ORIGINAL RESEARCH

Noninvasive Ventilatory Support of Patients with COVID-19 outside the Intensive Care Units (WARd-COVID)

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Abstract

Rationale: Treatment with noninvasive ventilation (NIV) in coronavirus disease (COVID-19) is frequent. Shortage of intensive care unit (ICU) beds led clinicians to deliver NIV also outside ICUs. Data about the use of NIV in COVID-19 is limited.

Objectives: To describe the prevalence and clinical characteristics of patients with COVID-19 treated with NIV outside the ICUs. To investigate the factors associated with NIV failure (need for intubation or death).

Methods: In this prospective, single-day observational study, we enrolled adult patients with COVID-19 who were treated with NIV outside the ICU from 31 hospitals in Lombardy, Italy.

Results: We collected data on demographic and clinical characteristics, ventilatory management, and patient outcomes. Of 8,753 patients with COVID-19 present in the hospitals on the study day, 909 (10%) were receiving NIV outside the ICU. A majority of patients

(778/909; 85%) patients were treated with continuous positive airway pressure (CPAP), which was delivered by helmet in 617 (68%) patients. NIV failed in 300 patients (37.6%), whereas 498 (62.4%) patients were discharged alive without intubation. Overall mortality was 25%. NIV failure occurred in 152/284 (53%) patients with an arterial oxygen pressure (Pa_{O_2})/fraction of inspired oxygen ($F_{I_{O_2}}$) ratio <150 mm Hg. Higher C-reactive protein and lower $Pa_{O_2}/F_{I_{O_2}}$ and platelet counts were independently associated with increased risk of NIV failure.

Conclusions: The use of NIV outside the ICUs was common in COVID-19, with a predominant use of helmet CPAP, with a rate of success >60% and close to 75% in full-treatment patients. C-reactive protein, $Pa_{O_2}/F_{I_{O_2}}$, and platelet counts were independently associated with increased risk of NIV failure.

Clinical trial registered with ClinicalTrials.gov (NCT04382235).

Keywords: noninvasive ventilatory support; COVID-19; coronavirus

After report of the first cases, coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) rapidly spread worldwide, affecting millions of patients and killing several 100,000. Coronavirus disease (COVID-19) is well known to cause severe acute respiratory failure with profound hypoxemia, chest X-ray infiltrates, and dyspnea, often requiring intubation and mechanical ventilation. Mortality of the disease is elevated, ranging from 16% to 78% overall and is even higher for patients admitted to intensive care units (ICUs). In this context, clinicians have attempted the application of noninvasive respiratory support (NIV), including continuous positive airway pressure (CPAP) (1) and noninvasive pressure support ventilation (NPPV). In this study, for the reasons expressed below, high-flow nasal oxygen (HFNC), which is frequently applied in COVID-19 (2–4), is treated separately. On one hand, avoiding intubation might reduce complications associated with invasive ventilation and, ultimately, morbidity and possibly mortality. On the other hand, several concerns exist on the use of this strategy, as follows: Similarly to acute respiratory distress syndrome (ARDS) (5, 6), NIV might only delay (and not avoid) intubation, carrying additional risks primarily related to the lack of monitoring and control over both tidal volume and transpulmonary pressure, with risk of patient self-inflicted lung injury (5, 7). Moreover, deferring intubation to the point when it is performed in a condition of emergency may increase the likelihood of complications related to the procedure itself (8). In addition, the exhaled gas leaking from patient's interface (an inherent risk to the use of NIV), might contaminate the ambient air and cause infection of healthcare providers (9, 10).

Published data on the use of NIV in patients with COVID-19 with acute respiratory failure is very limited, and indications are largely adapted from ARDS literature. The recent Surviving Sepsis Campaign COVID-19 guidelines (11) expressed a weak statement in favor of the use of HFNC over NIV and did not make any recommendation on the use of helmets ("it is an option, but we are not certain about its safety or efficacy in COVID-19"). More recently, the Managing ICU Surge during the COVID-19 Crisis rapid guidelines expressed a weak recommendation for hospitals to "develop and implement... the use of high-flow nasal oxygen (HFNO) and noninvasive ventilation (NIV) to reduce the need for intubation" (12).

Another peculiar aspect of COVID-19 pandemic is the overwhelming number of patients needing respiratory assistance, causing a rapid shortage of ICU beds (13). Hence, doctors, nurses, and respiratory therapists have been forced to apply NIV not only in the "classical" environments, such as ICUs or high-dependency units, but also in regular hospital wards (14). This practice has been particularly frequent in Italy, where the application of helmet CPAP in low-intensity floors has been rather common for several years. NIV is also often provided to those patients for whom a do-not-intubate (DNI) decision has been made. However, the high volume of patients, the lack of familiarity of nurses and clinicians with the device, and the limited monitoring possibilities represent additional concerns in this practice (15).

The primary aim of this study was to describe the prevalence and clinical characteristics of patients with COVID-19 treated with NIV outside the ICUs on a single day. Patients receiving HFNC were excluded from main analysis, given the very limited number and the differences with classical positive pressure ventilation systems. Moreover, we investigated the factors associated with NIV failure in the entire population and, separately, in patients with and without a DNI decision.

Methods

This is a single-day observational study. The institutional Ethics Board of Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda Ospedale Maggiore Policlinico, Milan, and local ethics committees of participating centers (listed in Appendix E1 in the online supplement, recruited in the COVID-19 Lombardy Network) approved the study. Informed consent from individual patients was waived in most cases. Investigators from each center collected data on March 26th or 31st at their choice. In the selected day, all patients present in the hospital were screened for enrollment in the study. Inclusion criteria were as follows:

- Age ≥18 years
- Diagnosis of COVID-19 pneumonia
- Noninvasive respiratory support (HFNC, NPPV, or CPAP) performed outside the ICU

The only exclusion criterion was the lack of informed consent, when required. All eligible patients were enrolled. The following variables were collected: age, sex, main comorbidities, smoking history, Clinical Frailty Score (16), type of respiratory support (NPPV, CPAP, or HFNC), level of positive end-expiratory pressure (PEEP), and fraction of inspired oxygen (F_{IO_2}). When available, arterial blood gas and peripheral oxygen saturation, hemodynamic parameters, main blood chemistry, and number of quadrants involved on the chest X-ray were also collected. If more than one value was available for the day, investigators were pragmatically asked to input the most "representative" value, using their clinical judgment. Patients were then followed-up, and the need for intubation, decision to limit the intensity of treatment, and status at hospital discharge (alive, transferred to another hospital, or dead) was recorded. We defined NIV failure as intubation (independently from the subsequent outcome) or death without intubation.

Statistics

Data collection was performed using an electronic case-report form implemented in the platform RedCapCloud (powered by nPhase) in accordance with the European Statement 679/2016/UE, with online access available to the participating centers. The databases were compiled in compliance with the International Conference on Harmonization Good Clinical Practice. Continuous data were described by mean and standard deviation (SD) or median and interquartile range depending on the distributional shape. Comparison across groups was performed by t test or Wilcoxon nonparametric test depending on the distributional shape. Categorical data were described by absolute frequencies and percentages, and comparison across groups was performed by the χ^2 test on association. A horizontal bar plot was used for graphical representation of categorical variables. Univariate and multivariable analysis relating binary outcome to explanatory variables were obtained by logistic regression. The significance level was set equal to 5%; tests were two sided. Given the purpose of the study, we did not prespecify a sample size but enrolled all patients fulfilling inclusion criteria on the study day.

A logistic regression of a binary response variable on a continuous, normally distributed variable X with a sample size of 800 observations achieves 90% power at a 5% significance level to detect a change in the probability of observing the endpoint from the percentage of 30% at the mean of X to 35% when X is increased to one SD above the mean. This change corresponds with an odds ratio of 1.284. When the percentage at the mean of X is raised to 35%, 40%, or 45%, the detectable change is 5.5%, 5.7%, or 5.7%. Stata version 16 software was used for data quality assessment, statistical analysis, and graphics.

Results

Of 37 centers initially expressing their interest in participating in the study, 31 enrolled patients. On average, the number of ICU beds dedicated to patients with COVID-19 was increased by 223% ± 86% compared with the pre–COVID-19 period, but 96% ± 8% of the beds were occupied on the study date. A study flowchart is presented in Figure E1 in the online supplement. Overall, 8,753 patients with COVID-19 were present in these hospitals on the study day (accounting for 62% ± 25% of total hospital beds). Of these, 909 (10.4%) were receiving NIV outside the ICU, whereas 854 (9.7%) were being treated in the ICUs; of these, only 53 (6.2%) were receiving NIV (after extubation in 40 cases), whereas the remaining were intubated. There was a weak negative correlation ($r = -0.34$; $P = 0.07$) between the fraction of patients treated with NIV in the ICU (as percentage of total ICU beds) and those outside (as percentage of total nonintensive COVID-19 beds). For the 909 patients treated with NIV outside the ICU, 778/909 (85%) patients were treated with CPAP, and NPPV was used in 90 (10%). In the majority of patients treated with NIV (617 [68%]), this was delivered by helmet, whereas face masks were used in 248 patients. HFNC was used in only 39 patients. Given the substantial difference between positive pressure devices and HFNC, we decided to remove this small subset of patients from the subsequent analyses (described in the Table E1) and to also remove the 33 (3.7%) patients who received NIV after extubation (described in the Table E2).

At the moment of database freezing (i.e., after a follow-up of 60 d), outcomes could be determined in 798 patients, while 37 were still in the hospital. Intubation occurred in 123 patients (15.4%), after 5 (3–9) days after the initiation of NIV, whereas 177 died without being intubated 8 (5–13) days after the initiation of NIV. In 138 (78%) of these patients, a DNI decision had been made. NIV failure, hence, occurred in 300 patients (37.6%), whereas 498 (62.4%) were discharged or transferred alive without intubation. The overall mortality of the cohort was 25%.

Table 1 summarizes main demographic variables and comorbidities of the patients. Patients failing NIV were older (72 [64–78] yr vs. 64 [56–73] yr) and more fragile (Figure E2) and more frequently had a history of ischemic heart disease, diabetes, malignancies, or active or former smoking history. No difference was observed regarding the presence of hypertension or the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

NIV was initiated shortly after hospital admission, with a median interval of 1 (0–4) days in the whole cohort, with no difference between NIV failure and success. No difference was also found in the time between symptom onset and hospital admission, which had a median of 7 [5–10] days. Overall, the population was moderately hypoxemic (arterial oxygen pressure (Pa_{O_2})/F_{IO_2} of 172 ± 102 mm Hg), and most patients were hypocapnic, as 430 (53.9%) patients had an arterial carbon dioxide pressure (Pa_{CO_2}) of <40 mm Hg. PEEP levels averaged 10.8 ± 2.6 cm H_2O (but the range was very high, 2–20 cm H_2O) without any association with the severity of radiological impairment. As expected, patients who failed NIV had a significantly lower Pa_{O_2}/F_{IO_2} ratio and a slightly lower Pa_{CO_2}, and they presented dyspnea more often than those who succeeded. NIV failure occurred in 50/279 (18%) patients with a Pa_{O_2}/F_{IO_2} ratio of >150 mm Hg and in 152/284 (53%) patients with a Pa_{O_2}/F_{IO_2} ratio of <150 mm Hg (Figure 1).

As shown in Table 1, patients failing NIV had also worse kidney function, higher white blood cell counts, lower platelet counts, and higher C-reactive protein concentrations. Regarding hemodynamics, heart rate was higher and so was systolic blood pressure, but the difference was clinically negligible. Only six patients (<1%) received vasopressors. When we separately analyzed the groups of patients with and without DNI decision, the same patterns

Table 1. Main demographic variables and comorbidities of the enrolled patients

	n	All population (N = 798)	Success (n = 498, 62.4%)	Failure (n = 300, 37.6%)
Sex, M, n (%)	798	595 (74, 56)	367 (73, 69)	228 (76, 0)
Age, median [IQR], yr	798	68 [59–75]	64 [56–72]	72 [64–78]*
Body mass index, median [IQR], kg/m²	539	27.2 [24.5–30.5]	27.3 [24.7–30.9]	27 [24.3–29.4]
Comorbidities, n (%)				
Ischemic or congestive heart disease	798	119 (14.9)	57 (11.4)	62 (20.7)*
Hypertension	798	438 (54.9)	262 (52.6)	176 (58.7)
Angiotensin-converting enzyme inhibitors	798	142 (17.8)	88 (17.8)	54 (18.0)
Angiotensin receptor blockers	798	115 (14.4)	71 (14.3)	44 (14.7)
Vascular disease	798	81 (10.2)	36 (7.2)	45 (15)*
COPD	798	76 (9.6)	49 (9.8)	27 (9.0)
Autoimmune disease	798	33 (4.1)	20 (4.0)	13 (4.3)
Diabetes	798	160 (20.0)	90 (18.1)	70 (23.3)
Chronic kidney disease	798	32 (4.0)	15 (3.0)	17 (5.7)
Malignancy	798	34 (4.3)	15 (3.0)	19 (6.3)*
Smoking history, n (%)	798	—	—	—
Active smoker	—	—	19 (3.8)	17 (5.8)†
Former smoker	—	—	87 (17.6)	77 (26.5)†
Never smoked	—	—	221 (44.7)	102 (35.1)†
Not declared	—	—	167 (33.8)	95 (32.7)†
Time between hospital admission and data collection, median [IQR], d	798	7 [4–10]	7 [5–11]	5 [3–8]*
Time between hospital admission and NIV initiation, median [IQR], d	763	1 [0–3]	1 [0–4]	1 [0–3]
Time between symptoms onset and hospital admission, median [IQR], d	772	7 [5–10]	7 [5–10]	7 [4–10]
Received seasonal flu vaccine, n (%)	—	92 (11.59)	28 (9.4)	64 (12.9)
DNI decision, n (%)	727	215 (28.4)	70 (14.6)	145 (52.3)*
Respiratory parameters				
$F_{I_{O_2}}$, mean (SD), %	758	67.5 (20.5)	61.2 (18.6)	78.2 (19.1)*
PEEP, mean (SD), cm H_2O	783	10.79 (2.5)	10.6 (2.6)	11.3 (2.5)*
pH, mean (SD)	598	7.45 (0.05)	7.445 (0.04)	7.44 (0.06)*
Pa_{O_2}, mean (SD), mm Hg	599	103 (52)	113 (56)	89 (43)*
$Pa_{O_2}/F_{I_{O_2}}$, mean (SD), mm Hg	592	168 (98)	198 (104)	122 (66)*
Pa_{CO_2}, mean (SD), mm Hg	599	37.4 (6.9)	37.9 (6.6)	36.6 (7.2)*
Pa_{CO_2} <40 mm Hg, n (%)	599	430 (53.9)	257 (51.6)	173 (57.7)
Sa_{O_2} mean (SD), %	576	95.4 (4.6)	96.5 (3.4)	93.7 (5.6)*
Sp_{O_2} mean (SD), %	164	94.6 (5.5)	96.5 (2.9)	90.8 (7.3)*
$Sp_{O_2}/F_{I_{O_2}}$, mean (SD)	141	160.3 (51.9)	175.2 (49.7)	126.5 (40)*
Respiratory rate	605	23.9 (6.6)	22.1 (5.4)	26.7 (7.4)*
Use of accessory respiratory muscles, n (%)	631	183 (27.64)	59 (14.4)	124 (49.2)*
Dyspnea, n (%)	631	179 (27.2)	60 (14.5)	119 (48.8)*
Laboratory values				
Creatinine, mean (SD), mg/dl	700	1.03 (0.8)	0.9 (0.6)	1.25 (1.0)*
Urea, mean (SD), mg/dl	493	56.8 (43.9)	47.3 (28.9)	71.7 (57.2)*
White blood cells, mean (SD), 10³/μl	708	10.2 (8.9)	9.4 (6.5)	11.6 (11.7)*
Platelets, mean (SD), 10³/μl	703	302 (130)	330 (131)	253 (114)
Hemoglobin, mean (SD), g/dl	708	12.4 (1.7)	12.4 (1.5)	12.4 (1.8)
Bilirubin, mean (SD), mg/dl	485	0.82 (1.02)	0.77 (0.92)	0.89 (1.15)
C-reactive protein, mean (SD), mg/L	675	106 (89)	82 (77)	148 (95)*
Procalcitonin, median [IQR], ng/dl	275	0.21 [0.1–0.63]	0.15 [0.08–0.37]	0.42 [0.2–1.3]*
Hemodynamic parameters				
Systolic blood pressure, mean (SD), mm Hg	741	130 (18)	1,290 (1)	132 (20)
Diastolic blood pressure, mean (SD), mm Hg	741	75 (11)	76 (11)	75 (12)
Heart rate, mean (SD), 1/min	734	81.2 (15.9)	78.4 (14.0)	86.0 (17.8)*
Temperature, mean (SD), °C	692	36.5 (0.7)	36.4 (0.7)	36.8 (0.8)*

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; DNI = do not intubate; $F_{I_{O_2}}$ = fraction of inspired oxygen; IQR = interquartile range; NIV = noninvasive ventilation; Pa_{CO_2} = arterial partial pressure of carbon dioxide; Pa_{O_2} = arterial partial pressure of oxygen; PEEP = positive end-expiratory pressure; Sa_{O_2} = arterial oxygen saturation; SD = standard deviation; Sp_{O_2} = oxygen saturation.
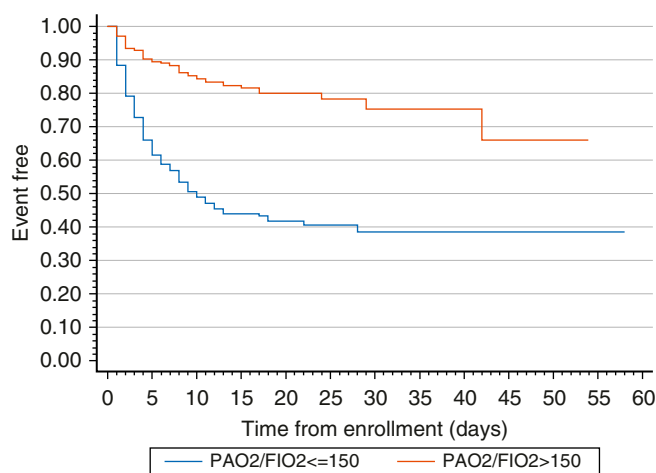*$P < 0.001$ vs. Success.
†$P < 0.001$ for overall Chi-square.

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Figure 1. Survival curves of patients with coronavirus disease (COVID-19) treated with noninvasive ventilation and stratified according to $Pa_{O_2}/F_{I_{O_2}}$ ratio on the date of data collection. Log-rank test, $P < 0.001$. $F_{I_{O_2}}$ = fraction of inspired oxygen; Pa_{O_2} = arterial oxygen pressure.

described above were found in each of the two groups (Table E3).

Multivariate analysis (Table 2) showed that higher C-reactive protein concentrations, lower $Pa_{O_2}/F_{I_{O_2}}$ ratio, and lower platelet counts were independently associated with increased risk of NIV failure. Increasing age showed a trend toward higher risk of failure but did not reach statistical significance ($P = 0.052$). When the presence of DNI care was introduced in the model, this was associated with an almost threefold risk of NIV failure, but the same variables remained significant, with the exception of age (Table E4).

Discussion

Treatment of COVID-19–associated respiratory failure constituted, during the surge phase, an incredible challenge for clinicians and healthcare systems because of the overwhelming number of patients requiring respiratory support (13). Hence, the need to provide effective treatments must be balanced with the available resources. A large uncertainty exists over the risk-to-benefit ratio of noninvasive treatment of acute hypoxemic respiratory failure in patients with COVID-19 (17) because the available literature data are rather scarce. To our knowledge, this is the report of the largest cohort of patients with COVID-19 (and one of the largest in acute respiratory failure from any cause) treated with NIV as first-line therapy. Our results show that, during the peak of the COVID-19

pandemic, the prevalence of NIV use outside ICUs was high, involving approximately 12% of hospitalized patients with COVID-19. For each patient treated in the ICU with invasive mechanical ventilation, approximately one other patient was assisted in other hospital environments with NIV. This is not surprising because the peak of patients with COVID-19 led to devoting ICU beds almost entirely to the intubated ones (18–20). This was also the case in our cohort, in which ICUs were basically saturated and almost 95% of patients were invasively ventilated, mandating the need for an alternative solution whenever possible. The incidence of NIV application in the examined setting was similar to that in previous reports from China (21) but was tenfold higher than that reported in the same period in New York City, where NIV was applied only in 1% of the hospitalized patients (18), clearly reflecting preexisting clinical practices and attitudes as well as the number of available ICU beds.

Overall, approximately one-third of the patients experienced NIV failure, whereas this strategy could be applied with success as the sole treatment in the remaining population. At variance with what is recommended by the guidelines (11), NIV was predominantly used over HFNC. The most common form of respiratory support was helmet CPAP, which was applied in 76% of the patients. This might reflect the availability of the device, the familiarity of the operators, and the efficacy of PEEP in improving gas exchange. A recent meta-

analysis showed that helmets had the highest probability of reducing the risk of endotracheal intubation and death over face masks and high-flow oxygen (22). Helmets allow the delivery of a constant and stable amount of PEEP with free-flow systems and a PEEP valve (23) without the need for a ventilator, making this choice particularly appealing for use in lower-intensity settings (24). In addition, the use of helmets carries the additional advantage of a lower risk of environmental contamination and of nosocomial transmission of the infection because this interface is characterized by reduced leaks compared with nasal high-flow masks and face masks (25). Finally, high-efficiency particulate air filters can be positioned on the exhalation port of the device, further reducing the risk of viral spread (26). In this respect, we did not directly assess whether the use of either form of NIV was associated with increased (or decreased) transmission of the virus to healthcare workers.

A crucial point in the decision to apply NIV as a first-line strategy in patients with acute hypoxemic respiratory failure is the balance between the potential benefits of avoiding intubation and the risks deriving from self-inflicted lung injury. The proposed pathophysiological mechanisms of patient self-inflicted lung injury in hypoxemic patients with high respiratory drive include volutrauma (due to the generation of high tidal volumes and excessive transpulmonary pressure swings) and capillary leak (due to increased transvascular pressures). Because of the prevalent use of free-flow CPAP with helmet, tidal volume (and, hence, minute ventilation) could not be monitored, but given the high incidence of hypocapnia, we speculate that it might have been quite high, particularly in consideration of the high dead space that characterizes lung involvement in COVID-19. Indeed, patients who failed NIV had a higher incidence of dyspnea and use of accessory muscles as well as lower Pa_{CO_2} levels, suggesting higher inspiratory efforts, respiratory drive, and work of breathing. However, we cannot determine to what extent the higher work of breathing was a contributor to NIV failure or simply a marker of a more severe disease.

In this cohort of patients with COVID-19, some of the factors independently associated with of NIV failure were in line with those previously reported for other forms of acute hypoxemic respiratory failure (5, 27), such as age and $Pa_{O_2}/F_{I_{O_2}}$, whereas

Table 2. Multivariate analysis of factors independently associated with probability of NIV failure

	Odds Ratio	SE	$P > z$	95% Confidence Interval	
Age (per yr increment)	1.04	0.02	0.052	1.00	1.08
Ischemic or congestive heart disease (ref. no)	1.84	0.87	0.2	0.73	4.66
Vascular disease (ref. no)	0.94	0.60	0.92	0.27	3.30
Malignancy (ref. no)	2.73	3.66	0.46.	0.20	37.87
Former smoker (ref. active smoker)	0.88	0.69	0.87	0.19	4.04
Never smoked (ref. active smoker)	0.52	0.38	0.37	0.12	2.21
Not declared (ref. active smoker)	0.96	0.74	0.96	0.21	4.38
PEEP, mean (SD), cm H_2O	0.95	0.07	0.52	0.83	1.10
pH, mean (SD)	0.01	0.04	0.22	0.00	15.90
$Pa_{O_2}/F_{I_{O_2}}$ (per mm Hg increment)	**0.99**	**0.003**	**<0.001**	**0.99**	**1.00**
Pa_{CO_2} (per mm Hg increment)	0.97	0.02	0.23	0.92	1.02
Respiratory rate (per 1/min increment)	1.04	0.03	0.15	0.99	1.10
Creatinine (per 1 mg/dl increment)	0.88	0.26	0.65	0.49	1.55
Urea (per 1 mg/dl increment)	1.01	0.01	0.21	1.00	1.02
White blood cells (per $10^3/\mu l$ increment)	0.99	0.03	0.75	0.94	1.05
Platelets (per $10^3/\mu l$ increment)	**1.006**	**0.001**	**<0.01**	**0.99**	**1.00**
Hemoglobin (per g/dl increment)	0.97	0.12	0.79	0.76	1.23
C-reactive protein (per g/dl increment)	**1.01**	**0.003**	**<0.01**	**1.00**	**1.01**
Procalcitonin <0.5 (ref. missing value)	1.10	0.44	0.81	0.51	2.39
Procalcitonin >0.5 (ref. missing value)	0.78	0.40	0.63	0.29	2.12
Systolic blood pressure (per mm Hg increment)	1.01	0.01	0.41	0.99	1.03
Heart rate (per 1/min increment)	1.02	0.01	0.10	1.00	1.05

Definition of abbreviations: $F_{I_{O_2}}$ = fraction of inspired oxygen; NIV = noninvasive ventilation; PEEP = positive end-expiratory pressure; Pa_{CO_2} = arterial partial pressure of carbon dioxide; Pa_{O_2} = arterial partial pressure of oxygen; ref. = reference; SD = standard deviation; SE = standard error. Bold indicates statistical significance.

others appear more specific of COVID 19, such as serum concentrations of C-reactive protein (28) or platelet counts (29), likely indicating an hyperinflammatory status or a progression toward multiple organ failure. Concerning the $Pa_{O_2}/F_{I_{O_2}}$ ratio, the threshold value of 150 mm Hg was highly predictive of NIV outcome, and, albeit that this is still a speculation, it could probably be used as a simple criterion to decide which patients should undergo early intubation. Careful continuous monitoring of hypoxemic patients treated with first-line NIV remains of cornerstone importance to detect early signs of failure and avoid delays in tracheal intubation. Interestingly, the sensitivity analyses revealed that patients with or without a DNI decision do not present relevant differences regarding the factors associated with the risk of NIV failure, albeit that 24 patients with a DNI

decision were at greater risk because of higher severity. Although this sensitivity analysis is reassuring regarding the robustness and generalizability of our findings, it must be interpreted cautiously given its post hoc nature, heterogeneity in group size, and possible differences among centers in DNI dispositions.

This study has several limitations. First, this study is purely descriptive, and all enrolled patients were being treated with NIV; hence, it is not possible to draw conclusions regarding the superiority or inferiority of NIV to other forms of support (e.g., standard oxygen or invasive ventilation). The single-day approach was chosen to minimize the burden on the investigators but does not allow a longitudinal follow-up of patients (including the reason from NIV discontinuation, i.e., improvement

vs. intolerance), who are then captured at different stages of the disease. Moreover, this approach could underestimate the actual use of NIV because patients treated with NIV for shorter periods of time (either because of failure or low severity) have less chances of being captured. We also had to keep the number of variables within a reasonable limit; hence, we did not collect data regarding various drugs that were inconsistently administered during pandemics and that might have influenced outcomes. Sleep apnea is a frequent cause for CPAP application, but, unfortunately, we did not capture this data in our database; hence, it is possible that some of the patients (particularly those treated with a face mask as an interface) presented this as the main indication for NIV. However, in a context in which all patients had COVID-19 pneumonia and were hypoxemic in most cases, we believe that the incidence of these patients was minimal. We did not have access to or the possibility to monitor the source data, which were, however, quite straightforward to collect. The centers participating in the study are in a specific geographic region in northern Italy, where the use of helmet CPAP outside the ICU was quite common even before COVID-19 and where resources were particularly strained during the surge; hence, results might not be generalizable elsewhere.

In conclusion, this single-day observational study shows that NIV outside the ICU is feasible because approximately 10% of COVID-19 patients present in the hospital were treated with NIV outside the ICUs, with a predominant use of helmet CPAP. The overall rate of success was approximately 65% (73% in full-treatment patients, although only one-third of DNI patients survived). C-reactive protein, $Pa_{O_2}/F_{I_{O_2}}$, platelet counts, and probably age were independently associated with increased risk of NIV failure. ■

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