Timing and outcomes of noninvasive ventilation in 307 ARDS COVID-19 patients: an observational study in an Italian third level COVID-19 hospital

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Abstract

Purpose

Coronavirus disease 2019 (COVID-19) is a novel cause of Acute Respiratory Distress Syndrome (ARDS). With the increase of ARDS cases during COVID-19 pandemic, the use of non-invasive ventilation (NIV) has grown significantly in the hospital ward. However, there is a lack of evidence to support its efficacy in these patients.

Methods

We conducted an observational cohort study including adult ARDS COVID-19 patients admitted in a third level COVID-center in Rome, Italy (Jan-Sep 2020). The study analyzed the rate of NIV failure defined by the occurrence of orotracheal intubation and/or death within 28 days from starting NIV, its effectiveness, and its relative risk of death. The factors associated with the outcomes were identified through a logistic regression analysis.

Results

During the study period, a total of 942 COVID-19 patients were admitted, of which 307 (32.5%) with ARDS at hospitalization. Overall, 224 (23.8%) were treated with NIV. NIV failure occurred in 84 (37.5%) patients. Moderate and severe ARDS had an increased risk of NIV failure within 28 days from starting NIV of 5- (aOR = 5.01, 95% CI 2.08–12.09) and 20-fold (aOR = 19.95, 5.31–74.94) respectively, compared to patients with mild ARDS. A total of 128 patients (13.5%) were admitted to the Intensive Care Unit (ICU). At 28-day from ICU admission, COVID-19 patients treated with NIV without intubation had 96% lower mortality (aOR 0.04, 0.01–0.32) in comparison with patients that underwent orotracheal intubation without prior NIV.

Conclusions

NIV failure was independently associated with COVID-19 ARDS severity. Starting NIV in COVID-19 patients with already mild ARDS (P/F > 200 mmHg) appears to increase NIV effectiveness and reduce the risk of orotracheal intubation and/or death. Moreover, early NIV treatment seems to reduce the risk of ICU mortality within 28 days from ICU admission.

Take-home Message

- Non-invasive ventilation (NIV) is a useful mode of therapy in COVID-19 patients with ARDS and was effective in approximately two-thirds of the patients in preventing a negative outcome (either need of intubation or death).
Starting NIV earlier in COVID-19 patients with already mild ARDS (P/F>200 mmHg) appears to reduce the risk of orotracheal intubation and/or death

Early NIV treatment seems to reduce the risk of mortality in ICU within 28 days from ICU admission.

Introduction

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by a coronavirus discovered in December 2019, named Severe Acute Respiratory Syndrome Corona-Virus-2 (SARS-CoV-2), and it is responsible for the current global pandemic that started in March 2020 [1]. SARS-CoV-2 is transmitted from person-to-person via droplets, contact and, also from aerosolized particles [2].

COVID-19 is an important novel cause of acute respiratory distress syndrome (ARDS) [3, 4]. ARDS severity is assessed by the degree of hypoxemia, quantified by the ratio of arterial partial pressure of oxygen (PaO2) to the fraction of inspired oxygen (FiO2) as per the Berlin criteria, which is strongly predictive of worsening survival, when P/F Ratio of 300 to 200 is mild, 200 to 100 is moderate and less than 100 is severe ARDS with PEEP $\geq$ 5 [5].

COVID-19 patients with progressive disease should be monitored closely for worsening respiratory status, presentencing dyspnea, hypoxemia and decreased PaO2/FiO2, and typically require an incremental respiratory support [6, 7]. During the COVID-19 pandemic, noninvasive ventilation has been extensively used to avoid intubation in ARDS COVID-19 patients and the overload of Intensive Care Unit (ICU) admissions, especially in conditions of limited resources [8, 9]. Noninvasive Ventilation (NIV), as biphasic positive airway pressure (BiPAP) and continuous positive airway pressure (CPAP), are recommended for acute hypoxemic respiratory failure due to cardiogenic respiratory failure and ARDS in the pre-COVID-19 era [10, 11]. Moreover, NIV is commonly used for the treatment of acute respiratory failure in COVID-19 patients, which is also used in the ordinary ward at the bedside and allows multiple and rapid adjustments of ventilatory parameters such as positive end-expiratory pressure, PEEP, pressure support, PS and fraction of inspired oxygen, FiO2 [8, 12]. But so far, no clinical practice guidelines have been developed for COVID-19 acute respiratory failure; the timing of starting NIV treatment, its safety and the risk of NIV failure in these patients, although its benefit in reducing the need for invasive mechanical ventilation has been shown in some studies published recently in JAMA [13, 14], is still debated and unclear in the medical literature [8, 15, 16].

Hence the purpose of our study is to analyze:

- The factors associated with NIV failure defined by the occurrence of orotracheal intubation and/or death within 28 days from NIV start as a combined outcome.
- The factors associated with the risk of death within 28 days from ICU admission in COVID-19 patients, treated with or not with NIV prior OTI.

Methods
Study Design and Participants

The study was conducted at the National Institute of Infectious Diseases Lazzaro Spallanzani, Rome, Italy, which is a third level COVID-19 center with over 200-beds hospital for infectious diseases and up to 55-beds in ICU. This observational cohort study included adult ARDS COVID-19 patients hospitalized in our covid-center from January 29, 2020 to September 30, 2020.

To simplify the reading of the article we have assigned the common term “noninvasive ventilation” (NIV), referring to both biphasic positive airway pressure (BiPAP) and continuous positive airway pressure (CPAP). The diagnosis of ARDS COVID-19 was performed based on thoracic CT scans and fulfilling Berlin criteria [17].

Inclusion criteria were adult patients with confirmed SARS-CoV-2 by nasal pharyngeal swab for reverse transcriptase polymerase chain reaction (rtPCR) assay and COVID-19 pneumonia admitted in our hospital.

Exclusion criteria were patients with negative rtPCR for SARS-CoV-2 and with no ARDS COVID-19 pneumonia diagnosed clinically and/or by radiological imaging.

NIV group included all patients treated with noninvasive ventilation for more than 24 hours.

All patients underwent chest CT scan or x-ray at hospital admission. The patients with diagnosed ARDS (fulfilling the Berlin criteria), dyspnea, hypoxemia and/or decreasing of the PaO$_2$/FiO$_2$ were treated as a first step with conventional supplemental oxygen therapy, and then gradually increased the support with noninvasive ventilation according to patient’s condition.

All clinical decisions and management of the patients were performed by attending physicians, according to institutional protocols and regular practice. NIV was applied in patient with a worsening of respiratory failure represented by a PaO$_2$/FiO$_2$ ratio mostly below 300 mmHg, a respiratory rate more or equal of 25 breaths per minute, important lung involvement in radiological images, non-responsiveness to conventional supplemental oxygen therapy and persistent low peripheral oxygen saturation, SpO$_2$ < 92–94%. The scarce availability of beds during the waves of the pandemic did not allow us to always treat all COVID-19 patients in respiratory failure with early NIV treatment.

The NIV included continuous positive airway pressure (CPAP) via helmet, Boussignac mask or ventilator machine, and bilevel positive airway pressure (BiPAP) via ventilator machine. We did not use high-flow nasal oxygen therapy (HFNOT) during the study period as the hospital was not provided.

The decision for ICU admission and/or OTI was made by physicians considering the sum of several parameters such as hemodynamic instability, neurological deterioration, worsening respiratory failure despite noninvasive oxygen therapy, increased respiratory rate, increased effort of the respiratory muscles and acidosis. The noninvasive or invasive ventilation, and ICU admission was not applied in patients who
refused the treatment or were uncooperative. Patients were managed according to recommendations from published guidelines and good medical practice on protective ventilation, which is an optimal PEEP with a target peak inspiratory pressure (PIP) less than 30 cmH\textsubscript{2}O, tidal volume 6–8 ml/kg of ideal body weight (IBW), plateau pressure \( \leq 30 \) cmH\textsubscript{2}O, driving pressure \( \leq 15 \) cmH\textsubscript{2}O, to keep low the risk of barotrauma and self-inflicted lung injury [18–20].

**Data Collection**

Data were collected for the ReCOVeRI project, a register of hospitalized COVID-19 patients since the beginning of the pandemic, for clinical Research of the National Institute for Infectious Diseases L. Spallanzani IRCCS, approved by the internal Ethical Committee (decision number 164, 26 June 2020). The management of the registry is adapted according the standards of EUnetHTA reported in the Registry Evaluation and Quality Standards Tool (EUnetHTA, 2019). All clinical decisions and management of the patients are performed by attending physicians, according to institutional protocols and regular practice. The set of data collected was first structured into an electronic dataset (a case report form-like, CRF) consisting of 5 main sections: laboratory data (laboratory); daily clinical data (daily); administered drugs (drugs); notification data (notification) and summary clinical data (clinical), following specific criteria and definitions. The data was then entered into a database created \textit{ad hoc} according to the CRFs, based on Microsoft SQL Server database, accessed by trained personal for data entry and management.

PaO\textsubscript{2}/FiO\textsubscript{2} ratio (P/F) was categorized into four classes (> 300, 200–299, 100–199 and < 100) and collected at hospital admission and at the start of NIV treatment. The comorbidities (as arterial hypertension, cardiovascular diseases, diabetes, obesity (BMI > 30 Kg/m\textsuperscript{2}), kidney disease on stage 3–5 of CKD, COPD, neoplasm in the last 5 years and chronic neurological disorders) were collected as dichotomous variable (yes/no). All patients gave informed consent for collecting personal data for research purposes.

**Statistical Analysis**

Quantitative variables are expressed as medians (interquartile range, IQR), while categorical variables were expressed as counts (N) and percentages (%). We compared the collected data of patients treated with NIV and without NIV. The statistical comparison was performed by means of the Mann-Whitney test for continuous variables and Chi-Square test (or Fisher or Chi-Square test for trend where necessary) for categorical variables.

In order to identify the factors associated with NIV failure, the latter was defined as the necessity of orotracheal intubation or death within 28 days after the start of NIV treatment, considering all COVID-19 patients treated with NIV. Factors were identified through a logistic regression analysis allowing the calculation of Odds Ratio (OR) and their 95% confidence intervals first in univariate analysis, and subsequently with multivariable logistic regression analysis selecting all potential cofounding factors through backward elimination, abolishing from the model all nonsignificant confounders (p-value > 0.10). The adjusted Odds Ratio (aOR) values and 95% CI were reported.
A similar approach was used for the second main objective, where we intended to identify those factors associate with the risk of death within 28-days from ICU admission.

All statistical analysis were performed using the statistical software SPSS version 27 (IBM Corp. IBM SPSS, Armonk, NY: IBM Corp).

**Results**

From January 29, 2020 to September 31, 2020, a total of 942 COVID-19 patients with pneumonia were admitted to our COVID hospital. Of these, 224 (23.8%) were treated with noninvasive ventilation (NIV) and 718 (76.2%) with conventional supplemental oxygen therapy (non-NIV) during hospitalization, of which, respectively 88 (39.3%) and 40 (5.6%) were then admitted in the ICU. Therefore, a total of 128 patients (13.5% of all 942) were admitted to the ICU, as schematically shown in the flow-chart depicted in Figure 1.

**Baseline characteristics of NIV patients**

Demographics, comorbidities and clinical course of the overall COVID-19 patients are shown in Table 1. Patients treated with NIV were more frequently male (72.8% vs 62.5% in untreated, p=0.005), older (median age 63 vs 59 years, p=0.048), had hypertension (45.1% vs 35.7%, p=0.011)) and were obese (25.9% vs 11.8%, p<0.001)). Chronic neurological disease was less frequent in treated patients (8.5% vs 15.7%, p=0.006). Cardiovascular diseases, diabetes, chronic kidney disease, COPD and neoplasm in the last 5 years didn't show statistically significant differences between the two groups, as reported in Table 1.

Three hundred and seven COVID-19 patients (32.5%) fulfilled Berlin criteria for ARDS at hospital admission, of these, 141 were treated with the NIV. Thirty-five patients died in the ward from complications from COVID-19 and untreated with NIV, and 40 patients were admitted in ICU and subsequently intubated. Three patients in NIV were intubated in the ward and then transferred to another hospital to competence, Figure 1.

Before starting NIV, 218 of 224 patients had COVID-19 ARDS at hospital admission, of which 59 (26.3%) with mild, 135 (60.3%) moderate and 24 (10.7%) severe ARDS. The median time from hospital admission to NIV start was 3 days (IQR, 2-6).

A lower P/F ratio at hospitalization was significantly associated with NIV treatment, when compared between NIV and non-NIV groups: with a clear gradient of P/F ratio (p<0.001).

The length of stay in hospital was significantly longer in patients treated with NIV (median of 15 days vs 13 days, p<0.001). Moreover, the patients that needed noninvasive ventilation had an higher rate of ICU admission (39.3% vs 5.6%, p<0.001), need of orotracheal intubation (28.6% vs 5.7%, p<0.001) and death (19.2% vs 7.9%, p<0.001) (see Table 1).

**Table 1.** Baseline demographics and clinical features of COVID-19 patients
| Characteristics                                      | COVID-19 patients | NIV group | Non-NIV Group | \( p^1 \) |
|-----------------------------------------------------|-------------------|-----------|---------------|---------|
|                                                     | 942               | 224       | 718           |         |
| Age, median (IQR)                                   | 60 (48–73)        | 63 (51–73)| 59 (47–74)    | 0.048   |
| Male, \( n \) (%)                                   | 612 (65)          | 163 (72.8)| 449 (62.5)    | 0.005   |
| Female, \( n \) (%)                                 | 330 (35)          | 61 (27.2) | 269 (37.5)    |         |
| Comorbidities, \( no. \) (%)                        |                   |           |               |         |
| Arterial hypertension                               | 357 (37.9)        | 101 (45.1)| 256 (35.7)    | 0.011   |
| Cardiovascular disease                              | 236 (25.1)        | 62 (27.7) | 174 (24.2)    | 0.299   |
| Diabetes \(^a\)                                     | 168 (17.8)        | 49 (21.9) | 119 (16.6)    | 0.070   |
| Obesity                                             | 143 (15.2)        | 58 (25.9) | 85 (11.8)     | \(<0.001\) |
| Chronic renal disease \(^b\)                        | 58 (6.2)          | 18 (8.0)  | 40 (5.6)      | 0.180   |
| COPD                                                | 82 (8.7)          | 17 (7.6)  | 65 (9.1)      | 0.498   |
| Neoplasm \(^c\)                                     | 88 (9.3)          | 19 (8.5)  | 69 (9.6)      | 0.613   |
| Chronic neurological disorders                       | 132 (14.0)        | 19 (8.5)  | 113 (15.7)    | \(0.006\) |
| ARDS patients at hospital admission, \( no. \) %    | 307 (32.5)        | 141 (63)  | 166 (23.1)    |         |
| PaO\(_2\)/FiO\(_2\) at hospital admission          |                   |           |               |         |
| >300                                                | 635 (67.4)        | 83 (37.1) | 552 (76.9)    | \(<0.001\) |
| 201-300                                             | 187 (19.9)        | 74 (33.0) | 113 (15.7)    |         |
| 101-200                                             | 94 (10.0)         | 51 (22.8) | 43 (6.0)      |         |
| ≤ 100                                               | 26 (2.8)          | 16 (7.1)  | 10 (1.4)      |         |
| ARDS patients at starting NIV, \( no. \) %          | 218 (97.3)        |           |               |         |
| PaO\(_2\)/FiO\(_2\) at starting NIV                |                   |           |               |         |
| >300                                                | 6 (2.7)           |           |               |         |
| 201-300                                             | 59 (26.3)         |           |               |         |
| 101-200                                             | 135 (60.3)        |           |               |         |
| ≤ 100                                               | 24 (10.7)         |           |               |         |
| Pre-NIV hospitalization, days, median               | 3 (2-6)           |           | N.A.          |         |
| (IQR)                                                                 |
|----------------------------------------------------------------------|
| Total length of stay, days, median (IQR)                             |
| 15 (9-25)                                                            |
| 26 (18-35)                                                           |
| 13 (8-19)                                                            |
| <0.001                                                              |
| Overall follow-up, no. %                                             |
| Admitted in ICU                                                     |
| 128 (13.6)                                                           |
| 88 (39.3)                                                            |
| 40 (5.6)                                                             |
| <0.001                                                              |
| Underwent OTI                                                       |
| 104 (11.0)                                                           |
| 64 (28.6)                                                            |
| 40 (5.6)                                                             |
| <0.001                                                              |
| Death                                                               |
| 100 (10.6)                                                           |
| 43 (19.2)                                                            |
| 57 (7.9)                                                             |
| <0.001                                                              |
| 28-day follow-up from NIV, no. %                                     |
| Admitted in ICU                                                     |
| 86 (38.4)                                                            |
| Underwent OTI                                                       |
| 63 (28.1)                                                            |
| Dead                                                                |
| 37 (16.5)                                                            |
| OTI and/or death (combined variables)                               |
| 84 (37.5)                                                            |

Abbreviations: IQR: interquartile range; COPD, chronic obstructive pulmonary disease; obesity is defined as BMI > 30 kg/m²; stage 3-5 of CKD, chronic kidney disease; solid neoplasia or hematological malignancy in the last 5 years; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; OTI, orotracheal intubation; ¹ Chi square test was performed between the two groups.

**NIV failure in COVID-19 patients**

Within 28 days from starting NIV, 86 patients were admitted in ICU, of which 63 were intubated, and 138 patients were not admitted in ICU, with 20 deaths occurred in this latter group, Figure 2. Table 2 shows the comparison between the 224 patients underwent NIV and patients that failed NIV consisting of 84 (37.5%), defined by the requirement for OTI and/or dead (combined outcome) within 28-day of follow-up from the start of the noninvasive ventilation.

In the univariate analysis, factors significantly associated with NIV failure were: female with a twice higher risk than male (OR 2.15, 95% CI 1.18-3.91, p=0.013); older age (with a 62% risk increased (OR 1.62, 95% CI 1.31-2.01, p<0.001) for each 10-year increase; hypertension with a 2.6 times increased risk (OR 2.57, 95% CI 1.47-4.47, p=0.001); COPD which confers a 6.2-times higher risk (OR 6.23, 95% CI 1.96-19.80, p=0.002) and history of neoplasm in the last 5 years with a 3.2-fold higher risk (OR 3.17, 95% CI 1.19-8.40, p=0.021). The presence of diabetes, neurological disease, obesity and chronic renal diseases were not significantly associated with NIV failure.

The multiple regression analysis shows that female had a risk twice higher than male (aOR 2.12, 95% CI 1.07-4.20, p=0.031). Also, age and COPD show respectively and independently an increase of 25% for each 10-year increase (aOR=1.25, 95% CI 0.98-1.59, p=0.068) and about 3.5-fold (aOR=3.44, 95% CI 0.95-12.48, p=0.060) of NIV failure with a significance slightly above 0.05.
The overall rate of NIV failure was 37.5% (84 patients) in 224 NIV patients. NIV failure occurred in 7 patients (10.8%) with P/F >200 mmHg (mild ARDS), 58 (43%) with P/F 101-200 (moderate ARDS) and 19 (79.1%) when P/F ≤ 100 mmHg (severe ARDS). To be noted that on six patients treated with NIV with P/F >300 mmHg at NIV start, none of them failed the treatment.

In the univariate analysis a P/F ratio of 101-200 and ≤100 mmHg before NIV treatment had an increased risk of NIV failure of 6-fold (OR 6.24, 95% CI 2.65-14.68, p<0.001) and 31.5-fold (OR 31.5, 95% CI 8.94-110.91, p<0.001) respectively, compared to patients with P/F ratio >200 mmHg. In the multiple regression analysis these risks become 5-fold (aOR 5.01, 95% CI 2.08-12.09, p<0.001) and 20-fold (aOR 19.95, 95% CI 5.31-74.94, p<0.001) higher, respectively.

Table 2. Unadjusted and adjusted predictors of NIV failure
| Characteristics                        | NIV group | NIV failure* | Univariate                  | Multivariate               |
|---------------------------------------|-----------|--------------|------------------------------|----------------------------|
|                                       | N (%)     | OR (95% CI)  | p                            | aOR (95% CI)               |
|                                       |           | p            |                              | p                          |
| **Male**                              | 163       | 53 (32.5)    | 1.00 (1.00-1.00)              | 1.00 (1.00-1.00)            |
| **Female**                            | 61        | 31 (50.8)    | 2.15 (1.18-3.91)              | 2.12 (1.07-4.20)            |
| **Age (for 10 years of increase)**    |           |              | 1.62 (1.31-2.01)              | <0.001                     |
| **Comorbidities**                     |           |              |                              |                            |
| **Arterial hypertension**             | 101       | 50 (49.5)    | 2.57 (1.47-4.47)              | <0.001                     |
| **Cardiovascular disease**            | 62        | 29 (46.8)    | 1.71 (0.94-3.10)              | 0.078                      |
| **Diabetes**                          | 49        | 16 (32.6)    | 0.76 (0.39-1.49)              | 0.429                      |
| **Obesity a**                         | 58        | 25 (43.1)    | 1.37 (0.75-2.53)              | 0.307                      |
| **Chronic renal disease b**           | 18        | 10 (55.5)    | 2.23 (0.84-5.9)               | 0.106                      |
| **COPD**                              | 17        | 13 (76.5)    | 6.23 (1.96-19.80)             | 0.002                      |
| **Neoplasm c**                        | 19        | 12 (63.1)    | 3.17 (1.19-8.40)              | 0.021                      |
| **Neurological disorders**            | 19        | 10 (52.6)    | 1.97 (0.77-5.06)              | 0.160                      |
| **PaO2/FiO2 at NIV**                  |           |              |                              |                            |
| >200                                  | 65        | 7 (10.8)     | 1.00 (1.00-1.00)              | <0.001                     |
| 101-200                               | 135       | 58 (43.0)    | 6.24 (2.65-14.68)             | 5.01 (2.08-12.09)          |
| ≤ 100                                 | 24        | 19 (79.1)    | 31.49 (8.94-110.91)           | 19.95 (5.31-74.94)         |

Abbreviations: ICU: intensive care unit; OTI: orotracheal intubation; NIV: noninvasive ventilation; CI: Confidence Intervals; *NIV failure is defined as combined variable of orotracheal intubation or death at 28-follow-up from starting NIV; IQR, interquartile range; COPD, chronic obstructive pulmonary disease;


a obesity is defined as BMI > 30 kg/m²; b stage 3-5 of CKD, stages of chronic kidney disease; c solid neoplasia or hematological malignancy in the last 5 years;

Risk of death in COVID-19 patients treated with NIV

Figure 3 and Table 3 show schematically the occurrence of death in ICU patients (35/128, 27.3%) within 28-days of follow-up from ICU admission. Sixty-one patients (47.7%) of those previously treated with NIV admitted in ICU were subsequently intubated, of which 17 (27.9%) died within 28 days from ICU admission. Further 27 patients NIV treated and admitted in ICU, did not require intubation, and only one patient, who repeatedly refused orotracheal intubation, died while still in NIV. The remaining 40 patients (31.3%) admitted in ICU and not previously treated with NIV were all intubated, and 17 (42.5%) died within 28-day from ICU admission. The mortality among intubated patients in ICU was 33.7% overall (34/101 patients).

Table 3. Multifactorial analysis of the factors associated with the outcome death.
| COVID-19 patients | ICU patients | Deceased* | Univariate | Multivariate |
|-------------------|--------------|-----------|------------|--------------|
|                   | 128          | 35 (27.3) | OR (95% CI) | p            |
| Male, n (%)       | 87           | 24 (27.6) | 1          |              |
| Female, n (%)     | 41           | 11 (26.8) | 0.96 (0.42-2.20) | 0.929 |
| Age (for 10 years of increase) |       |           | 1.25 (0.91-1.71) | 0.168 |
| Comorbidities, no. (%) | | | | |
| Arterial hypertension | 64 | 12 (18.7) | 2.43 (1.08-5.46) | 0.031 |
| Cardiovascular disease | 33 | 15 (45.5) | 3.13 (1.34-7.27) | 0.008 4.56 (1.73-12.03) | 0.002 |
| Diabetes | 20 | 7 (35) | 1.54 (0.56-4.24) | 0.405 |
| Obesity a | 45 | 15 (33.3) | 1.58 (0.71-3.50) | 0.265 |
| Chronic renal disease b | 12 | 7 (5.8) | 4.40 (1.29-14.96) | 0.011 |
| COPD | 11 | 4 (4.4) | 1.56 (0.43-5.79) | 0.486 |
| Neoplasm c | 10 | 1 (10) | 0.28 (0.03-2.25) | 0.228 |
| Neurological disorders | 10 | 3 (33.3) | 1.45 (0.39-5.40) | 0.580 |
| NIV/OTI | | | | |
| No NIV, yes OTI | 40 | 17 (42.5) | 1 | 0.014 0.010 |
| Yes NIV, yes OTI | 61 | 17 (27.9) | 0.52 (0.23-1.21) | 0.60 (0.25-1.46) |
| Yes NIV, no OTI | 27 | 1 (3.7) | 0.05 (0.01-0.42) | 0.04 (0.01-0.32) |

Abbreviations: ICU: intensive care unit; OTI: orotracheal intubation; NIV: noninvasive ventilation; CI: Confidence Intervals; COPD: chronic obstructive pulmonary disease; a obesity is defined as BMI>30 kg/m²; b stage 3-5 of CKD, stages of chronic kidney disease; c solid neoplasia or hematological malignancy in the last 5 years; *At ICU 28-day follow up.
In the univariate analysis factors found to be significantly associated with the risk of death were: chronic renal disease with more than 4-fold increased risk (OR 4.4, 95% CI: 1.29-14.96, p=0.011), hypertension with a 2.4-fold greater risk (OR=2.43, 95% CI: 1.08-5.46, p=0.031) and other cardiovascular diseases with a 3-risk times greater (OR 3.13, 95% CI: 1.34-7.27, p=0.008). Instead, female sex, age variation, COPD, diabetes, neurological disease, obesity and history of neoplasm were not significantly associated with a different risk of death.

The multivariable regression analysis showed the cardiovascular diseases was statistically significant and independently associated with the outcome (death), with a 4.6-fold increased risk (aOR=4.56, 95% CI: 1.73-12.03, p=0.002).

Moreover, we observed that when comparing with the group of those who underwent OTI without prior-NIV, those who were intubated after NIV treatment showed a tendency of decreased mortality risk (OR=0.52, 95% CI: 0.23-1.21, but more interestingly those admitted in ICU with previous NIV treated who did not required orotracheal intubation showed a significant 95% reduction of mortality (OR=0.05, 95% CI: 0.01-0.42). The adjusted model also confirms these findings, with a significant 94% reduction of mortality (aOR=0.04, 95% CI: 0.01-0.32) for those who did not required OTI.

**Discussion**

**Baseline characteristics of NIV patients**

Noninvasive ventilation in our hospital was a commonly used treatment in patients with severe COVID-19 pneumonia already in the hospital ward, while also facing the overload of ICU beds. During the period of the study, 23.8% of all COVID-19 patients were treated with NIV.

COVID-19 patients who required NIV were more frequently male, older and with more comorbidities such as arterial hypertension and obesity, compared to those never treated with NIV. Chronic neurological disease was less frequently found in patients treated with NIV, and this could be explained by assuming that these patients for their underlying disease (such as senile dementia, Alzheimer’s disease etc.) were less compliant and therefore more difficult to treat them with noninvasive ventilation which requires cooperation. Cardiovascular diseases, diabetes, chronic kidney disease, COPD and history of neoplasm in the last 5 years did not show to be significant predictors for NIV requirement.

At hospitalization 307 (32.5%) COVID-19 patients fulfilled Berlin criteria for ARDS, and the latter had a statistically significant increased need for NIV treatment. However, some patients refused NIV treatment despite the indications and others were uncooperative, which is why we had 53 patients with moderate-severe ARDS (P/F ratio $\leq$ 200 mmHg) non treated with noninvasive ventilation, but only with conventional supplemental oxygen therapy. Indeed, 40 (5.6%) of these were admitted in ICU and subsequently intubated due to the worsening of their clinical conditions, of which 17 (42.5%) died within 28 days from ICU admission.
At starting of NIV treatment, 218 patients (97.3% of NIV group) were diagnosed with ARDS (59 with mild, 135 with moderate and 24 with severe ARDS). The length of stay in hospital was significantly longer in patients treated with NIV. Also, the patients that required noninvasive ventilation showed a higher rate of ICU admission, orotracheal intubation and death than patients who did not require NIV.

**NIV failure in COVID-19 patients**

Among 224 NIV patients, NIV failure occurred in 84 (37.5%) patients, defined by the occurrence of intubation and/or death within 28 days from starting NIV. Patients that failed NIV were female with a twice higher risk than male, older and with more comorbidities as arterial hypertension, COPD and neoplasm. The significant predictor independently associated with a higher risk of NIV failure included being female, and slightly above the significance level an older age and having COPD, while other comorbidities such as diabetes, neurological disease, obesity or chronic renal diseases were not found to significantly associated with NIV failure.

The failure rate of noninvasive ventilation was independently correlated with the category of severity COVID-19 ARDS (PaO$_2$/FiO$_2$ ratio categories). Indeed, NIV failure occurred in 11.8% in COVID-19 patients with mild ARDS, 43% with moderate ARDS and 79% in those with severe ARDS.

In a large multicenter observational study LUNG SAFE in 2016, with data from 50 countries and 2,813 patients with ARDS in era pre-COVID-19, NIV failure occurred in 22.2% of mild, 42.3% of moderate and 47.1% of severe ARDS patients [10,21]. Therefore, from results of our study, we can observe that in comparison with non-COVID-19 ARDS patients in the cited study, in the mild ARDS patients (with P/F 200-299 mmHg) the risk of NIV failure was lower (11.8% vs 22.2%), it was similar for the moderate ARDS (for P/F 100-199 category, 43% vs 42.3%), but became quite higher in severe ARDS when the P/F ratio drops below 100 mmHg (79.1% vs 47.1%). Studies carried out during the COVID-19 outbreak show that noninvasive ventilation may have some benefit in postponing or avoiding non-invasive ventilation but with limitation to patient severity and PaO$_2$/FiO$_2$ value, although with a smaller sample size [22,23].

Therefore, we observed that in the early stages of COVID-19 the risk of NIV failure is low, indicating that an early start of NIV treatment at stages when COVID-19 patients have a P/F ratio >200 mmHg increases the chance of NIV success, consequently avoiding orotracheal intubation. But in the more advanced stages, especially when P/F falls below 100 mmHg we should not hesitate to intubate these patients because they would have a very high risk of NIV-failure.

**Risk of death in COVID-19 patients treated with NIV**

During the period of study 13.6% of COVID-19 patients in-hospital ward were admitted in ICU. Of the population treated with NIV, 39.3% were admitted in ICU. Overall mortality within 28-days from ICU admission in those admitted to ICU was slightly higher than one quarter (27.3%).
At 28-day follow up from ICU admission, arterial hypertension, cardiovascular diseases and chronic renal disease were significantly associated in the univariate regression analysis with an increased risk of death, but, only cardiovascular diseases was found to be independently and significantly associated with a 4.5-fold higher risk of death.

The mortality among those who were intubated in ICU was 33.7%. Patients treated with NIV that subsequently admitted in ICU and underwent OTI had a mortality of 27.9% and was significantly lower than the mortality of intubated patients who didn't treated with prior-NIV, 42.5%, at 28 days of ICU admission. One patient died while still in NIV, who had expressively given do-not-intubate (DNI) order.

These findings showed that early noninvasive ventilation prior to OTI is independently associated with a significantly decreased risk of mortality in ICU.

Before drawing conclusions, several limitations should be considered. First, this is a retrospective observational study designed in a single third level COVID-19 center and controlling for confounders as in any observational study may be incomplete despite all efforts. Second, the decision about the timing and management of the NIV treatment, OTI and ICU admission were made by the intensive care physicians based on institutional protocols and good medical practice. Therefore, we cannot rule out the possibility that physicians have decided for NIV placement, OTI or ICU admission based on pre-existing medical conditions (comorbidities, age etc.), or the availability of medical devices and ICU beds, especially during multiple COVID-19 waves that overwhelmed the hospital. Additionally, patients who have refused NIV, OTI, or ICU admission despite clinical severity and some of those died, may have generated an unmeasured bias that could underestimate the effectiveness of NIV. Third, we considered NIV treatment as both BiPAP and/or CPAP, without the possibility based on clinical charts to have a reliable more accurate classification on the type of interface used for NIV, which may be a potentially determinant of the outcomes. Thereafter, further research on larger prospective studies is required. However, this study also has some strengths, including a large sample size and the full representativeness of real-life clinical practice, and management of ICU COVID-19 patients with severe respiratory failure, which cannot be represented by a randomized controlled trial study. The findings of this study seemed in line with some of the aforementioned studies already presented in medical literature [8,22,23]. Observational retrospective studies are the first step to formulate hypothesis that could incentivize the design of larger prospective studies.

Conclusion

In conclusion, our study found that noninvasive ventilation was a useful mode of therapy in COVID-19 patients with ARDS. The study showed that NIV was effective in approximately two-thirds of the patients with COVID-19 ARDS treated with this procedure in preventing a negative outcome (either need of intubation or death).

NIV failure occurred in 37.5% of COVID-19 ARDS patients, in almost half of patients (43%) with moderate ARDS, and in about 80% of patients with severe ARDS, within 28 day from starting NIV. The presence
of cardiovascular diseases was an independent risk factor for increasing mortality.

Starting NIV at earlier stages of COVID-19 when P/F >200mmHg showed to be associated with a lower risk of NIV failure, avoiding orotracheal intubation and/or death.

Patients treated with NIV that subsequently admitted in ICU and underwent OTI had a 28 days mortality after ICU admission, significantly lower than intubated patients who weren’t previously treated with NIV. These findings suggest that NIV treatment is independently associated with a decreased risk of ICU mortality.

**Declarations**

**Other members of the ReCOVeRI Study Group:** Maria Alessandra Abbonizio, Amina Abdeddaim, Chiara Agrati, Fabrizio Albarello, Gioia Amadei, Alessandra Amendola, Tommaso Ascoli Bartoli, Francesco Baldini, Raffaella Barbaro, Barbara Bartolini, Alessia Beccacece, Rita Bellagamba, Martina Benigni, Nazario Bevilacqua, Gianlugi Biava, Michele Bibas, Licia Bordi, Veronica Bordoni, Evangelo Boumis, Marta Branca, Marta Camici, Flaminia Canichella, Maria Rosaria Capobianchi, Emanuela Caraffa, Ilaria Caravella, Fabrizio Carletti, Concetta Castilletti, Adriana Cataldo, Daniele Centanni, Stefano Cerilli, Carlotta Cerva, Elena Cesì, Roberta Chiappini, Pierangelo Chinello, Carmine Ciaralli, Stefania Cicalini, Francesca Colavita, Angela Corpolongo, Massimo Cristofaro, Salvatore Curiale, Alessia De Angelis, Maria Grazia De Palo, Federico De Zottis, Virginia Di Bari, Mattia Di Frischia, Rachele Di Lorenzo, Federica Di Stefano, Davide Donno, Giovanni Marco Dutti, Francesca Evangelista, Alessandro Falcione, Francesca Faraglia, Anna Farina Federica Ferraro, Lorena Fiorentini, Andrea Frustaci, Marisa Fusto, Roberta Gagliardi, Vincenzo Galati, Paola Galli, Saba Gebremeskel Tekle, Maria Letizia Giancola, Filippo Giansante, Emanuela Giombini, Guido Granata, Maria Cristina Greci, Elisabetta Grilli, Adele Grisaro, Susanna Grisetii, Marta Iaconi Giuseppina Iancicelli, Carlo Inversi, Giuseppe Ippolito, Eleonora Lalle, Maria Elena Lamanna, Simone Lanini, Daniele Lapa, Luciana Lepore, Raffaella Libertone, Raffaella Lionetti, Giuseppina Liuzzi, Laura Loiacono, Patrizia Lorenzini, Andrea Lucia, Manuela Macchione, Gaetano Maffongelli, Maria Grazia Maglie, Alessandra Marani, Andrea Mariano, Micaela Maritti, Alessandra Mastrobattista, Giulia Matusali, Valentina Mazzotta, Paola Mencarini, Ricardo Jose Merino Cabas, Silvia Meschi, Francesco Messina, Sibiana Micarelli Paolo Migliorisi Ramazzini, Giulia Mogavero, Annalisa Mondi, Marzia Montalbano, Chiara Montaldo, Silvia Mosti, Silvia Murachelli, Maria Musso, Pasquale Noto, Roberto Noto, Alessandra Oliva, Sandrine Ottou, Claudia Palazzolo, Emanuele Pallini, Carlo Pareo, Federico Pelliccioni, Antonella Petecchia, Ada Petrone, Valeria Petroselli, Nicola Petrosillo, Elisa Pianura, Maria Pisciotta, Silvia Pittalis, Agostina Pontarelli, Costanza Proietti, Alessandro Puleio, Vincenzo Puro, Giuseppina Ragosta, Chiara Reggiani, Alessia Rienda, Gabriele Rinonapoli, Silvia Rosati, Martina Rueca, Alessandra Sacchi, Alessandro Sampaolesi, Francesco Sanasi, Carmen Santagata, Alessandra Scarabello, Gianpaolo Scarfo, Vincenzo Schininà, Paola Scognamiglio, Laura Scorzolini, Chiara Taibi, Giorgia Taloni, Roberto Tonnarini, Francesco Vairo, Maria Beatrice Valli, Alessandra Vergori, Laura Vincenzi, Ubaldo Visco-Comandini, Serena Vita, Pietro Vittozzi, Mauro Zaccarelli.
Author Contributions: Study design: GDA, LM, NT, PP, SZ.; Data acquisition of clinical data: SZ, GDA, MCM, DR, IO, IG, MVA, EA, CPo, GVS, GGa, DB, SSDA, ST, FI, ADA, CPI, GGa, AC, AV; Formal analysis, and interpretation of data: CC, AN, TN, PP; Validation: LM, PP, EG and EN; Drafting the manuscript: NT, PP, SZ; Supervision: AA, FP, GDO, SI, PC, FT, FV; Review and editing: All authors; Funding acquisition: EN. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of IRCCS L. Spallanzani. Data acquisition and analysis were performed in compliance with protocols approved by the Ethical Committee of the National Institute for Infectious Diseases IRCCS Lazzaro Spallanzani, Rome, Italy (ethical approval number 164, 26 June 2020).

Informed Consent Statement: Informed consent was obtained for all subjects involved in the study. No identifying images or other personal or clinical details of participants that could compromise anonymity have been included. Request of consent for publication is therefore not applicable.

Data Availability Statement: The data presented in this study are available on reasonable request from the corresponding author. The data are not publicly available because of patient privacy and the General Data Protection Regulation (GDPR).

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Figures
Figure 1

Flowchart of study selection. Abbreviations: COVID-19, coronavirus disease 2019; NIV, noninvasive ventilation; ICU, intensive care unit; OTI, orotracheal intubation.
Figure 2

Flowchart of the patients underwent NIV. Abbreviations: NIV: noninvasive ventilation; ICU: intensive care unit; OTI: orotracheal intubation.
Figure 3

Flowchart of the patients admitted in ICU. Abbreviations: NIV: noninvasive ventilation; ICU: intensive care unit; OTI, orotracheal intubation.