

# High-Flow Nasal Oxygen for Severe COVID-19 Pneumonia in Greek Patients: A Prospective Observational Study

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**Summary: Introduction:** High-flow nasal oxygen (HFNO) and prone positioning may improve outcomes of coronavirus disease 2019 (COVID-19) patients treated in the intensive care unit (ICU). The aim of this study was to describe outcomes following the timely application of HFNO and prone positioning in COVID-19 patients treated in a ward setting.

**Methods:** The study included 89 prospectively recruited subjects at the COVID-19 ward unit of the University Hospital of Heraklion, Greece, between March and December 2020.

**Results:** Seventy-four (83%) of the 89 subjects in the study had severe COVID-19. Of those, 33 (45%) required HFNO treatment and prone positioning and 15 (45%) were transferred to the ICU, with 4 of them being intubated. Severe COVID-19 and HFNO needs were associated with an increased pneumonia severity index (PSI) score on admission and a worse PaO<sub>2</sub>/FiO<sub>2</sub> ratio. In multivariate analysis, PSI was the only independent predictor of subsequent HFNO needs (OR=1.022). Overall intubation and mortality rates were 5.6% and 3.4%, respectively.

**Conclusion:** This study shows that for patients with severe COVID-19 hospitalized in medical wards, standard COVID-19 treatment, along with the timely utilization of HFNO and prone positioning, resulted in excellent outcomes with fewer ICU admission rates.

**Keywords** COVID-19, SARS-CoV-2, high-flow nasal oxygen therapy, prone position, intensive care, critical care

## INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), has until now infected more than 465,000,000 people and caused more than 6,000,000 deaths worldwide. A considerable proportion of pa-

tients with COVID-19 develop severe pneumonia and respiratory failure, which may require treatment in the Intensive Care Unit (ICU) [1]. Supportive care, including oxygen therapy and often empirical antimicrobial therapy, remains the cornerstone of treatment until effective antiviral medications become available.

High-flow nasal oxygen (HFNO) has increasingly

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Abbreviations:  $\gamma$ GT, gamma-glutamyl transferase; COVID-19, coronavirus disease 19; CRP, c-reactive protein; CT, computed tomography; FiO<sub>2</sub>, fraction of inspired oxygen; HFNO, high-flow nasal oxygen; ICU, intensive care unit; IDSA, infectious diseases society of America; IQR, interquartile range; NIV, non-invasive ventilation; PSI, pneumonia severity index; ROX index, ratio of pulse oximetry/fraction of inspired oxygen to respiratory rate; RR, respiratory rate; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SD, standard deviation; SGPT, alanine aminotransferase.

emerged as an effective therapy for patients with acute hypoxemic respiratory failure, with recent studies supporting reduced rates of intubation for patients treated with HFNO compared to patients treated with a non-rebreather mask or non-invasive ventilation (NIV) [2,3]. Importantly, HFNO is a modality that may not necessarily require ICU admission, as long as effective monitoring by experienced personnel is available. To that end, there have been reports of small case studies of COVID-19 patients suggesting that HFNO therapy can be safely administered in the ward [4].

On the other hand, prone positioning, which has been widely used in patients with acute respiratory distress syndrome, and is known to reduce mortality, has recently emerged as a therapeutic modality in patients with hypoxemic respiratory failure due to COVID-19 [5,6]. Specifically, awake prone positioning has been found to safely reduce the incidence of treatment failure and the need for intubation in patients with hypoxemic respiratory failure due to COVID-19 [6,7].

This study describes the results of using HFNO and prone positioning in a cohort of subjects admitted in a ward setting in a Greek tertiary hospital due to COVID-19 infection.

## METHODS

### *Study population*

This study included 89 subjects consecutively admitted to the COVID-19 ward unit of the University Hospital of Heraklion between March and November 2020. Diagnosis of COVID-19 was performed with a positive RT-PCR test for SARS-CoV-2. Admission criteria included at least one of the following: a) need for supplemental oxygen therapy, b) prolonged fever  $>38^{\circ}\text{C}$  for more than a week, c) Pneumonia severity index (PORT score/PSI) higher than 70 (class III) or d) presence of radiographic pulmonary infiltrates in chest X-ray or computed tomography (CT) [8]. All study protocols were in accordance with the declaration of Helsinki and formally approved by the local ethics committee.

### *Therapeutic protocols and algorithms*

Subjects were considered to have severe COVID-19 according to the IDSA criteria [9]. The need for supplemental oxygen was decided on the basis of respiratory failure (type I defined by  $\text{PaO}_2 < 60$  mmHg or type II characterised by  $\text{PaCO}_2 > 50$  mmHg) or respiratory distress defined by a respiratory rate (RR)  $> 30$  breaths per minute, use of accessory respiratory muscles, dia-

phoresis, shortness of breath (i.e. inability to complete sentences), tachycardia, or hypertension. All subjects received prophylactic anticoagulant treatment with low molecular weight heparin, adjusted to body weight and anti-factor Xa levels [10]. All subjects with radiographic findings consistent with pulmonary alveolar infiltrates were treated with empirical antimicrobial treatment as per community-acquired pneumonia guidelines [11]. Subjects requiring oxygen therapy were additionally treated with dexamethasone (starting from July), based on then-published evidence suggesting a beneficial effect of corticosteroid treatment on COVID-19 mortality [12]. Subjects with early symptom duration on admission ( $< 10$  days) were also treated with remdesivir [13]. HFNO with an inspiratory flow of 60 lt/min was administered when subjects consistently displayed respiratory failure or respiratory distress whilst on a 50% Venturi mask [14]. Intermittent prone positioning was applied on subjects requiring  $\text{FiO}_2 > 80\%$  whilst on HFNO for as long as possible, depending on patient tolerance [15]. Admission to the ICU was reserved for subjects experiencing respiratory distress, impaired level of consciousness, agitation, or development of organ failure (renal failure, myocardial infarction, arrhythmia, etc.) whilst on maximal  $\text{FiO}_2$  HFNO therapy ( $\text{FiO}_2 = 100\%$ ).

### *Statistics*

Categorical data were analysed with Fisher's exact test or Pearson's chi-square test, as appropriate. Continuous variables were tested for normality using the D'Agostino & Pearson omnibus normality test. Continuous variables were compared using Student's t-test for normally distributed variables and the Mann-Whitney U-test for non-normally distributed variables. All tests were two-tailed, and p-values  $< 0.05$  were considered significant. Data are presented as numbers (% of total) for categorical variables and median (interquartile range, IQR) or mean ( $\pm$  standard deviation, SD) for continuous variables with non-normally or normally distributed data, respectively. Logistic regression analysis models were developed to evaluate the association between patient demographics and laboratory characteristics on admission with the need for HFNO and intubation. All the above-mentioned statistics were calculated with GraphPad Prism 6.0 (GraphPad Software, Inc., San Diego, CA). Separate multivariate logistic regression analysis models were developed to evaluate the association of factors identified in the univariate analyses with a  $p < 0.05$  needing HFNO or intubation. Multivariate analysis was performed using the SPSS version 23.0

(IBM Corp., Armonk, N.Y., USA).

## RESULTS

### *Patient characteristics and outcomes*

In total, 89 consecutive subjects were admitted during the study period. The demographic and clinical characteristics of the subjects are presented in Table 1. The median age was 61 years (range 20-92 years), whilst 58 subjects (65.2%) were male. In total, 62 (69.7%) had at least one co-morbidity or risk factor associated with severe COVID-19. Hypertension had been diagnosed in 39 (43.8%), diabetes mellitus in 18 (20.2%), cardiovascular disease in 17 (19.1%), and chronic lung disease in 13 (14.6%), while 18 (20.2%) were smokers. The mean body mass index (BMI) was 28.3 kg/m<sup>2</sup>.

All subjects were treated according to national guidelines for COVID-19 treatment. Among all subjects, 71 (79.8%) received dexamethasone, and 76 (85.4%) received antimicrobial treatment. Of the 89 participants, 74 (83%) had severe COVID-19 per IDSA criteria (Table 2). Subjects with severe COVID-19 were older, had a higher PSI on admission, higher ferritin and CRP values, higher neutrophil to lymphocyte ratio, lower worst PaO<sub>2</sub>/FiO<sub>2</sub> ratio during their hospitalization (Table 2), and longer length of hospital stay. No patient with non-severe COVID-19 disease was intubated or died. Intubation and mortality rates in the subgroup of patients with severe COVID-19 were very low, 6.8 and 4.1%, respectively.

### *Associates of HFNO needs: Ward versus ICU setting comparison*

In a subgroup of subjects with refractory hypoxemia or respiratory distress despite conventional oxygen therapy as defined above, HFNO, along with prone positioning, were utilized (n=33, 37% of subjects). Subjects requiring HFNO had more PSI points on admission, lower worst PaO<sub>2</sub>/FiO<sub>2</sub> ratio during their hospitalization (often at the time point when HFNO treatment was decided), and a longer length of hospital stay (reflecting longer weaning process from high HFNO, Table 3). Among subjects on HFNO, 15 out of 33 (45%) were eventually admitted to the ICU based on aforementioned criteria and only 4 out of 33 (12%) were intubated. Importantly, in the group of subjects needing HFNO therapy, clinical and laboratory characteristics and mortality were not different in subjects treated exclusively in-ward compared to subjects admitted to the ICU, with the exception of the 4 subjects who were eventually intubated (Tables 4 and 5).

Interestingly, a univariate logistic regression analysis model with the need for HFNO as the dependent variable as well as patient demographics and bio-

TABLE 1.  
*Participant characteristics*

	All patients (n=89)
Age, median (IQR)	61 (52-72)
Male gender, n (%)	58 (65.2)
Hypertension, n (%)	39 (43.8)
Dyslipidemia, n (%)	24 (27)
Diabetes mellitus, n (%)	18 (20.2)
Smoking, n (%)	18 (20.2)
Cardiovascular disease, n (%)	17 (19.1)
Chronic lung disease, n (%)	13 (14.6)
BMI, mean (SD), kg/m <sup>2</sup>	28.3 (4.6)
Previous medication use	
Diuretics, n (%)	22 (24.7)
Statins, n (%)	19 (21.3)
ACE inhibitors, n (%)	20 (22.5)
Proton pump inhibitors, n (%)	17 (19.1)
Antipsychotics, n (%)	12 (13.4)
Calcium channel blockers, n (%)	12 (13.4)
Biguanides, n (%)	12 (13.4)
Dipeptidyl peptidase-4 inhibitor, n (%)	8 (9)
Immunomodulating agents, n (%)	7 (7.9)
Sulfonylureas, n (%)	5 (5.6)
Corticosteroids, n (%)	5 (5.6)
Insulin, n (%)	4 (4.4)
Glucagon-like peptide-1 agonists, n (%)	3 (3.4)
SGLT2 inhibitors, n (%)	2 (2.2)
Days of symptoms before admission, median (IQR)	6 (4-8)
D-dimers, median (IQR), µg/ml	0.78 (0.43-1.15)
CRP, median (IQR), mg/ml	4.93 (1.97-11.8)
Ferritin, median (IQR), ng/ml	647.7 (333.1-1330)
Neutrophil to lymphocyte ratio, median (IQR)	6 (2.8-10.6)

ACE: angiotensin converting enzyme; BMI: body mass index; CRP: C-reactive protein; IQR: Interquartile range; SD: Standard deviation; SGLT2: sodium-glucose transport protein 2

TABLE 2.  
Comparison of subjects with severe and non-severe COVID-19 (IDSA criteria)

	All patients (n=89)	Severe COVID-19 (n=74)	Non severe-COVID-19 (n=15)	P
Age, median (IQR)	61 (52-72)	64 (53.8-74)	48 (28-60)	0.0011
Male gender, n (%)	58 (65.2)	49 (66.2)	9 (60)	0.7677
Hypertension, n (%)	39 (43.8)	35 (47.3)	4 (26.7)	0.1652
Diabetes Mellitus, n (%)	18 (20.2)	16 (21.6)	2 (13.3)	0.7263
Smoking, n (%)	18 (20.2)	14 (18.9)	4 (26.7)	0.4933
Cardiovascular disease, n (%)	17 (19.1)	15 (20.3)	2 (13.3)	0.7263
Chronic lung disease, n (%)	13 (14.6)	9 (12.2)	4 (26.7)	0.2213
BMI, mean (SD), kg/m <sup>2</sup>	28.3 (4.6)	28.8 (4.9)	25.8 (0.9)	0.3194
ACE inhibitors, n (%)	20 (22.5)	18 (24.3)	2 (13.3)	0.5051
PSI upon admission, median (IQR)	76.5 (55.3-100.8)	82 (60.8-103.3)	51.5 (27-64)	<0.0001
Worst PaO <sub>2</sub> /FiO <sub>2</sub> , mean (SD)	196 (108)	166.5 (86.2)	365.7 (44.6)	<0.0001
D-dimers, median (IQR), µg/ml	0.78 (0.43-1.15)	0.8 (0.46-1.23)	0.41 (0.14-0.98)	0.057
CRP, median (IQR), mg/ml	4.93 (1.97-11.8)	5.32 (2.84-12.25)	1.43 (0.72-4.51)	0.0061
Ferritin, median (IQR), ng/ml	647.7 (333.1-1330)	663 (379-1334)	180.4 (133.3-421.5)	0.0031
Neutrophil to lymphocyte ratio, median (IQR)	6 (2.8-10.6)	7.16 (3.71-12.46)	1.85 (1.34-3.25)	<0.0001
Hospital stay, median (IQR)	7 (4-10)	8 (6-12)	4 (2.5-6)	0.0063
Intubation, n (%)	5 (5.6)	5 (6.8)	0 (0)	0.5842
Mortality, n (%)	3 (3.4)	3 (4.1)	0 (0)	1

ACE: angiotensin converting enzyme; BMI: body mass index; COVID-19: Coronavirus disease 2019; CRP: C-reactive protein; IDSA: Infectious diseases Society of America; IQR: Interquartile range; PSI: Pneumonia severity index; SD: Standard deviation

chemical characteristics on admission as independent variables identified PSI, alanine aminotransferase (SGPT), and gamma-glutamyl transferase ( $\gamma$ GT) to be positively associated with the need for HFNO.

Thus, a multivariate regression analysis model was used to identify independent factors associated with the need for HFNO using those factors found to be significant in the univariate analysis (PSI on admission, SGPT, and  $\gamma$ GT). Only PSI on admission was found to be independently associated with the need for HFNO [odds ratio=1.022 per 1 PSI unit (p=0.01, 95% CI for OR 1.005-1.039)].

The results of the multivariate analysis are shown in Supplementary Table 1. Further analysis was performed in order to identify factors independently associated with the need for intubation. Thus, an univariate logistic regression analysis model with the need for intubation as the dependent variable and the need for HFNO and patient demographics along with biochemical characteristics on admission as independent

variables identified a history of heart failure, mean corpuscular hemoglobin, amylase, and ferritin to be associated with the need for intubation.

A multivariate regression analysis model was used to identify independent factors associated with the need for HFNO using factors found to be significant in the univariate analysis. However, it did not identify any. The results of the multivariate analysis are shown in Supplementary Table 2.

## DISCUSSION

Severe respiratory disease manifested by acute hypoxemic respiratory failure is the main cause of mortality in the COVID-19 pandemic [1]. HFNO therapy, often combined with prone positioning, is effective in respiratory failure refractory to conventional oxygen therapy, and it may prevent unnecessary intubations and their resulting complications [14,16,17]. Whilst HFNO is primarily used in the ICU setting, there is

TABLE 3.  
Comparison of subjects with severe COVID-19 (IDSA criteria) treated with HFNO or without HFNO

	HFNO (n=33)	No HFNO (n=41)	p
Age, median (IQR)	67 (56-77.5)	61 (53-73)	0.46
Male gender, n (%)	23 (69.7)	26 (63.4)	0.6271
Hypertension, n (%)	15 (45.5)	20 (48.8)	0.8181
Diabetes Mellitus, n (%)	6 (18.2)	10 (24.4)	0.5802
Smoking, n (%)	9 (27.3)	5 (12.2)	0.1375
Cardiovascular disease, n (%)	6 (18.2)	9 (22)	0.7762
Chronic lung disease, n (%)	2 (6.1)	7 (17.1)	0.2831
BMI, mean (SD), kg/m <sup>2</sup>	28.8 (5.9)	28.9 (4.1)	0.9739
ACE inhibitors, n (%)	9 (27.3)	9 (22)	0.7858
PSI upon admission, median (IQR)	93.5 (76.3-115)	67.5 (53.5-99.5)	0.0029
Worst PaO <sub>2</sub> /FiO <sub>2</sub> , mean (SD)	102.2 (35.3)	222.1 (78.1)	<0.0001
D-dimers, median (IQR), µg/ml	1.03 (0.66-1.33)	0.67 (0.37-0.89)	0.0139
CRP, median (IQR), mg/ml	5.79 (3.74-13.11)	5.23 (1.67-12.15)	0.2212
Ferritin, median (IQR), ng/ml	895.3 (598.8-1521)	565.7 (299.8-892)	0.0151
Neutrophil to lymphocyte ratio, median (IQR)	9.42 (6.49-18.6)	4.13 (2.64-17.35)	0.0009
Hospital stay, median (IQR)	10 (8-14)	6 (4.8-9)	0.005
Intubation, n (%)	4 (12.1)	1 (2.4)	0.0001
Mortality, n (%)	2 (6.1)	1 (2.4)	0.5826

ACE: angiotensin converting enzyme; BMI: body mass index; COVID-19: Coronavirus disease 2019; CRP: C-reactive protein; HFNO: High flow nasal oxygen; ICU: Intensive care unit; IDSA: Infectious diseases Society of America; IQR: Interquartile range; PSI: Pneumonia severity index; SD: Standard deviation

evidence for its successful use in the ward [4,18].

Prone positioning could also be used in conjunction with HFNO in awake patients in order to reduce the need for intubation [7]. In a recently published study of patients with COVID-19 where awake prone positioning was used as a variable, and patients with COVID-19 not treated with prone positioning served as a control, awake prone positioning was found to be associated with a reduction in the risk of intubation and even hospital mortality [19]. Specific guidance regarding prone positioning in awake patients with COVID-19 was released in 2020 and suggested prone positioning for as long as possible in cooperative patients requiring at least FiO<sub>2</sub> 28% of supplementary oxygen in the absence of contraindications to achieve adequate oxygen saturation [20]. Patients included in the present study were strongly encouraged to maintain a prone position for as long as possible when oxygen requirements were higher or equal to 80% with

HFNO since patient compliance was low in patients with lower oxygen requirements. Recent studies suggest that prone positioning is associated with optimal outcomes in patients with COVID-19, depending on the duration of prone position application. More specifically, a recent study identified that prone positioning for at least 6 hours per day is associated with a reduction in need for intubation, while prone positioning for at least 8 hours per day is associated with a reduction of hospital mortality risk [19]. However, no specific studies have been conducted until now to identify the optimal duration for the application of prone positioning in awake patients with COVID-19 [21]. Even though the optimal aim is to maintain the prone position for as long as possible, a significant proportion of patients fail to maintain it for at least 8 hours [7,21]. To that end, since patient compliance is crucial to increase the duration of prone positioning, measures such as additional pillows may be needed to

TABLE 4.  
Comparison of subjects treated with HFNO admitted to the ICU or treated exclusively on the ward

	ICU (n=15)	Ward only (n=18)	p
Age, median (IQR)	64 (56-70)	67.5 (56.8-78.5)	0.53
Male gender, n (%)	10 (66.7)	13 (72.2)	1
Hypertension, n (%)	5 (33.3)	10 (55.6)	0.2964
Diabetes Mellitus, n (%)	3 (20)	3 (16.7)	1
Smoking, n (%)	5 (33.3)	4 (22.2)	0.6968
Cardiovascular disease, n (%)	2 (13.3)	4 (22.2)	0.6648
Chronic lung disease, n (%)	0 (0)	2 (11.1)	0.4886
BMI, mean (SD), kg/m <sup>2</sup>	30.3 (4.2)	27.9 (7)	0.6137
ACE inhibitors, n (%)	3 (20)	6 (33.3)	0.4585
PSI upon admission, median (IQR)	86 (70.3-103.3)	99 (80.3-120.5)	0.3198
Worst PaO <sub>2</sub> /FiO <sub>2</sub> , mean (SD)	95.3 (30.1)	107.5 (38.8)	0.3415
D-dimers, median (IQR), µg/ml	1.1 (0.6-1.19)	0.94 (0.7-1.93)	0.7028
CRP, median (IQR), mg/ml	10.05 (4.51-16.65)	4.75 (3.02-10.22)	0.1253
Ferritin, median (IQR), ng/ml	651.1 (536.3-1851)	1085 (654.8-1806)	0.4234
Neutrophil to lymphocyte ratio, median (IQR)	9.76 (6.61-17.35)	9.18 (5.37-19.76)	0.7289
Hospital stay, median (IQR)	11.5 (1.8-15.8)	9 (8-14)	0.9451
Intubation, n (%)	4 (26.7)	0 (0)	0.0334
Mortality, n (%)	1 (6.7)	1 (5.6)	1

Angiotensin converting enzyme; BMI: body mass index; COVID-19: Coronavirus disease 2019; CRP: C-reactive protein; HFNO: High flow nasal oxygen; ICU: Intensive care unit; IDSA: Infectious diseases Society of America; IQR: Interquartile range; PSI: Pneumonia severity index; SD: Standard deviation

increase patient comfort and cooperation, especially in specific patient groups, such as those with obesity or pregnancy [21].

On the other hand, HFNO use in adult patients with COVID-19 has been shown to reduce the days on invasive mechanical ventilation and the need for a stay in the ICU compared to a group where early invasive mechanical ventilation was used [22]. In another study, where HFNO was compared to conventional oxygen therapy in patients with COVID-19, HFNO use was associated with a reduced need for mechanical ventilation and time to clinical recovery [23]. In our cohort of COVID-19 subjects, low overall intubation and mortality rates were documented, confirming the importance of HFNO therapy in combating COVID-19. Crucially, there were no laboratory, clinical or outcome differences among subjects subjected to HFNO in ICU and those subjected to HFNO in the ward. Our findings imply that HFNO and prone positioning may be effectively and safely used in the ward

in the hands of experienced staff. This would allow, in the context of dramatic ICU overload due to the pandemic, for ICU transfer filtering, prioritizing patients with a clear indication for invasive mechanical ventilation whilst preserving the quality of care and favorable outcome across all patients. This is in line with literature, where HFNO use has been shown to be effectively used in the wards in several studies, thus, reducing both the need for mechanical ventilation as well as transfers to the ICU for patients that could be treated with HFNO in the ward [4,18,24,25]. Importantly, HFNO use was not shown to increase COVID-19 infections in healthcare personnel when used both in an ICU and in a ward setting [4,26].

Multivariate regression analysis did not identify any factors independently associated with the need for intubation. Other studies have identified the ROX index, PaO<sub>2</sub>/FiO<sub>2</sub> ratio, old age, male gender, and a history of diabetes mellitus to be associated with an increased risk of intubation. In contrast, advanced age

TABLE 5.  
Comparison of subjects treated with HFNO admitted to the ICU (but not intubated) or treated exclusively on the ward

	ICU not intubated (n=11)	Ward only (n=18)	p
Age, median (IQR)	64 (56-70)	67.5 (56.8-78.5)	0.59
Male gender, n (%)	8 (72.7)	13 (72.2)	1
Hypertension, n (%)	4 (36.4)	10 (55.6)	0.4497
Diabetes Mellitus, n (%)	3 (27.3)	3 (16.7)	0.6457
Smoking, n (%)	5 (45.5)	4 (22.2)	0.2371
Cardiovascular disease, n (%)	2 (18.2)	4 (22.2)	1
Chronic lung disease, n (%)	0 (0)	2 (11.1)	0.5123
BMI, mean (SD), kg/m <sup>2</sup>	30.3 (4.2)	27.9 (7)	0.6137
ACE inhibitors, n (%)	2 (18.2)	6 (33.3)	0.6706
PSI upon admission, median (IQR)	84 (69-100.5)	99 (80.3-120.5)	0.1722
Worst PaO <sub>2</sub> /FiO <sub>2</sub> , mean (SD)	101.5 (30.4)	107.5 (38.8)	0.6671
D-dimers, median (IQR), µg/ml	1.02 (0.55-1.25)	0.94 (0.7-1.93)	0.5126
CRP, median (IQR), mg/ml	9.33 (3.96-15.92)	4.75 (3.02-10.22)	0.3738
Ferritin, median (IQR), ng/ml	620.5 (463.1-1372)	1085 (654.8-1806)	0.1878
Neutrophil to lymphocyte ratio, median (IQR)	12.87 (6.38-19.4)	9.18 (5.37-19.76)	0.3882
Hospital stay, median (IQR)	13.5 (7-16.8)	9 (8-14)	0.3791
Mortality, n (%)	1 (9.1)	1 (5.6)	1

ACE: angiotensin converting enzyme; BMI: body mass index; COVID-19: Coronavirus disease 2019; CRP: C-reactive protein; HFNO: High flow nasal oxygen; ICU: Intensive care unit; IDSA: Infectious diseases Society of America; IQR: Interquartile range; PSI: Pneumonia severity index; SD: Standard deviation

and obesity are associated with a need for extended intubation [27,28].

Several laboratory biomarkers have been proposed to predict COVID-19 mortality, including ferritin, troponin I, C-reactive protein (CRP), and D-dimer levels [29–33], and scoring stratification systems have been developed [34,35]. Prediction of the need for HFNO, an earlier severity readout as compared to mortality, has not been equally addressed to date. In our study, PSI on admission was an independent predictor for HFNO needs. PSI has a moderate predictive value for COVID-19 mortality [36], but it may be more useful in the early prediction of HFNO needs regardless of the outcome. We also propose that  $\gamma$ GT and SGPT levels on admission may have some value in this regard, although they did not reach significance in the multivariate model. Given the established acute liver injury associated with SARS-CoV2 infection [37–39], the contribution of these biomarkers in predicting HFNO needs and mortality warrants further investigation in larger study populations.

Overall COVID-19 mortality is high compared to influenza but lower compared to other emerging coronaviruses (estimated ~5%) [40–43], rising to almost 20-30% in patients with severe COVID-19 pneumonia [35,44,45] and approximating 50% in critically ill patients [45]. However, these may be affected by site-specific variability in practices, policies, and demographics.

This is decisively affected by the acute and massive burden of admitted and hospitalized COVID-19 patients, leading to triaging and compromising the quality of care, leading to highly variable mortality rates in the literature. A more efficient algorithm is thus required to manage admitted patients within national health systems to protect wards and ICUs whilst maintaining appropriate patient care.

COVID-19 mortality is mainly attributed to subsequent hyper-inflammation [46], when adequate support with HFNO is crucial to reduce mortality, as demonstrated here. A secondary observation of our study involves the use of antimicrobials, which has been

understudied, given the low reported rates of bacterial co-infection in COVID-19 [47]. Lung microbial burden and dysbiosis, an imbalance between respiratory tract flora and host immune mechanisms, predicts mortality in critically ill patients [48]. This may be relevant in COVID-19, given the immune component of the disease and the occult microbial co-infection risk under corticosteroid treatment. This, however, remains a hypothesis warranting investigation.

This study has certain limitations, including its single-center design and relatively small size. Accordingly, the main findings should be confirmed in more extensive studies.

In summary, we demonstrate that careful assessment of respiratory distress markers, timely application of HFNO, and prone positioning are associated with excellent outcomes in COVID-19 in a ward setting, reserving ICU beds for patients with an absolute indication for mechanical intubation.

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Supplementary TABLE 1.  
*Logistic regression analysis of need for high-flow oxygen therapy*

	Univariate analysis p	Multivariate analysis p	OR (95% CI)
PSI upon admission (per unit)	0.003	0.01	1.022 (1.005-1.039)
SGPT (per U/l)	0.01	0.543	1.007 (0.984-1.031)
$\gamma$ GT (per U/l)	0.02	0.444	1.005 (0.992-1.018)

$\gamma$ GT: Gamma-Glutamyl Transpeptidase; CI: confidence interval; OR: odds ratio; PSI: Pneumonia severity index, SGPT: Serum Glutamic Pyruvic Transaminase

Supplementary TABLE 2.  
*Logistic regression analysis of need for intubation*

	Univariate analysis p	Multivariate analysis p	OR (95% CI)
History of heart failure	0.000	0.993	1.810*10 <sup>40</sup> (0.000-Infinity)
MCH (per pg/cell)	0.008	0.993	90,594,807.6 (0.000-Infinity)
Amylase (per U/l)	0.015	0.999	1.514 (0.000-2,995*10 <sup>223</sup> )
Ferritin (per $\mu$ g/l)	0.047	0.996	1.019 (0.001-1,909.687)

CI: confidence interval; MCH: mean corpuscular hemoglobin; OR: odds ratio