspnea and respiratory rate. Similar to previous studies, this improvement in oxygenation was maintained only in half of their patients after returning to the supine position. Of note, awake-PP was applied earlier (median of 1.9 days) in responders. However, no differences in the need for intubation were found between responders and non-responders (26% vs. 30%).[16] Taken together all these small studies -that barely exceed a hundred of patients-, in patients managed with non-invasive ventilatory support methods, awake-PP was differently applied both in length and frequency. These issues make the interpretation of their findings and the comparison with our analysis extremely difficult. Nevertheless, those previous reports together with our current study do not support the use of awake-PP as an effective adjunctive strategy for preventing intubation.

As oxygenation is generally improved on awake-PP, one potential risk would be an undue delay in intubation which could potentially worsen prognosis, as demonstrated in previous studies in non-COVID-19 patients.[8] Coppo et al.[16] did not find any differences in time to intubation between responders and non-responders to awake-PP in their cohort of COVID-19 patients. In our adjusted cohort, patients in the HFNO+awake-PP had a strong trend towards a delay in intubation of 2 days, although 28-day mortality was similar in both treatment groups.

This study has several strengths. First, it is the largest study including 199 patients from 36 intensive care units. Second, this multicentre nationwide prospective daily data collection protocol provided a very detailed description of the patient course during the study period. Third, to the best of our knowledge, this is the first study that prospectively explored the association between awake-PP and the risk for intubation in original and adjusted COVID-19 samples with a severe hypoxemic ARF. However, we acknowledge some limitations. First, we were unable to determine whether clinicians used awake–PP as usual practice for COVID-19 patients or as a rescue strategy. Second, as in our case report

form prone was only considered when it was applied for >16h/day, we cannot extend our results to patients proned for shorter periods time. Third, intubation criteria were not uniformly defined and protocolized, which may limit the generalizability of our results. Finally, due to the pragmatic nature of our data collection, variables such as SpO_2, PaO_2/FiO_2, RR or ROX index were not collected before and after awake-PP sessions, and therefore, individual responses could not be determined, limiting the possibility of analyzing the effects of prone on intubation in certain subpopulations of patients. Nevertheless, current data showed that responders, defined as those patients that improved oxygenation when managed with HFNO and awake-PP, did not decrease their risk for intubation.

CONCLUSIONS

To the best of our knowledge, this is the first multicentre study that prospectively evaluated the benefits and the role of HFNO combined with awake prone positioning in the prevention of intubation in a matched large cohort of COVID-19 patients. We found that this combined approach did not reduce the risk of intubation, but could increase the risk of delaying intubation. In the current study, a delayed intubation did not affect 28-day mortality. The interpretation of these results may be limited by the observational design, and therefore future studies are needed to identify potential subpopulations that may benefit from awake prone positioning in COVID-19 patients with acute hypoxemic respiratory failure.

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REFERENCES

1. Huang C, Yeming W, Xingwang L et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 497-506.
2. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet 2020; 395:1054-1062.
3. Rochwerg B, D. Granton D, Wang X et al. High Flow Nasal Cannula Compared with Conventional Oxygen Therapy for Acute Hypoxemic Respiratory Failure: A Systematic Review and Meta-Analysis. Intensive Care Medicine 2019; 45:563-72.
4. Grasseli G, Pesenti A, Cecconi M. Critical Care utilization for the COVID-19 outbreak in Lombardy, Italy. Early experience and forescat during an emergency response. JAMA 2020; 323:1545-1546.
5. https://www.formacionsanitaria.eu/documentos/Recomendations_WeVent.pdf. Last access on 23/06/2020
6. Alhazzani W, Møller MH, Arabi YM et al. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med 2020; 46:854-887.
7. Cinesi C, Peñuelas O, Luján M.I, et al. Clinical consensus recommendations regarding non-invasive respiratory support in the adult patient with acute respiratory failure secondary to SARS-CoV-2 infection. Rev Esp Anestesiol Reanim 2020; 67:245-252.
8. Kang BJ, Koh Y, Lim CM et al. Failure of high flow nasal cannula therapy may delay intubation and increase mortality. Intensive Care Med 2015; 41:623–632.
9. Brochard L, Slutsky A, Pesenti A. Mechanical Ventilation to Minimize Progression of Lung Injury in Acute Respiratory Failure. Am J Respir Crit 2017; 195: 438-442.
10. Telias I, Katira B, Brochard L. Is the prone position helpful during spontaneous breathing in patients with COVID-19? JAMA 2020; 323:2265-2267.
11. Elharrar X, Trigui Y, Dols A-M, et al. Use of prone positioning in nonintubated patients with COVID-19 and hypoxemic acute respiratory failure. JAMA 2020; 323:2336-2338.

12. Thompson A.E, Ranard B.L, Wei Y, et al. Prone positioning in awak, nonintubated patients with COVID-19 hypoxemic respiratory failure. JAMA Intern Med. Published online 17, 2020.
13. Ng Z, Chiao W, Ho C.H.B. Awake prone position for non-intubated oxygen dependent COVID-19 pneumonia patients. Eur Respir J 2020; 2001198.
14. Sartini C, Tresoldi M, Scarpellini P, et al. Respiratory parameters in patients with COVID-19 after using noninvasive ventilation in the prone position outside the intensive care unit. JAMA 2020; 323:2338-2340.
15. Xu Q, Wang T, Qin X, Jie Y, Lu W. Early awake prone position combined with high-flow nasal oxygen therapy in severe COVID-19: a case series. Crit Care 2020; 24:250.
16. Coppo A, Bellani G, Winterton D, et al. Feasibility and physiological effects of prone positioning in non-intubated patients with acute respiratory failure due to COVID-19 (PRON-COVID): a prospective cohort study. Lancet Respir Med 2020; Published online June 19.
17. Von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vanderbrouche JP. STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007; 335:806-808.
18. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. Epidemiology 2004; 15:615-25.
19. The COVID-19 Lombardy ICU Network «Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020; 323:1574-1581.
20. Ferrando C, Suárez-Sipmann F, Mellado-Artigas R, et al. Main features, ventilatory management and outcomes of patients with COVID-19 induced ARDS. Intensive Care Med 2020; DOI: 10.1007/s00134-020-06192-2
21. Hopkins SR, Henderson AC, Levin DL, et al. Vertical gradients in regional lung density and perfusion in the supine human lung: the Slinky effect. J Appl Physiol (1985) 2007; 103: 240–48.
22. Broccard AF, Shapiro RS, Schmitz LL, Ravenscraft SA, Marini JJ. Influence of prone position on the extent and distribution of lung injury in a high tidal volume oleic acid model of acute respiratory distress syndrome. Crit Care Med 1997; 25: 16–27.

23. Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013; 368:2159-2168.

24. Ding L, Wang L, Ma W, He H. Efficacy and safety of early prone positioning combined with HFNT or NIV in moderate to severe ARDS: a multi-center prospective cohort study. Crit Care 2020; 24:28.

Table 1. Baseline characteristics of the original-eligible population and weighted population.

	Original sample		Weighted sample	
	HFNO (n=144)	HFNO + awake-PP (n=55)	HFNO 68.43%	HFNO + awake-PP 31.57%
Patients demographics and comorbidities				
Age	63.0 [55.0-71.0] /144	60.0 [54.0-70.0] /55	60.3	60.9
Gender, female	39/143 (27.3%)	13/54 (24.1%)	28.8%	33.9%
Body mass index, kg/m^2	27.3 [25.1-29.4] /120	26.8 [24.8-31.2] /49	28.6	28.2
Arterial Hypertension	60/144 (41.7%)	20/55 (36.4%)	42.8%	34.3%
Diabetes Mellitus	23/144 (16.0%)	9/55 (16.4%)	18.1%	10.7%
Chronic cardiac failure	2/144 (1.4%)	2/55 (3.6%)	1.4%	5.2%
Chronic renal failure	14/144 (9.7%)	4/55 (7.3%)	6.4%	6.2%
Asthma	5/144 (3.5%)	1/55 (1.8%)	7.6%	6.3%
COPD	6/144 (4.2%)	4/55 (7.3%)	4.2%	8.2%
Obesity	25/120 (20.8%)	17/49 (34.7%)	30.2%	32.4%
Dyslipidemia	15/144 (10.4%)	4/55 (7.3%)	8.1%	4.5%
Malignancy	9/144 (6.3%)	3/55 (5.5%)	4.9%	3.2%
Medical treatment				
Anti-hypertensive agents	62/144 (43.1%)	19/55 (34.6%)	43.9%	35.9%
Hypoglycemic agents	18/144 (12.5%)	7/55 (12.7%)	17.8%	17.0%
Antiplatelet agents	17/144 (11.8%)	5/55 (9.1%)	8.8%	12.8%
Anticoagulants	10/144 (6.9%)	1/55 (1.8%)	10.7%	1.2%
Bronchodilators	35/144 (24.3%)	10/55 (18.2%)	22.4%	23.3%
Lipid lowering agents	8/144 (5.6%)	3/55 (5.5%)	7.8%	3.2%
Thyroid hormone replacement	10/144 (6.9%)	9/55 (16.4%)	12.4%	25.5%
Immunossupressors	9/144 (6.3%)	1/55 (1.8%)	4.1%	0%
Corticosteroids	9/144 (6.3%)	2/55 (3.6%)	4.1%	0%
Chronology				
Days from symptoms onset to hospital admission	7.0 [4.0-9.0] /141	7.0 [4.0010.0] /55	7.4	7.6
Days from symptoms onset to HFNO	10.0 [8.0-13.0] /142	11.0 [8.0-13.0] /55	10.1	10.2
Symptoms at ICU admission				
Fever	121/144 (84.0%)	51/55 (92.7%)	87.0%	90.0%
Cough	94/144 (65.3%)	36/55 (65.5%)	69.3%	62.2%
Dyspnea	92/144 (63.9%)	39/55 (70.9%)	62.4%	73.8%
Malaise	57/144 (39.6%)	27/55 (49.1%)	42.1%	56.3%
Myalgia	22/144 (15.3%)	10/55 (18.2%)	18.0%	18.8%
Headache	12/144 (8.3%)	6/55 (10.9%)	7.8%	5.8%
Rhinorrhea	1/144 (0.7%)	1/55 (1.8%)	1.1%	3.3%
Vomiting	10/144 (6.9%)	4/55 (7.3%)	4.6%	7.9%
Arthralgia	6/144 (4.2%)	4/55 (7.3%)	3.4%	5.5%
Chest pain	12/144 (8.3%)	1/55 (1.8%)	9.2%	0%

Increased sputum	14/144 (9.7%)	6/55 (10.9%)	7.7%	11.0%
Anosmia	6/144 (4.2%)	4/55 (7.3%)	6.5%	6.5%
Pharyngodynia	5/144 (3.5%)	1/55 (1.8%)	3.5%	1.2%
Diarrhea	20/144 (13. 9%)	9/55 (16.4%)	15.8%	15.0%
Fatigue	1/144 (0.7%)	4/55 (7.3%)	0%	6.6%
Scores				
APACHE II	11.0 [8.0-14.0] /107	8.5 [6.0-13.0] /46	10.8	11.0
Non-respiratory SOFA	4.0 [4.0-5.0] /116	4.0 [4.0-4.0] /46	4.6	4.7
Vital Signs				
Temperature, ºC	36.9 [36.1-37.6] /141	36.8 [36.2-37.3] /54	36.9	36.8
Mean arterial pressure, mmHg	87.3 [79.7-95.0] /142	85.8 [78.0-92.0] /54	89.1	82.9
Heart rate, bpm	81.0 [73.0-91.0] /141	78.5 [66.0-88.0] /54	82.5	78.9
SpO_2, %	90.0 [88.0-94.0] /141	90.0 [88.0-92.0] /54	90.4	90.4
Respiratory rate, bpm	25.0 [22.0-30.0] /136	23.0 [20.0-30.0] /54	25.7	25.5
Arterial blood gas				
PaO_2/FiO_2	111.0 [83.0-144.0] /124	125.0 [99.0-187.0] /51	123.9	148.2
$PaCO_2$, mmHg	33.1 [30.0-37.0] /129	34.7 [30.8-39.0] /51	34.7	34.0
Laboratory findings				
Ferritin, ng/mL	1265 [755-1904]/87	934 [597-2092]/41	1640	1766
D-Dimer, ng/mL	925 [600.0-1800]/114	931 [549-1790]/48	1605	1608
CRP, mg/dL	16.82 [8.31-30.40] /131	21.51 [8.46-145.00] /53	56.39	57.7
Lymphocytes, 10e3/µL	0.61 [0.40-0.90] /132	0.61 [0.40-0.89] /53	0.8	0.7
IL-6, pg/mL	135.0 [61.8-202.0] /17	93.0 [35.5-301.0] /11	186.6	134.4
LDH, U/L	396.0 [331.0-480.0] /125	380.0 [313.0-528.0] /51	417.3	434.3
Leukocytes, 10^3/µL	7.1 [5.0-11.2] /131	6.5 [4.4-9.0] /52	8.1	6.7
Procalcitonin, ng/mL	0.2 [0.1-0.6] /99	0.1 [0.1-0.3] /39	0.7	0.3
Platelets, 1000/mm^3	232.0 [152.0-342.0] /133	233.0 [153.0-274.0] /53	261.9	221.3
Bilirrubin, mg/dL	0.6 [0.4-1.0] /124	0. 7 [0.5-0.9] /48	0.9	0.7
GPT, U/L	43.5 [23.0078.0] /130	37.0 [25.5-71.0] /52	65.5	62.6
Creatinin, mg/dL	0.8 [0.6-1.1] /132	0.8 [0.7-1.0] /52	1.0	1.0
Urea, mg/dL	36.0 [27.2-53.0] /76	33.6 [21.0-49.0] /42	45.5	33.7
Troponin, ng/mL	14.0 [4.4023.4] /69	8.0 [2.8-15.1] /33	17.3	13.2
NTproBNP, pg/mL	418.0 [125.5-1529.0] /16	225.5 [50.0-1263.00 /6	760.1	731.9
Hematocrit, %	38.0 [35.0-42.0] /126	40.7 [36.0-44.0] /50	38.7	39.4
Lactate, mmol/L	1.5 [1.0-2.1] /82	1.6 [1.3-2.00 /33	1.8	1.8

Abbreviations. HFNT: high flow nasal therapy; COPD: chronic obstructive pulmonary disease; SOFA: sequential organ failure assessment; CRP: C-reactive protein; IL: interleukine; LDH: lactate dehydrogenase; GPT: Glutamate pyruvate transaminase. Values were obtained from each patient on day 1 of HFNT. Categorical variables are expressed as proportion, and continuous variables as median (IQR) for original-eligible population and percentage and mean for weighted population**.**

Table 2. Clinical evolution (maximum or minimum values) of the original-eligible population and weighted population while treated with HFNO.

º	Original sample		Weighted sample	
	HFNO (n=133)	HFNO + awake-PP (n=51)	HFNO 68.4%	HFNO + awake-PP 31.6%
Scores				
Non-respiratory SOFA	4.0 [4.00-5.00] /125	4.0 [4.00-5.00] /46	4.8	5.0
Vital Signs				
Temperature, ºC	37.2 [36.50-38.00] /141	37.1 [36.60-37.80] /54	37.2	37.3
Mean arterial pressure, mmHg	77.0 [70.50-83.83] /140	76.2 [68.00-84.00] /54	77.8	73.4
Heart rate, bpm	85.0 [75.00-96.00] /141	85.0 [79.00-100.00] /54	87.2	91.4
SpO_2, %	89.0 [86.00-92.00] /141	88.0 [84.00-90.00] /54	88.8	87.6
Respiratory rate minimum, bpm	21.0 [18.00-24.00] /141	19.0 [16.00-23.00] /54	20.8	19.7
Respiratory rate maximum, bpm	27.0 [24.00-32.00] /141	27.0 [23.00-30.00] /54	27.7	27.1
Arterial blood gas				
PaO_2/FiO_2	92.5 [77.00-125.50] /128	103.0 [80.00-125.00] /53	109.7	113.8
$PaCO_2$, mmHg	39.9 [35.50-48.00] /131	41.2 [36.20-46.00] /53	44.8	42.4
Laboratory findings				
Ferritin, ng/mL	1279.0 [694.00-2151.00] /107	1499.0 [809.00-2425.00] /45	1817.2	1955.0
D- Dimer, ng/mL	1681.0 [820.00-4200.00] /122	1590.0 [1030.00-3200.00] /50	2799.7	2624.9
RCP, mg/dL	21.3 [9.32-33.19] /132	22.7 [8.66-146.14] /53	62.4	62.6
Lymphocytes, µL	0.47 [0.30-0.74] /135	0.44 [0.30-0.60] /53	0.56	0.42
IL-6, pg/mL	177.0 [42.70-415.90] /17	87.5 [24.00-301.00] /14	832.7	221.6
LDH, U/L	429.0 [345.00-561.00] /125	449.0 [352.00-602.00] /51	451.2	490.3
Leukocytes, $10^3/\mu L$	8.3 [5.80-12.00] /122	7.7 [5.21-12.33] /51	9.7	9.0
Procalcitonin, ng/mL	0.22 [0.11-0.57] /114	0.20 [0.09-0.34] /45	1.24	0.34
Platelets, $1000/mm^3$	319.0 [212.50-410.50] /136	303.0 [244.00-358.00] /53	330.6	329.7
Bilirrubin, mg/dL	0.80 [0.50-1.10] /130	0.84 [0.60-1.18] /50	1.23	0.90
ALT, U/L	66.0 [30.00-104.00] /135	52.0 [32.00-116.00] /53	85.2	105.6
Creatinin, mg/dL	0.90 [0.70-1.18] /136	0.86 [0.75-1.02] /52	1.10	1.09
Urea, mg/dL	42.0 [30.00-64.00] /91	39.5 [26.00-61.00] /50	52.0	42.7
Troponin, ng/mL	11.8 [4.30-25.00] /89	9.6 [4.60-27.52] /39	18.8	9.3
NTproBNP, pg/mL	335.5 [125.50-938.80] /20	303.1 [91.00-1019.00] /14	727.9	660.9
Hematocrit, %	38.00 [34.70-42.00] /111	39.20 [36.00-42.50] /45	38.2	39.4
Lactate, mmol/L	1.5 [1.16-2.10] /77	1.5 [1.20-2.10] /31	1.85	1.88

Maximum or minimum values during the period of HFNT. Categorical variables are expressed as proportion, and continuous variables as median (IQR) for original-eligible population and percentage and mean for weighted population. Abbreviations. HFNT: high flow nasal oxygen therapy; SpO_2: peripheral oxyhemoglobin saturation; SOFA: sequential organ failure assessment; RCP: C-reactive protein; IL: interleukine; LDH: lactate dehydrogenase; GPT: Glutamate pyruvate transaminase.

Table 3. Outcomes of the original-eligible population and weighted population.

Outcome	Original sample			Weighted sample		
	HFNO (n=144)	HFNO+awake-PP (n=55)	p-value	HFNO 67.4%	HFNO+awake-PP 32.5%	p-value
Intubated	60 (41.7%)	22 (40.0%)	0.481	35.0%	37.3%	0.824
Days from HFNO start to intubation*	1 [1-2.5]	2 [1-3]	0.055	2.05	4.18	0.054
ICU length of stay**	7.5 [4-14]	8 [5-14]	0.276	11.6	11.4	0.950
ICU length of stay of discharge patients**	7 [4-12]	8 [5-13]	0.417	10.5	9.3	0.472
Discharge from ICU**	105/122 (86.1%)	41/49 (83.7%)	0.427	90.8%	80.0%	0.18
ICU mortality**	17/122 (13.9%)	8/49 (16.3%		9.2%	20.0%	

Categorical variables are expressed as proportion, and continuous variables as median (IQR) for original-eligible population and percentage and mean for weighted population. P-value cut-off at 0.05. * Intubated patients, **Excluding patients who still in ICU. Abbreviations. HFNO: high flow nasal oxygen therapy; ICU: intensive care unit.

Table 4. Associations between HFNO plus awake prone positioning and the endpoint of 28-day mortality in the original population and weighted population.

Analysis	Hazard ratio (95% confidence interval); p value
Intubation	
Crude analysis	0.879 (0.538, 1.435); p=0.60
Inverse probability weighting analysis	1.002 (0.531, 1.890); p=0.99
28 day mortality	
Crude analysis	1.046 (0.402, 2.722); p=0.92
Inverse probability weighting analysis	2.411 (0.556, 10.442); p=0.23

Logistic models were fitted to predict treatment at baseline using the following variables as predictors of treatment: age, sex, obesity, non-respiratory sequential organ failure assessment severity score, APACHE II, C-reactive protein, days from symptoms onset to high flow nasal therapy start, respiratory rate, peripheral oxyhemoglobin saturation. Abbreviations. ICU: intensive care unit.

FIGURES

Figure 1. Patient Flowchart

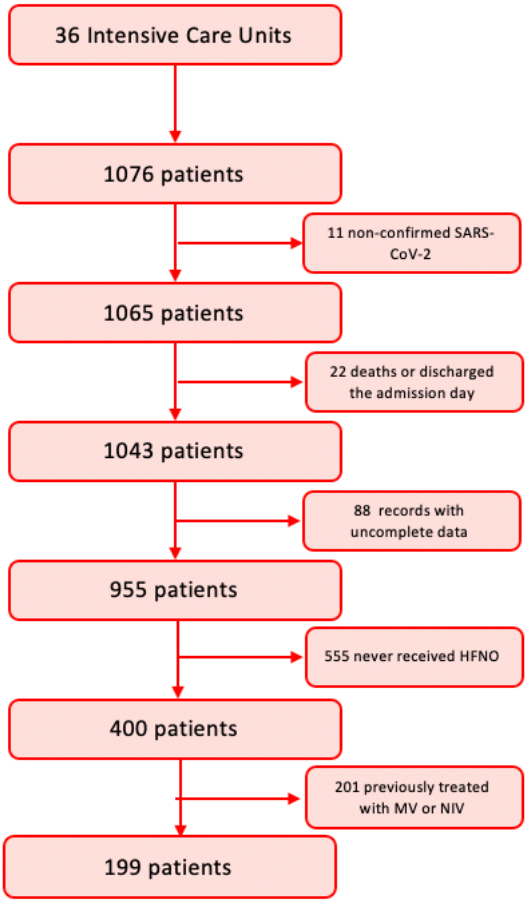

Figure 1. Patient flowchart. HFNO: high flow nasal oxygen therapy; MV: invasive mechanical ventilation; NIV: noninvasive ventilation.

Figure 2. Time to event curves using Kaplan-Meier with multivariate Cox regression. The probability of been intubated in the original (top-left) and weighted (top-right) samples and the probability of 28-day mortality in the original (bottom-left) and weighted (bottom-right) samples were not affected by the use of awake prone positioning. HFNO: high flow nasal oxygen therapy; HFNO + awake-PP: high flow nasal oxygen therapy plus awake prone positioning.