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Feasibility and clinical impact of out-of-ICU non-invasive respiratory support in patients with COVID-19 related pneumonia

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Abstract

Introduction: The Coronavirus 2(SARS-CoV-2) outbreak spread rapidly in Italy and the lack of intensive care unit(ICU) beds soon became evident, forcing the application of noninvasive respiratory support(NRS) outside the ICU, raising concerns over staff contamination. We aimed to analyze the safety of the hospital staff, the feasibility, and outcomes of NRS applied to patients outside the ICU.

Methods: In this observational study, data from 670 consecutive patients with confirmed COVID-19 referred to the Pulmonology Units in nine hospitals between March 1st and May 10th,2020 were analyzed. Data were collected including medication, mode and usage of the NRS (i.e. high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), noninvasive ventilation(NIV)), length of stay in hospital, endotracheal intubation(ETI) and deaths.

Results: Forty-two health-care workers (11.4%) tested positive for infection, but only three of them required hospitalization. Data are reported for all patients (69.3% male), whose mean age was 68 (SD 13) years. The PaO_2/FiO_2 ratio at baseline was 152±79, and the majority of patients (49.3%) were treated with CPAP. The overall unadjusted 30-day mortality rate was 26.9% with 16%, 30%, and 30%, while the total ETI rate was 27% with 29%, 25% and 28%, for HFNC, CPAP, and NIV, respectively, and the relative probability to die was not related to the NRS used after adjustment for confounders. ETI and length of stay were not different among the groups. Mortality rate increased with age and comorbidity class progression.

Conclusions: The application of NRS outside the ICU is feasible and associated with favourable outcomes. Nonetheless, it was associated with a risk of staff contamination.

Introduction

On February 20th 2020, Coronavirus disease 19 (COVID-19) severely hit the Northern part of Italy. It was reported that, in Lombardy, the most populated region of the country, more

than 1500 patients required intensive care unit (ICU) admission over only 4 weeks, largely exceeding the actual capacity (1). In the same period, the number of hospital admissions was 7285 (2). Approximately 35% of these patients experienced Acute Respiratory Failure (ARF) requiring any form of respiratory support. A mathematical model of the occupation of intensive care resources in Italy predicted saturation of the theoretically available beds in the national territory by mid-April 2020 (3).

Under these circumstances, despite extraordinary efforts aimed at increasing the availability of ICU resources, the Italian Societies of Respiratory Medicine proposed a protocol to provide ventilatory support outside the ICU in dedicated Respiratory COVID Units, reinforced by a higher number of nurses and noninvasive monitoring (4). This recommendation was somehow in contrast to most of the available guidelines that contraindicated using noninvasive respiratory support (NRS) in these patients due to the major concerns over using bio-aerosol producing techniques, because of possible contamination of the hospital staff (5).

This “emergency” situation gave us the unique opportunity to challenge the hypothesis that NRS should not be used outside the ICU during pandemics. We have therefore analyzed the feasibility and safety, in terms of staff contamination, of NRS applied to severely ill patients outside the ICU. Patients’ characteristics and clinical outcomes were also analyzed.

Methods

The study was conducted in four out of five hospitals in the Area Vasta Emilia network and in five hospitals in the neighbouring regions, serving a population of approximately 8 million people. Institutional Review Boards reviewed the protocol and authorized prospective data collection. Informed consent was waived. A confirmed case of COVID-19 was defined as a patient with a positive result on high throughput sequencing or real-time reverse

transcriptase–polymerase chain reaction assay of nasal and pharyngeal swab specimens. Data were collected from registries of the Respiratory Disease Units coordinators at the nine hospitals identifying all of the patients receiving NRS outside the ICU.

Excluding standard oxygen administration, patients were treated with three different types of NRS, namely high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), or noninvasive ventilation (NIV), which also represented the three different groups in the analysis.

The triage of patients was performed according to the Italian Respiratory Societies Joint Guidelines based on severity. In particular, the following categories were proposed: a) green (SaO_2>94%, respiratory rate (RR)<20 breaths/min); b) yellow (SaO_2<94%, RR>20 but responds to 10–15 L/min oxygen); c) orange (SaO_2<94%, RR>20 but poor response to 10–15 L/min oxygen and requiring CPAP/NIV with very high FiO_2); d) red (SaO_2<94%, RR>20 but poor response to 10–15 L/min oxygen, CPAP/NIV with very high FiO_2 or presenting respiratory distress with PaO_2/FiO_2<200 and requiring ETI and intensive care). Patients belonging to these latter two categories were therefore considered eligible for NRS in dedicated respiratory COVID areas (see below) set up for the isolation of confirmed cases and ARF treatment.

These patients were not “usually” treated outside the ICU but, given the “emergency” situation, the lack of ICU beds and only once multiorgan disfunction was excluded, they still resulted eligible for an NRS trial.

The transfer of severely ill patients to the ICU for intubation, with compromised haemodynamic parameters, low PaO_2/FiO_2 or ’not responding to NRS’, was discussed with the intensivists, based on prognosis, and obviously was only possible if beds were available.

Although not specifically mentioned in the guidelines, HFNC was also used in these two categories, during breaks in ventilation or as a stand-alone support.

The use of helmet CPAP devices was suggested as first-line treatment, mainly for safety reasons. Clearly, this technique requires a sufficient supply of helmet interfaces (which ran out quite rapidly) and a high flow of O_2 (which exceeded the O_2 capacity in some hospitals), so that NIV and HFNC were used as alternatives, the first when it was necessary to "save" oxygen, and the second when CPAP availability finished.

The respiratory COVID areas consisted mainly of two different units, both present in all of the hospitals. The first one, formerly a respiratory ward, was an ad-hoc dedicated Respiratory Monitoring Unit consisting of specialized monitored areas with an active full-day shift run by a fixed group of pulmonologists and with a "reinforced" nurse–patient ratio varying from 1:4 to 1:6 depending on the hospital. The second unit, called Respiratory Intermediate Care Units, consisted of a fixed medical team. These had a monitoring system similar to that of the Respiratory Monitoring Units, together with the availability of ICU ventilators and a nurse–patient ratio from 1:2 to 1:4, where more severely affected patients were usually treated.

Patients were continuously monitored with electrocardiogram trace, noninvasive blood pressure, arterial oxygen saturation, and respiratory rate (RR). Intensive Care Medicine doctors were eventually available around the clock at the request of the ward teams. Great care was taken to keep a distance of >1.5 metres between each bed and to provide natural ventilation and airflow of at least 160 $L \cdot s^{-1}$ per patient.

Concerning staff protection, first of all, courses were quickly organized for staff in the correct use of personal protective equipment (PPE), dressing and undressing. Filtering facepiece class 3 (FFP3) or FFP2 masks, double non-sterile gloves, long-sleeved water-resistant gowns, goggles or face shields were mandatory in the presence of aerosol producing procedures.

NIV was delivered mainly by dedicated single circuit NIV platforms provided with an oxygen blender and ad-hoc filters placed in the single tube circuit before the non-rebreathing devices to minimize bio-aerosol dispersion, or by ICU ventilators. HFNC was delivered using standard devices (Nasal High Flow Therapy, Fisher and Paykel Healthcare Ltd, New Zealand), while helmet CPAP dedicated devices, designed for pandemics, were simply activated by connecting them to the O_2 source available in the hospital with blender systems applied to obtain adequate values of delivered FiO_2 (Intersurgical SpA, Mirandola, Italy and Dimar srl, Medolla, Italy).

Data collection

Data were collected prospectively from registries of the Respiratory Disease Units identifying all of the patients receiving NRS outside the ICU.

Variables recorded for each patient were obtained for the period from March 1st until May 10th 2020 and included the following: demographics (age, sex), comorbidities (type and number), respiratory condition at admission (respiratory rate (RR), PaO_2/FiO_2 ratio), medications (type of drugs prescribed), mode and usage of the NRS (ventilatory settings for NIV and CPAP, and flow rate for HFNC), and stay in hospital (days). The number of patients who died, either in the respiratory unit or in the hospital, and the patients who received endotracheal intubation (ETI) within the same time frame were recorded. Patients who were still hospitalized at the time of data analysis were excluded.

The health status of the staff working in the respiratory unit was closely monitored. All staff with fever or respiratory symptoms underwent chest radiography, and nasal and pharyngeal swab specimens were taken. Serology for SARS-CoV-2 antibodies and pharyngeal swab was also periodically performed for all staff.

Statistical analysis

No statistical sample size assessment was performed a priori, and sample size was the number of patients treated during the study period in the participant centres. Baseline characteristics of patients treated with HFNC, CPAP and NIV were compared. Across the treatment subgroups, continuous variables were expressed as means and standard deviation (SD) and were compared with the Kruskal–Wallis test and one-way ANOVA test, while categorical variables were expressed as numbers and percentages (%) and were compared using the χ2 test or Fisher's exact test. Percentages of available data for the overall study population were based on the total number of patients included in the study, while the distribution of available data over the treatment subgroups was based on the available data for that variable, and the percentages were calculated using the number of available data for that subgroup. The fraction of infected professional health care workers was presented as numerical and percentage values. The association between ventilatory treatment and clinical outcomes was calculated using a logistic regression model. The 30-day mortality rate was calculated adjusted for baseline confounders (age, P/F ratio, steroid usage and number of comorbidities).

Patients were grouped by age and PaO_2/FiO_2 ratio. Age groups were defined as follows: 21 through 40 years; 41 through 50 years; 51 through 60 years; 61 through 70 years; 71 through 80 years; 81 through 90 years; and 91 through 100 years. PaO_2/FiO_2 ratio groups were defined as follows: below 50 mmHg; 51 through 100 mmHg; 101 through 150 mmHg; 151 through 200 mmHg; 201 through 250 mmHg; 251 to 300 mmHg. For age subgroups, patients were further stratified according to the presence of comorbidities as follows: patients with ≤2 comorbidities and patients with >2 comorbidities. A dedicated composite index including 30-day mortality and intubation rate, was also considered.

The main clinical outcomes were presented across the age and comorbidity subgroups and across PaO_2/FiO_2 ratio strata. Continuous variables were expressed as means and SD and compared with the Kruskal–Wallis test and one-way ANOVA test while $\chi 2$ or Fisher's exact test was used to compare categorical variables between median age and comorbidity subgroups as appropriate. A two-sided test of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 8.4.1 (GraphPad Software, Inc., La Jolla, CA, USA) unless otherwise indicated.

Results

A total of 704 patients were considered and of these, 670 patients were included and their data analyzed. **Table 1** lists the patients' characteristics. CPAP, as applied by helmet, was used on the majority of patients (Supplementary Table 1). Twenty-eight out of 670 (4.2%) had a Do Not Intubate (DNI) order. Figure 1 illustrates the patients' allocation to NRS and clinical outcome. A total amount of 180 patients died at 30 days. Twenty of the 28 DNI patients died (9% of the total number of deaths). In total, 114 patients died on spontaneous breathing without an expressed written DNI order.

Most of the study patients were male (69.3%). Hypertension, diabetes, dyslipidemia, obesity and chronic cardiovascular disorders were the comorbidities most represented, evenly distributed among the groups with the exception of obesity, which was more prevalent in the NIV group. Hydroxychloroquine, methylprednisolone, low molecular weight heparin and tocilizumab were the drugs most used for treatment. The frequency distribution of age and PaO_2/FIO_2 ratio in the whole study population are shown in Supplementary Figure 1.

As shown in **Table 2**, 353 health care workers, including doctors, nurses, and health-care assistants, had been taking care of patients receiving NRS. Forty-two of them (12%) tested positive for SARS-CoV-2 infection showing symptoms of mild (n=9) or moderate disease requiring hospitalization (n=3). All infected workers recovered well. The overall rate of workers infected, in personnel not specifically involved in the care of COVID-19 patients, in the nine hospitals was 3.8±1.9%.

Table 3 illustrates the 30-day mortality rate in the overall population and in the three NRS subgroups with crude values and values adjusted for age, baseline PaO_2/FiO_2, number of comorbidities and steroid usage. The three modes of NRS had a similar impact on mortality outcome, as well as on intubation rate and length of stay.

In **Table 4**, outcome measures stratified by age-class and number of comorbidities are reported in the overall study population. Notably, the mortality rate increased with age-class progression and was significantly lower in younger (median ≤ 69 years) compared to older patients (> 69 years) (12.5% versus 41.2%, difference 28.7%, p<0.0001). Mortality rate was higher in highly comorbid patients compared with patients with <2 comorbidities (34.4% versus 19.6%, difference 14.8%, p=0.0006). The percentage of patients subjected to ETI was higher among younger patients and in patients with lower comorbidities compared to older and highly comorbid patients, although not reaching statistical significance in the latter comparison (34.3% versus 18.8%, difference 15.5%, p<0.001, and 29% versus 20.4%, difference 8.6%, p=0.06, respectively). No difference in length of hospital stay was present among the age and comorbidity classes (19.6 versus 20.6 days, p=0.3, and 21.9 versus 22.1 days, p=0.9).

Outcome measures stratified by PaO_2/FiO_2 ratio classes and according to NRS are reported in **Table 5**. Patients with a PaO_2/FiO_2 ratio below 50 mmHg presented a higher 30-day mortality rate and a higher rate of ETI (p<0.001 and p<0.001, respectively).

NRS settings are shown in Supplementary Table 1. NIV was used as much as the patients could tolerate and in a small percentage of cases (43/177=24%), HFNC was applied during the intervals. Patients with bilateral posterior infiltrates were also usually placed in the prone position for few hours a day, in all three NRS groups, with a schedule dependent on their tolerance.

Discussion

This study showed that using NRS devices is feasible in patients with ARF due to SARS-CoV-2 infection treated outside ICUs, in newly developed dedicated COVID Respiratory Monitoring Units, formerly respiratory wards, and in Respiratory Intermediate Care Units.

Despite using the recommended PPE, a 11.4% contamination rate was observed among healthcare workers treating the infected patients.

After adjusting for potential confounders, 30-day mortality rates using HFNC, CPAP and NIV were not significantly different.

One of the major concerns of using bio-aerosol generating devices is that healthcare workers are at high risk of contracting the infection and therefore most international guidelines recommend being cautious or even contraindicate their use (6–8). Nevertheless, WHO advocate using CPAP or NIV for the management of respiratory failure in COVID-19 patients, provided that appropriate PPE is worn by the personnel (9).

Several studies have found that the maximum exhaled air dispersion via different oxygen administration and ventilatory support strategies is minimal for CPAP through an oronasal mask or NIV through a helmet equipped with an inflatable neck cushion, and is much less when compared with any kind of oxygen delivery system (10).

Interestingly enough, so far, studies have been conducted in negative pressure hospital rooms with at least six air changes per hour (minimum number of air changes recommended by WHO is 12 per hour). When these rooms were not available, as was the case for most of our patients, alternative hospital areas including rooms with natural ventilation (expressed as the product of room volume and air change rate) of at least 160 $L \cdot s^{-1}$ per patient were routinely employed, in keeping with the WHO statement (11). Indeed, according to the Italian recommendations (4), the large majority of our study population

received CPAP (by helmet or face mask), mask-NIV, and HFNC with a medical mask over the nasal prongs.

Taking all these precautions into account and using all of the appropriate protection, the number of health workers who tested positive at serology or pharyngeal swab was still quite high (11.4%); however, those who became ill (12/369, i.e. 3.3% of the staff involved) were in line with the 3.5% of health care workers requiring hospital admission in China (12), the only study so far that has reported this outcome during the COVID-19 outbreak. One may claim that our staff could have been infected in the community rather than by exposure to NRSs; however, in the nine hospitals in this study, the overall rate of infection of health workers, in personnel not specifically involved in the care of COVID-19 patients. The dramatic and rapidly increasing wave of the pandemic obliged us to treat a high number of severely hypoxic patients with NRS outside the ICU. These patients are usually admitted to "protected" environments. The ATS/ERS Guidelines (13) for example suggested using NIV in *de-novo* respiratory failure only when managed by an experienced clinical team, and closely monitored in the ICU. Concerning the first point, all of the Units involved had extensive experience in NRS use over a long period, and the nurse–patient ratio was "unusually" high for a ward, since during the outbreak, the nursing staff was reinforced in the locations where the acutely ill patients were admitted. In addition, fully equipped noninvasive monitoring systems were available.

This is by far the largest report on the use of NRS outside the ICU; however, our COVID dedicated Respiratory Units cannot be considered equivalent to the "usual" respiratory wards. Previous studies conducted in ICUs where NRS use was reported (1,15-21) account for 188 patients treated with NIV and 61 by HFNC, without showing their characteristics and severity or the outcomes (in all but one study). Interestingly, this latter study (19) showed a very high mortality rate both with NIV and HFNC (80% and 52%, respectively). Indeed, only a

few patients were treated in the respiratory ward or unit, namely 80 and 33 patients using NIV and HFNC respectively, with a poor survival rate (22,23).

Despite the fact that comparison among studies is extremely difficult due to the potential heterogeneity of patients included and/or to differing local hospital organization, the failure rate (i.e. mortality and/or ETI) was much lower in our population, even when adjusted for potential confounders (see Table 3), and it was comparable to what was observed (26%) in a large Italian study performed in the ICU in patients mostly intubated and with a PaO_2/FiO_2 ratio similar to ours (1). In addition, in a recent two-period retrospective case–control study, Oranger et al. (24) demonstrated that CPAP could avoid intubation at 7 days and at 14 days, particularly in COVID patients with a previous DNI decision.

The mortality rate was similar with all of the NRS modes used after adjustment for confounders; however, it has to be noted that HFNC was usually applied in less sick patients compared with NIV and CPAP, and this may reflect the attitude of the clinicians to start these latter two modes in patients where they judged that applying a relatively high level of external positive end expiratory pressure (PEEP) was more appropriate.

It has been suggested that using any form of NRS might unduly delay the start of ETI; however, it should be noted that 28 patients received a DNI order (20 of them died), and that an ICU bed was not promptly available at the time of deterioration, as reported in a specific small subset of the patient population. It may also be argued that "*only*" less than 5% of patients signed a DNI order.

In Italy, the very large majority of the population are not sufficiently aware of the new Advanced Directive Law (25), or they do not want to complete in advance any document in this respect. Therefore, most of our patients arrived at hospital without any DNI or Do Not Resuscitate directives. The reasons for not proceeding to ETI in the absence of a written DNI order might be explained by: presumed lack of benefit from ETI or mechanical ventilation

(MV) based on clinical judgement, sudden death, or verbal refusal from the patient at the time of clinical deterioration. However, the majority of patients received “full treatment” when needed.

Despite the fact that this retrospective analysis in a large population indicates that NRS may help to treat severely affected COVID-19 patients outside the ICU, in newly dedicated respiratory areas with experienced staff, it also presents three main limitations. First, the design was retrospective, like most of the studies published during this terrible period. Second, the decision to start one of the NRS modes was left to the attending physicians and mainly relied on the actual availability of equipment, so that the proportion of devices used was not evenly distributed. Third, as in most real-life studies dealing with the COVID-19 pandemic (1), missing data may be quite relevant; however, the critical nature of the situation did not always allow detailed information to be collected.

To conclude, this is the first observational, large multicentre study showing that the application of noninvasive respiratory devices outside the ICU is feasible but is associated with a risk of staff contamination; however, the retrospective study design precludes drawing firm conclusions about its effectiveness despite the fact that the mortality and intubation rates compare favourably with those of previous reports.

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1 **Table 1. Demographic and clinical characteristics of the study population and according to cohort**

Variable	Total n=670 (100%)	Cohort			p value
		HFNC n= 163 (24.3%)	CPAP n= 330 (49.3%)	NIV = 177 (26.4%)	
Age, years (SD)	68.3 (13.3)	65.7 (14.7)	70.3 (12.1)	66.8 (13.5)	<0.001
Male, n (%)	464 (69.3)	114 (69.9)	223 (67.6)	127 (71.8)	n.s. (0.6)
SOFA, score (SD)	3.3 (1.7)	2.5 (0.9)	3.3 (1.7)	4 (1.9)	<0.0001
PaO_2/FiO_2, mmHg (SD)	152 (79)	166 (65)	151 (90)	138 (66)	<0.01
Respiratory rate, bpm (SD)	28 (7)	25 (5)	28 (7)	31 (7)	<0.0001
Comorbidities					
Hypertension, n (%)	311 (51.2) *	74 (47) §	153 (55) ç	84 (49) ^	n.s. (0.15)
Dyslipidemia, n (%)	84 (15.8) **	20 (12.6) §	53 (19.2) ç	11 (10.5) ^^	n.s. (0.06)
Diabetes mellitus, n (%)	125 (20.6) *	32 (20.1) §	60 (21.7) ç	33 (19.1) ^	n.s. (0.82)
Chronic cardiovascular disease, n (%)	105 (17.3) *	29 (18.2) §	54 (19.6) ç	22 (12.7) ^	n.s. (0.16)

Obesity, n (%)	108 (17.8) *	33 (20.8) §	31 (11.3) ç	44 (25.3) ^	<0.001
Chronic kidney disease, n (%)	34 (6.4) **	12 (7.6) §	17 (6.2) ç	5 (4.8) ^^	n.s. (0.59)
COPD, n (%)	46 (7.6) *	9 (5.7) §	12 (4.4) ç	25 (14.5) ^	<0.001
Chronic hepatic disease, n (%)	3 (0.6) **	1 (0.6) §	2 (0.7) ç	0 (0) ^^	n.s. (0.71)
Cancer, n (%)	53 (10) **	17 (10.7) §	28 (10.1) ç	8 (7.6) ^^	n.s. (0.72)
Treatment					
Hydroxychloroquine, n (%)	263 (82) °	128 (91) @	108 (72) %	27 (90) &	<0.0001
Lopinavir/ritonavir, n (%)	74 (23.1) °	58 (41) @	10 (7) %	6 (20) &	<0.0001
Darunavir/cobicistat, n (%)	47 (15) °	37 (26) @	9 (6) %	1 (3) &	<0.0001
Remdesivir, n (%)	2 (0.6) °	1 (0.8) @	1 (0.7) %	0 (0) &	n.s. (0.89)
Tocilizumab, n (%)	161 (34) °°	47 (34) @	65 (28) %%	49 (50) &&	<0.001
Methylprednisolone, n (%)	275 (69) °°°	105 (75) @	113 (75) %	57 (58) &&	<0.01
Prophylactic LMWH, n (%)	90 (35) °°°°	63 (45) @	20 (21) %%%	7 (23) &	<0.001
Therapeutic LMWH, n (%)	130 (50) °°°°	69 (49) @	48 (49) %%%	13 (43) &	n.s. (0.78)

The data are presented as numerical and percentage values for dichotomic variables and as mean and standard deviation (SD) for continuous variables. Statistical significance was set for $p<0.05$.

COPD = Chronic Obstructive Pulmonary Disease; LMWH = Low Molecular Weighted Heparin; SOFA = Subsequent Organ Failure Assessment; HFNC = High Flow Nasal Cannula; CPAP = Continuous Positive Airway Pressure; NIV = Noninvasive Mechanical Ventilation.
**n=608, **n=532, §n=159, çn=276, ^n=173,^^n=105, °n=321, °°n=475, °°°n=400, °°°°n=259, °°°°n=259, @n=140, %n=151, %%n=229,n=%%%=97, &n=30, &&n=98.*

Table 2. Fraction of active professional health care workers and percentage of infection

Role	At work	Infected
Physician, n (%)	108	8 (7.4)
Nurse, n (%)	210	29 (13.8)
Health care worker, n (%)	45	5 (11)
Physiotherapist	16	0 (0)
Total	369	42 (11.4)

Data are presented as numerical and percentage values.

Table 3. Clinical outcomes and relative probability for the whole population and according to ventilatory support

Outcome	Total	Cohort								
		HFNC	OR	p value	CPAP	OR	p value	NIV	OR	p value
	n=670 (100%)	n= 163 (24.3%)	(95%CI)		n= 330 (49.3%)	(95%CI)		= 177 (26.4%)	(95%CI)	
Crude										
30-day mortality, n (%)	180 (26.9)	26 (15.9)	0.43 (0.3–0.7)	<0.01	100 (30.3)	1.4 (0.9-2)	0.05	54 (30.5)	1.3 (0.5-1.9)	0.20
Adjusted*										
			0.52 (0.2-1.2)	0.10		1.7 (0.8–4.3)	0.11		1.1 (0.3–3.7)	0.88
Crude										
ETI, n (%)	178 (26.6)	47 (28.8)	1.1 (0.8-1.7)	0.45	82 (24.8)	0.8 (0.6-1.2)	0.32	49 (27.7)	1.1 (0.7-1.6)	0.80
Adjusted*										
			1.5 (0.6–4.1)	0.39		0.9 (0.5-1.7)	0.76		1.2 (0.5–3.3)	0.65

Crude										
30-day mortality/ETI, n (%)	312 (46.5)	62 (38)	0.6 (0.4–0.9)	0.01	156 (47.3)	1.06 (0.8-1.4)	0.7	94 (53)	1.4 (1.2)	0.04
Adjusted*										
			0.89 (0.4-2.1)	0.79		0.9 (0.5-1.7)	0.76		1.1 (0.5-2.7)	0.78
Length of hospital stay, days	20.3 (13.2)	19.2 (13.3)	0.91 (0.4-1.13)	0.87	19.8 (12.1)	0.95 (0.5-1.14)	0.82	21.5 (15.1)	1.2 (0.6-1.5)	0.47

Clinical outcomes and relative probability from fitting a logistic regression model for the whole study population and according to ventilatory support. The data are presented as numerical and percentage values for dichotomic variables and as mean and standard deviation (SD) for continuous variables. Statistical significance was set for $p<0.05$.

HFNC = High Flow Nasal Cannula; CPAP = Continuous Positive Airway Pressure; NIV = Noninvasive Mechanical Ventilation; ETI= Endotracheal Intubation; OR = odds ratio.

**Adjusted for age, baseline PaO_2/FiO_2, number of comorbidities and steroid usage.*

Table 4. Clinical outcomes for the whole study population and stratified according to both age and comorbidity class

	Patients by age, years, n (%)							
	All	21–40	41–50	51–60	61–70	71–80	81–90	91-100
	N=670	n=19 (2.8)	n=46 (6.8)	n=106 (15.8)	n=176 (26.3)	n=195 (29.1)	n=112 (16.7)	n=16 (2.3)
Overall								
Outcome, No, with data								
Died at 30 days, n (%)	180 (26.9)	0 (0)	7 (15.2)	6 (5.7)	31 (17.6)	71 (36.4)	55 (49.1)	10 (62.3)
ETI, n (%)	178 (26.6)	7 (36.8)	12 (26.1)	36 (34)	65 (36.9)	48 (24.6)	10 (8.9)	0 (0)
Length of hospital stay, days (SD)	20.3 (13.3)	16.8 (9.1)	19.1 (10)	20.6 (11.6)	22.7 (14.7)	21 (14.1)	16.6 (12.4)	13.7 (7.2)
Patients with ≤2 comorbidities*								
N (%)	423	19 (4.5)	33 (7.8)	75 (17.7)	113 (26.7)	118 (27.)	58 (13.7)	7 (1.7)
Outcome								
Died at 30 days, n (%)	83 (19.6)	0 (0)	5 (15.2)	6 (8)	18 (15.9)	40 (33.9)	12 (20.7)	2 (28.6)
ETI n (%)	123 (29)	7 (36.8)	8 (24.2)	29 (38.7)	46 (40.7)	27 (22.9)	6 (10.3)	0 (0)
Length of hospital stay, days (SD)	21.9 (15)	16.8 (9.1)	19.9 (11.1)	21.5 (12.4)	24.3 (15.6)	21.8 (14.7)	15.8 (11.3)	20.3 (5.9)
Patients with >2 comorbidities*								
N (%)	122	0 (0)	4 (3.3)	13 (10.7)	33 (27)	47 (38.5)	23 (18.9)	2 (1.6)
Outcome,								

Died at 30 days n (%)	42 (34.4)	---	2 (50)	0 (0)	10 (30.3)	18 (38.3)	11 (47.8)	1 (50)
ETI n (%)	25 (20.4)	---	1 (25)	3 (23.1)	14 (42.4)	6 (12.7)	1 (4.4)	0 (0
Length of hospital stay, days (SD)	22.1 (15.6)	---	21.7 (8.8)	21.2 (10.9)	23.1 (16.1)	21.3 (14.7)	23.3 (	21.5 (7.8)

*Comorbidity status for those with outcome data was available for 545 patients.
The data are presented as numerical and percentage values for dichotomic variables and as mean and standard deviation (SD) for continuous variables.

HFNC = High Flow Nasal Cannula; CPAP = Continuous Positive Airway Pressure; NIV = Noninvasive Mechanical Ventilation; ETI= Endotracheal Intubation; SD=Standard Deviation.

Table 5. Clinical outcomes and DNI state according to PaO_2/FiO_2 class

	Patients by PaO_2/FiO_2 strata, years, n (%)					
	<50	51-100	101-150	151-200	201-250	251–300
	n=11 (1.6)	n=222 (33.1)	n=173 (25.8)	n=127 (18.9)	n=69 (10.3)	n=68 (10.1)
Outcome						
Died at 30 days, n (%)	5 (45.5)	77 (34.7)	42 (24.2)	33 (26)	14 (20.3)	9 (13.2)
ETI, n (%)	7 (63.6)	76 (34.2)	42 (24.3)	32 (25.2)	16 (23.2)	5 (7.4)
Length of hospital stay, days (SD)	15.2 (10.1)	20.7 (14.6)	21.5 (14)	20.8 (12.5)	16.1 (9.8)	17.7 (9.8)
DNI, n (%)	0 (0)	6 (2.7)	8 (4.6)	4 (3.1)	5 (7.2)	5 (7.4)

The data are presented as numerical and percentage values for dichotomic variables and as means and standard deviation (SD) for continuous variables.

HFNC = High Flow Nasal Cannula; CPAP = Continuous Positive Airway Pressure; NIV = Noninvasive Mechanical Ventilation; ETI= Endotracheal Intubation; DNI, Do Not Intubate; SD=Standard Deviation.

Figure legends

Figure 1. Patient allocation to NRS and related clinical outcomes.

Legend. *COVID19=Severe Acute Coronavirus (SARS-CoV2) induced Disease; ARF= Acute Hypoxic Respiratory Failure; DNI=Do not Intubate Order; NRS=Noninvasive respiratory support; HFNC = High Flow Nasal Cannula; CPAP = Continuous Positive Airway Pressure; NIV = Noninvasive Mechanical Ventilation; ETI= Endotracheal Intubation; SB=Spontaneous Breathing.*

Supplementary Figure 1. Frequency distribution of age classes and PaO_2/FIO_2 ratio in the whole population.

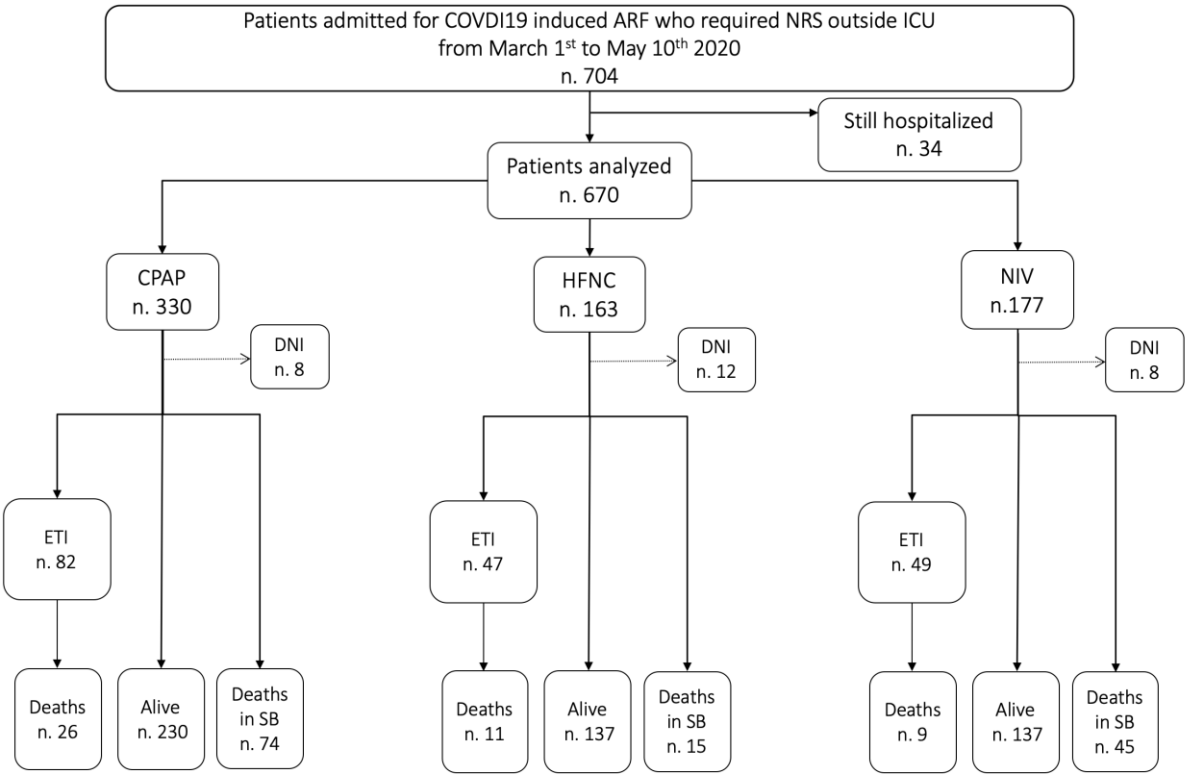
Table 1

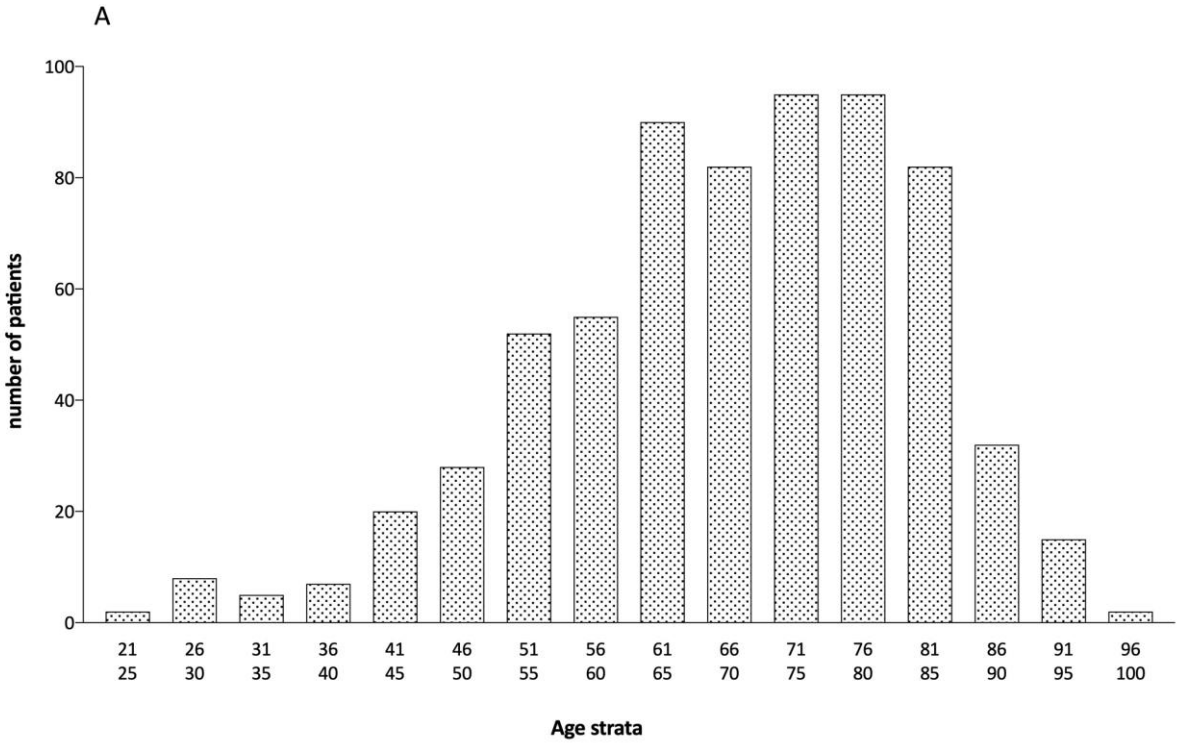
Support	**Value**
CPAP	
PEEP, cmH_2O (SD)*	10.2 (1.6)
Interface$	
Helmet, n (%)	149 (99)
Facemask, n (%)	2 (1.3)
NIV	
PEEP, cmH_2O (SD) §	9.5 (2.2)
Pressure support, cmH_2O (SD) ^	17.3 (3)
Interface°	
Helmet, n (%)	15 (20.8)
Facemask, n (%)	57 (79.2)
HFNC	
Flow, L/min (SD) &	50.5 (8)

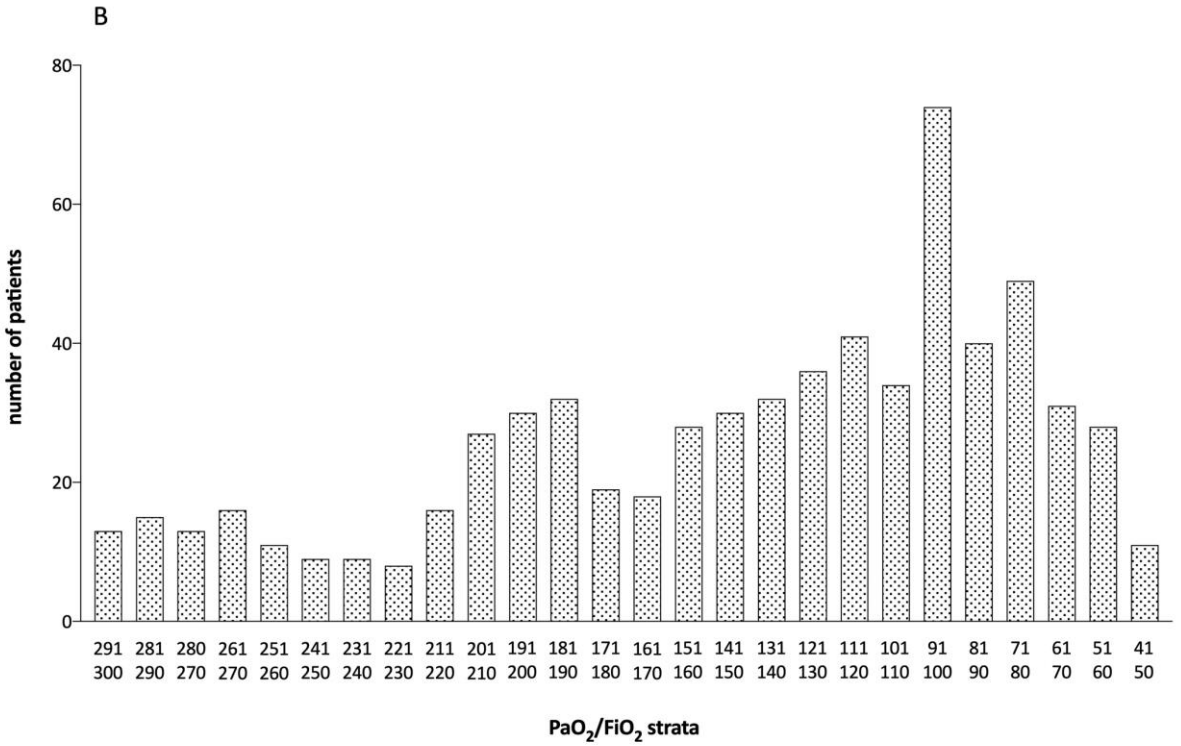
Setting parameters according to support. The data are presented as a numerical and percentage value and as mean and standard deviation (SD) for continuous variables.

HFNC = High Flow Nasal Cannula; CPAP = Continuous Positive Airways Pressure; NIV = Non-Invasive mechanical Ventilation

**n=66, $n=151, §n=82, ^n=87, °n=72, &n=48*


Patients admitted for COVDI19 induced ARF who required NRS outside ICU
from March 1st to May 10th 2020
n. 704
Still hospitalized
n. 34
Patients analyzed
n. 670
CPAP
n. 330
HFNC
n. 163
NIV
n.177
DNI
n. 8
DNI
n. 12
DNI
n. 8
ETI
n. 82
ETI
n. 47
ETI
n. 49
Deaths
n. 26
Alive
n. 230
Deaths
in SB
n. 74
Deaths
n. 11
Alive
n. 137
Deaths
in SB
n. 15
Deaths
n. 9
Alive
n. 137
Deaths
in SB
n. 45


A
number of patients
0
20
40
60
80
100
21 25
26 30
31 35
36 40
41 45
46 50
51 55
56 60
61 65
66 70
71 75
76 80
81 85
86 90
91 95
96 100
Age strata


B
number of patients
0
20
40
60
80
291 300
281 290
280 270
261 270
251 260
241 250
231 240
221 230
211 220
201 210
191 200
181 190
171 180
161 170
151 160
141 150
131 140
121 130
111 120
101 110
91 100
81 90
71 80
61 70
51 60
41 50
PaO2/FiO2 strata