Role of prognostic scores in predicting in-hospital mortality and failure of non-invasive ventilation in adults with COVID-19

Francesca Innocenti1 · Cristian Lazzari1 · Elisa Paolucci1 · Anna De Paris1 · Alessia Lagomarsini1 · Federica Guerra1 · Patrizia Alleonato1 · Lisa Casalini1 · Michele Buggea1 · Francesca Caldi1 · Maurizio Zanobetti1 · Filippo Pieralli2 · Giulia Guazzini2 · Lisa Lastraioli2 · Fabio Luise2 · Alessandro Milia2 · Lucia Sammicheli2 · Lucia Maddaluni1 · Federico Lavorini3 · Riccardo Pini1,3

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Abstract

We tested the prognostic performance of different scores for the identification of subjects with acute respiratory failure by COVID-19, at risk of in-hospital mortality and NIV failure. We conducted a retrospective study, in the Medical High-Dependency Unit of the University-Hospital Careggi. We included all subjects with COVID-19 and ARF requiring non-invasive ventilation (NIV) between March 2020 and January 2021. Clinical parameters, the HACOR score (Heart rate, Acidosis, Consciousness, Oxygenation, Respiratory Rate) and ROX index ((SpO2/FiO2)/respiratory rate) were collected 3 (-3) and 1 day (-1) before the NIV initiation, the first day of treatment (Day0) and after 1 (+1), 2 (+2), 5 (+5), 8 (+8) and 11 (+11) of treatment. The primary outcomes were in-hospital mortality and NIV failure. We included 135 subjects, mean age 69±13 years, 69% male. Patients, who needed mechanical ventilation, showed a higher HACOR score (Day0: 6 [5-7] vs 6 [6-7], p=.057; Day+2: 6 [6-6] vs 6 [4-6], p=.013) and a lower ROX index (Day0: 4.2±2.3 vs 5.1±2.3, p=.055; Day+2: 4.4±1.2 vs 5.5±1.3, p=.001) than those with successful NIV. An HACOR score >5 was more frequent among nonsurvivors (Day0: 82% vs 58%; Day2: 82% vs 48%, all p<0.01) and it was associated with in-hospital mortality (Day0: RR 5.88, 95%CI 2.01-17.22; Day2: RR 4.33, 95%CI 1.64-11.41) independent to age and Charlson index. In conclusion, in subjects treated with NIV for ARF caused by COVID19, respiratory parameters collected after the beginning of NIV allowed to identify those at risk of an adverse outcome. An HACOR score >5 was independently associated with increased mortality rate.

Keywords COVID-19 · Respiratory failure · Non-invasive ventilation · Prognosis

Introduction

Current guidelines on the management of hypoxemic respiratory failure are very cautious about the employment of non-invasive ventilator support, which did not prove to be effective in this condition [1]. A trial can be performed in selected subjects and in adequate clinical settings, with a close monitoring to prevent respiratory deterioration. In subjects with acute respiratory failure (ARF) induced by COVID-19, guidelines recommended early endo-tracheal intubation (ETI) [2, 3]. Among non-invasive supports, a trial of treatment with High-Flow Nasal Cannulas (HFNC) was preferred over Non-Invasive Ventilation (NIV). In fact, in previous pandemics, the employment of NIV was associated with a high failure rate and could be harmful from different points of view [4–6]. It might create high transpulmonary pressures and large tidal volumes, which may aggravate the lung injury, as well as delay ETI and the beginning of invasive ventilation. Finally, NIV is an aerosol-generating procedure, which can increase the risk of the spread of the disease among healthcare workers.

On the other side, the heavy workload imposed by the pandemic on healthcare systems and the shortage of
resources in the Intensive Care Units (ICUs) induced clinicians to employ non-invasive ventilation in subjects with acute respiratory failure caused by COVID-19 [7, 8]. Earliest reports showed a high failure rate, probably due to the overwhelming load of patients and inappropriate selection of those, who could be treated with NIV [7]. Thereafter, several authors showed a good rate of success [8, 9]. This finding, combined with a very high mortality rate in intubated patients, favored the employment of NIV in these subjects. Because the delay in intubation and invasive mechanical ventilation is associated with an increased mortality, the early identification of subjects at risk of failure of the non-invasive respiratory support remains a clinical challenge.

We evaluated the prognostic stratification ability of several scores, which were chosen based on the following criteria: (1) the ROX index, which includes a PIF ratio corrected by the respiratory rate, for its ease to use in daily clinical practice [10]; (2) the HACOR score, which includes Heart rate, Acidosis, Consciousness, Oxygenation, Respiratory Rate, easily available at the bedside, for its feasibility and known prognostic value [11, 12]; (3) the nomogram elaborated by Liu and coll., specifically designed for COVID patients and created to be used at the very beginning of the treatment with NIV [13].

The aim of the present study was to test the prognostic performance of different scores for the early identification of subjects with ARF by COVID-19, at high risk of in-hospital mortality and NIV failure.

Methods

Study design and setting

This was a retrospective study, performed in the High-Dependency Unit (ED-HDU) at the Careggi University Hospital. The ethics committee and institutional review board approved this study (NO. 17104). The Careggi University Hospital is an urban academic hospital and a tertiary care center (1300 beds, 130,000 visits in the Emergency Department per year). During the pandemic for COVID-19 disease, from March 2020, a 14-bed High Dependency Unit was created. Internists and emergency physicians, all experienced in critical care and in the management of subjects requiring NIV, managed the Unit.

Selection of participants

We included all consecutive subjects, who were admitted to the HDU for ARF and were treated with NIV between March, 2020 and January, 2021. No dedicated respiratory therapist or technician was available in the unit during the study period. The decision to initiate NIV (Philips Respironics, Carlsbad, CA) was made by the attending physician, experienced in critical care, based on the guidelines of the American Thoracic Society [1] and the British Thoracic Society [14]. Whenever possible, a management plan was made before initiating a NIV trial about what to do in case of failure, either to intubate and mechanically ventilate the patient or to consider the NIV trial as a “ceiling” treatment, considering the stage of underlying disease and the patient’s wishes about advanced life support.

Medical treatment for COVID-19 was based on available guidelines: hydroxychloroquine and lopinavir/ritonavir or darunavir/cobicistat were the standard of care during the first wave (March–May 2020), as well as corticosteroids during the second wave. Low Molecular Weight Heparin was employed in all patients, unless contraindicated. Therefore, we did not systematically annotate the administration of these drugs.

NIV was delivered by full-face or oro-nasal mask, which could be interchanged to avoid pressure ulcers. The Continuous Positive Airway Pressure (CPAP) ventilation was the first choice mode of ventilation. When symptoms and signs of respiratory distress or fatigue were present (increased respiratory rate and/or lactate levels), the pressure-support modality was employed. The fraction of oxygen in the gas flowing in the system was subsequently adjusted to maintain a peripheral saturation of O$_2$ (SpO$_2$) $\geq$ 94%.

We defined NIV failure by the need for ETI and invasive mechanical ventilation or death during NIV. Adhering to current guidelines, the attending physician decided to intubate the subjects. The primary outcomes were inhospital mortality and NIV failure.

Measurements and outcomes

Subjects were identified according to HDU admission diagnosis from electronic medical records. Demographic data, previous medical conditions and all the other parameters were extracted from a database, where we collected data of all subjects with COVID-19 admitted to our hospital, using a standardized collection template. For each patient, we collected data on the following days: three (Day-3) and one (Day-1) day before the NIV initiation, the day of the beginning of the treatment (Day 0) and one (Day1), two (Day2), five (Day5), eight (Day8) and eleven (Day11) days after NIV initiation. These time points were chosen to obtain the trend of respiratory parameters before, during and after the beginning of the treatment with NIV, to select the earliest evaluations with a good prognostic stratification ability. At every evaluation, we collected the following data: vital signs, arterial blood gas (ABG) parameters, laboratory data and ventilation modality. At
every evaluation, the worst vital signs and arterial blood gas parameters were collected.

Scores calculation

We calculated the following values: (1) $\text{paO}_2/\text{FiO}_2$ ratio; (2) alveolar-arterial (A-a) $\text{O}_2$ gradient; (3) HACOR (Heart rate, Acidosis, Consciousness, Oxygenation, Respiratory rate) score; (4) ROX index and (5) Charlson index, for the evaluation of comorbidities.

The HACOR score was calculated as follows:

- **Heart rate:**
  - $<$ 120 b/min 0
  - $\geq$ 120 b/min 1

- **Acidosis (pH):**
  - $\geq$ 7.350
  - 7.30–7.342
  - 7.25–7.293
  - $<$ 7.254

- **Consciousness (GCS):**
  - 150
  - 13–142
  - 11–125
  - $\leq$ 1010

- **Oxygenation (P/F):**
  - $\geq$ 2010
  - 176–2002
  - 151–1753
  - 126–1504
  - 101–1255
  - $\leq$ 1006

- **Respiratory rate:**
  - $\leq$ 300
  - 31–351
  - 36–402
  - 41–453
  - $\geq$ 464

It was analyzed as continuous value and dichotomized as $<\text{or} \geq 4.88$ [10].

Finally, we calculated the **nomogram specifically validated to predict NIV failure** in subjects with ARF induced by COVID-19 based on data recorded on the first day of NIV [13]:

$$\text{Total score} = (\text{age} \times 0.0817) - 1.633) + (7.819 - [0.521 \times \text{Glasgow coma scale}]) + (10 - [0.385 \times \text{ROX}]) + 3.844 \ (\text{if use of vasopressors} + (0.359 \times \text{number of comorbidities}).$$

The probability of NIV failure was calculated as follows:

$$\left(0.02354 \times [\text{total score}]^2 \right) - \left(0.00079 \times [\text{total score}]^3 \right) - (0.11954 \times \text{total score}) + 0.13527.$$  

Sequential Organ Failure Assessment (SOFA) score was calculated at every evaluation.

We collected data about the results of lung ultrasound performed within the first 48 h of the treatment with NIV, based on a standardized protocol. Each lung was divided in 6 zones (2 anterior, 2 lateral and 2 posterior) and each zone was cored as follows: (1) score 0: well-spaced B-lines < 3; (2) score 1: well-spaced B-lines $\geq$ 3; (3) score 2: multiple coalescent B-lines; (4) score 3: lung consolidation. The sum of the scores in all twelve zones yielded a final LUS score [15–17].

Statistical analysis

Due to the retrospective design of the study, we included all the subjects who underwent NIV in the study period. However, based on the reported mortality in the original paper (21% in patients with T0 HACOR score $\leq$ 5 and 65% in those with HACOR score $> 5$) [11], the required population size was 60 patients and the study population included in the present study was more than double of the required study sample.

Continuous variables were reported as mean $\pm$ standard deviation or as median and interquartile range, and comparisons between two groups were performed with the Student t-test for normally distributed data or by Mann–Whitney’s test for non-parametric data. Categorical data were reported as counts and proportions and analyzed using contingency tables and $\chi^2$ test. A multivariate regression logistic analysis was performed to verify the independent prognostic value of the scores. To assess the ability of the nomogram model to discriminate subjects who responded to NIV, a concordance statistic (C-statistic; equal to the area under the receiver operating curve) and 95% CIs were calculated.

A $p$-value $< 0.05$ was considered significant. All statistical analyses were carried out using IBM SPSS software package (version 27).
Results

We included 135 subjects, whose main anamnestic data are reported in Table 1. On Day-3 and Day-1, respectively 5/66 and 13/117 were not on O2 treatment, while 4/66 and 31/117 were treated with HFNC and all the others with conventional oxygen treatment. NIV was performed as continuous treatment in 31 subjects on Day0, 51 on Day1, 50 on Day2, 31 on Day5, 13 on Day8 and 6 on Day11. The remaining subjects alternated NIV and HFNC.

Mean latency between ED admission and the initiation of NIV was 2.7 ± 2.3 days and the mean duration of the treatment with NIV was 9.1 ± 5.9 days. Forty subjects underwent ETI and mechanical ventilation, with a mean latency

| Table 1 Characteristics of the whole study population and based on in-hospital outcome |
|-----------------------------------|------------------|-----------------|---------------------|     |
|                                   | All (n=135)      | Survivors (n=100) | Non-survivors (n=35) | p      |
| Age (years)                       | 69±13            | 65±13            | 76±9                | <0.001 |
| Male gender (%)                   | 92 (69%)         | 68 (68%)         | 24 (69%)            | 1.000  |
| Previous medical conditions       |                  |                  |                     |        |
| Arterial hypertension (%)         | 80 (59%)         | 54 (54%)         | 26 (74%)            | 0.057  |
| Diabetes (%)                      | 28 (21%)         | 21 (21%)         | 7 (20%)             | 1.000  |
| CAD (%)                           | 24 (18%)         | 15 (15%)         | 9 (26%)             | 0.242  |
| CHF (%)                           | 10 (8%)          | 6 (6%)           | 4 (11%)             | 0.506  |
| COPD (%)                          | 15 (11%)         | 8 (8%)           | 7 (20%)             | 0.107  |
| CKD (%)                           | 6 (4%)           | 1 (1%)           | 5 (14%)             | 0.005  |
| Neoplasia (%)                     | 3 (2%)           | 2 (2%)           | 1 (3%)              | 1.000  |
| Stroke (%)                        | 6 (5%)           | 4 (4%)           | 2 (6%)              | 1.000  |
| Symptoms                          |                  |                  |                     |        |
| Dyspnoea (%)                      | 90 (67%)         | 66 (66%)         | 24 (69%)            | 1.000  |
| Cough (%)                         | 64 (48%)         | 51 (51%)         | 13 (37%)            | 0.205  |
| Nausea (%)                        | 2 (2%)           | 2 (2%)           | 0                   | 0.966  |
| Diarrhea (%)                      | 10 (8%)          | 7 (7%)           | 3 (9%)              | 1.000  |
| Syncope (%)                       | 4 (3%)           | 4 (4%)           | 0                   | 0.529  |
| Fatigue (%)                       | 23 (17%)         | 15 (15%)         | 8 (23%)             | 0.436  |
| Parameters on Day 0               |                  |                  |                     |        |
| HR (b/min)                        | 82±20            | 81±18            | 83±22               | 0.674  |
| SBP (mmHg)                        | 130±25           | 130±25           | 132±26              | 0.643  |
| RR (b/min)                        | 29±9             | 29±10            | 29±8                | 0.897  |
| SpO2 (%)                          | 92±6             | 94±3             | 91±2                | <0.001 |
| GCS                                | 14.9±0.5         | 14.9±0.1         | 14.8±0.8            | 0.182  |
| pH                                | 7.45±0.04        | 7.45±0.04        | 7.45±0.05           | 0.962  |
| LAC (mEq/L)                       | 1.46±1.16        | 1.39±1.18        | 1.61±1.11           | 0.313  |
| WBC (10^9/L)                      | 9.9±4.9          | 9.7±4.8          | 10.3±5.1            | 0.549  |
| Platelets (10^9/L)                | 242±94           | 251±103          | 225±73              | 0.176  |
| Creatinine (mg/dL)                | 1.09±0.49        | 1.02±0.40        | 1.22±0.59           | 0.071  |
| Bilirubin (mg/dL)                 | 0.61±0.39        | 0.58±0.38        | 0.67±0.42           | 0.366  |
| Treatments                        |                  |                  |                     |        |
| Remdesivir (%)                    |                  |                  |                     |        |
| Tocilizumab (%)                   | 5                | 3 (3%)           | 2 (6%)              | 0.604  |
| Ventilation modality              |                  |                  |                     |        |
| Day0 CPAP                         |                  |                  |                     |        |
| Continuous                        | 13 (10%)         | 7 (8%)           | 6 (13%)             | 0.451  |
| Intermittent                      | 57 (42%)         | 39 (39%)         | 18 (49%)            |        |
| Day0 Bilevel                      |                  |                  |                     |        |
| Continuous                        | 11 (8%)          | 6 (7%)           | 5 (11%)             | 0.261  |
| Intermittent                      | 54 (40%)         | 33 (37%)         | 21 (47%)            |        |

CAD: coronary artery disease; CHF: cardiac heart failure; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease
of 6.5 ± 5.9 days after NIV initiation. Overall, the treatment with NIV was effective in 69 (51%) patients.

In the whole study population, in-hospital mortality rate was 33% (n=45). Compared to subjects successfully treated with NIV, those, who underwent ETI, showed a significantly higher mortality rate (60% vs 22%, p < 0.001). In Table 1, we reported anamnestic and clinical parameters based on the survival status. Compared to survivors, non-survivors were significantly older, and, among comorbidities, they showed a higher prevalence of chronic kidney disease. Non-survivors showed a significantly higher Charlson index than survivors (1 [0–2] vs 0 [0–1], p = 0.025). We did not observe any difference regarding symptoms of presentation. Among vital signs, ABG and laboratory parameters, only SpO_2 was significantly worse in non-survivors than in survivors. We firstly examined the trends of respiratory parameters and scores in survivors and non-survivors. In Fig. 1 (left), we reported the values of P/F ratio, alveolar-arterial gradient, ROX index and HACOR score at all the evaluations, before and after the beginning of NIV. Both survivors and non-survivors showed a rapid deterioration of respiratory parameters in the last three days before the initiation of NIV. In the same way, parameters evaluated at Day0 were similar regardless of prognosis. By Day1, survivors showed a slow improvement while subjects with an adverse prognosis continued worsening or did not show any improvement. Thereafter, we compared the distribution of dichotomized scores based on prognosis. Compared to subjects with a good outcome, a significant higher proportion of non-survivors showed a HACOR score > 5 at all the evaluations while a ROX index < 4.88 was more frequent only at the survival status. From Day1, parameters of respiratory function, both in terms of oxygenation and respiratory rate, as well as the scores, were significantly more compromised in subjects, in whom NIV failed. In Fig. 1 (right), we reported the values of the P/F ratio, alveolar-arterial gradient, HACOR score and ROX index at all the examinations. We confirmed the same trends evidenced in Table 3. When we considered the dichotomized values of the scores (Fig. 2C and D), a significantly higher proportion of subjects who underwent NIV failure had a HACOR score > 5 and a ROX index < 4.88. We did not perform a multivariate analysis for this outcome as subjects with successful and failed NIV showed similar age and Charlson index.

We finally calculated the nomogram to predict NIV failure with the parameters collected on Day-0 of treatment. Compared to subjects with successful NIV, the value was significantly higher in subjects with failed NIV (13.1 ± 1.1 vs 12.0 ± 1.4, p < 0.001), as well as the probability of NIV failure (83 ± 9% vs 71 ± 15%, p < 0.001), with a C-statistic 0.73. However, as shown in Fig. 3, there was a wide overlap of values of the probability of NIV failure between subjects with successful and failed NIV. We repeated the analysis with values collected at Day1. We confirmed the results obtained at Day0, with a nomogram significantly higher in intubated subjects than in those who did not (13.2 ± 1.0 vs 12.0 ± 1.5, p < 0.001) and a corresponding higher probability of being intubated (83 ± 9% vs 71 ± 15%, p < 0.001). C-statistic was also similar (0.75).

Among the 114 patients, who underwent lung ultrasound, the LUS score was similar in survivors and non-survivors (18 [14–23] vs 20.5 [14–24.3], p = 0.229) and in subjects with successful and failed NIV (18 [13–23] vs 20.5 [15.5–24], p = 0.166). Fifty-three subjects did not have any consolidation, while we observed them in 1 zone in 18 subjects (11 survivors and 7 non-survivors), in 2 zones in 22 subjects (16 survivors and 6 non-survivors), in 3 zones in 8 subjects (respectively, 4 in both subgroups) and more than 3 zones in 13 subjects (10 survivors and 3 non-survivors, p = 0.412).

**Discussion**

In a population of patients with interstitial pneumonia caused by COVID-19, treated with NIV, we confirmed that non-invasive respiratory support was successful in about half of the subjects. We evidenced that scores calculated before the NIV initiation or at the very beginning of the treatment...
Fig. 1 Values of \( P/F \) ratio, alveolar-arterial gradient, ROX index and HACOR score at all the evaluations in survivors and non-survivors (on the left) in subjects with successful and failed NIV (on the right). The values of the HACOR score are reported as median and interquartile range, while all the other parameters are reported as mean ± standard deviation.
Fig. 2 Proportion of survivors and non-survivors (A, B) and subjects with successful and failed NIV (C, D) with HACOR score > 5 and ROX index < 4.88.

| Table 2 | Univariate and multivariate analysis of the association between respiratory scores and in-hospital mortality |
|---------|----------------------------------------------------------------------------------------------------------------------------------|
| | Univariate analysis | Multivariate analysis | |
| | HR | 95% CI | P | HR | 95% CI | P |
| Age | 1.09 | 1.05–1.14 | <0.001 | 1.09 | 1.04–1.13 | <0.001 |
| Charlson Index | 1.39 | 1.03–1.87 | 0.031 | 1.47 | 1.03–2.09 | 0.033 |
| Day0 HACOR > 5 | 3.38 | 1.41–8.08 | 0.003 | 5.88 | 2.01–17.22 | 0.001 |
| Day0 HACOR | 1.14 | 0.97–1.35 | 0.111 | – | – | – |
| Age | 1.09 | 1.05–1.14 | <0.001 | 1.08 | 1.03–1.12 | <0.001 |
| Charlson Index | 1.39 | 1.03–1.87 | 0.031 | – | – | – |
| Day2 HACOR > 5 | 4.89 | 1.95–12.24 | <0.001 | 4.33 | 1.64–11.41 | 0.003 |
| Day2 HACOR | 1.40 | 1.09–1.78 | 0.008 | 1.34 | 1.03–1.74 | 0.027 |
| Day0 ROX < 4.88 | 1.80 | 0.83–3.88 | 0.134 | – | – | – |
| Day0 ROX | 0.99 | 0.88–1.12 | 0.886 | – | – | – |
| Day2 ROX < 4.88 | 1.88 | 0.82–4.30 | 0.136 | – | – | – |
| Day2 ROX | 0.83 | 0.66–1.05 | 0.116 | – | – | – |
| Day0 P/F | 0.99 | 0.98–1.01 | 0.066 | – | – | – |
| Day + 2 P/F | 0.99 | 0.98–0.99 | 0.019 | 0.99 | 0.98–0.99 | 0.016 |

The values of the scores were tested by univariate analysis and then introduced in a multivariate analysis, each including the score value, either continuous or dichotomized, adjusted by the age and Charlson index.
did not allow identifying subjects at high risk of adverse prognosis. By Day 1, the values of the scores were more compromised in subjects who underwent NIV failure and in non-survivors than in those with a favorable outcome. At the earliest evaluations after the beginning of NIV, an HACOR score > 5 was independently associated with a higher mortality rate and an increased need of invasive respiratory support. The aforementioned nomogram demonstrated a fair prognostic value, with a wide overlap of values between subjects with successful and failed NIV.

Our results are encouraging as to consider the possibility to attempt a trial of NIV in these subjects. In fact, it was not possible to identify those at high risk of an adverse outcome before the beginning of the treatment with NIV. In our study population, NIV was successful in a higher proportion of subjects compared to some of the previous studies in COVID patients, despite a similar deterioration of respiratory function at the beginning of the treatment with the NIV itself [7, 18]. The key issue remains the early and accurate identification of subjects in whom NIV will fail. Parameters, which measure oxygenation, showed a severe deterioration compared to subjects with hypoxic respiratory failure of other etiologies [19, 20]. This is consistent with the pathophysiology of pneumonia induced by COVID-19, which determines

### Table 3 Vital signs, arterial blood gas and laboratory parameters from Day -1 to Day-5 of ventilation

| Day -1 | NIV success (n=72) | NIV failure (n=40) | NIV success (n=72) | NIV failure (n=40) | NIV success (n=72) | NIV failure (n=40) | NIV success (n=72) | NIV failure (n=40) |
|--------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| Vital signs | HR (b/min) | 84 ± 18 | 79 ± 14 | 82 ± 18 | 84 ± 23 | 76 ± 18 | 77 ± 19 | 75 ± 17 | 83 ± 19 |
| | SBP (mmHg) | 124 ± 20 | 122 ± 21 | 132 ± 24 | 128 ± 26 | 130 ± 23 | 131 ± 28 | 133 ± 26 | 131 ± 26 |
| | RR (b/min) | 25 ± 7 | 26 ± 7 | 29 ± 11 | 31 ± 10 | 26 ± 7 | 30 ± 8* | 24 ± 5 | 28 ± 6* |
| | SpO2 (%) | 94.1 ± 3.6 | 91.4 ± 7.0* | 94 ± 3.1 | 92.7 ± 4.7 | 94.5 ± 3.6 | 93.1 ± 4.7 | 94.5 ± 3.0 | 90.0 ± 7.4* |
| | GCS | 14.9 ± 0.12 | 15.0 ± 0.0 | 14.9 ± 0.2 | 14.9 ± 0.2 | 14.9 ± 0.9 | 14.9 ± 0.2 | 14.9 ± 0.1 | 15.0 ± 0.0 |
| ABG | pH | 7.46 ± 0.04 | 7.46 ± 0.04 | 7.45 ± 0.04 | 7.46 ± 0.05 | 7.45 ± 0.04 | 7.45 ± 0.04 | 7.47 ± 0.03 | 7.48 ± 0.04 |
| | pCO2 | 36.0 ± 4.7 | 35.4 ± 4.9 | 37.6 ± 7.2 | 37.4 ± 8.3 | 38.4 ± 8.0 | 37.6 ± 4.9 | 38.7 ± 6.7 | 41.0 ± 4.9 |
| | LAC (mEq/L) | 1.26 ± 0.56 | 1.31 ± 0.53 | 1.42 ± 1.31 | 1.54 ± 1.09 | 1.18 ± 0.82 | 1.27 ± 0.41 | 1.36 ± 0.72 | 1.54 ± 0.49 |
| Labs | WBC (10–9/L) | 9.1 ± 4.2 | 9.2 ± 5.0 | 9.3 ± 4.5 | 10.6 ± 5.9 | 9.3 ± 4.6 | 10.3 ± 5.2 | 9.1 ± 3.8 | 13.4 ± 5.1* |
| | Platelets (10–9/L) | 215 ± 73 | 244 ± 116 | 240 ± 94 | 250 ± 106 | 248 ± 78 | 247 ± 117 | 303 ± 97 | 309 ± 118 |
| | Creatinine (mg/dL) | 0.98 ± 0.36 | 1.18 ± 0.47* | 0.98 ± 0.37 | 1.25 ± 0.61* | 0.89 ± 0.37 | 1.04 ± 0.49 | 0.87 ± 0.85 | 0.92 ± 0.41 |
| | Bilirubin (mg/dL) | 0.55 ± 0.22 | 0.72 ± 0.65 | 0.61 ± 0.41 | 0.57 ± 0.42 | 0.65 ± 0.43 | 0.61 ± 0.36 | 0.57 ± 0.55 | 0.55 ± 0.36 |
| | Ferritin (ng/mL) | 752 ± 554 | 1297 ± 1737 | 967 ± 473 | 2079 ± 2173* | 2152 ± 3400 | 1693 ± 1177 | 1135 ± 899 | 828 ± 636 |
| | CRP (mg/L) | 105 ± 74 | 115 ± 73 | 115 ± 72 | 113 ± 63 | 81 ± 42 | 145 ± 84* | 45 ± 45 | 84 ± 54* |
| | D-dimer (ng/mL) | 2099 ± 6510 | 1217 ± 891 | 2672 ± 9263 | 4781 ± 11,313 | 1958 ± 5715 | 7897 ± 21,556 | 3252 ± 6180 | 7899 ± 17,456 |
| | SOFA score | 4 [3–5] | 4 [3–5]* | 4 [4–5] | 5 [4–5]* | 4 [3–5] | 5 [3–5] | 4 [3–5] | 5 [4–5.75]* |

HR: heart rate; SBP: systolic blood pressure; RR: respiratory rate; GCS: Glasgow Coma Scale; LAC: lactates; WBC: white blood cells; CPR: C reactive protein

*p < 0.05

Fig. 3 Probability of NIV failure in subjects with good and adverse prognosis
an impairment of the oxygen exchange, for a ventilation-perfusion mismatch due to the microvascular dysfunction [21, 22]. The early limited alveolar infiltrates prevent the reduction of pulmonary compliance and the consequent increased work of breathing and sensation of dyspnea, even in the presence of an increased respiratory rate [23]. Therefore, subjects tolerated severe hypoxemia without significant respiratory distress [24]. In the earliest phases of the treatment, the degree of hypoxemia was similar in subjects with good and adverse prognosis and its response to the treatment with NIV seems to have a higher prognostic value, compared to baseline parameters. Alveolar-arterial gradient, an index of oxygenation, which considers the percentage of alveolar carbon dioxide, was severely compromised, but it was significantly worse in subjects with adverse prognosis only several days after the beginning of NIV. This is consistent with the finding that pCO2 tended to rise by Day-5, although in a non-significant way, in those who faced NIV failure.

The ROX index, which combines the evaluation of peripheral oxygen saturation and respiratory rate, was initially conceived to predict the failure of the treatment with HFNC among patients with acute respiratory failure due to pneumonia. It could be promising for the early prognostic stratification of patients with COVID, but it became significantly different based on prognosis from Day +1 [10]. Its limited discriminative value at the beginning of the treatment could be due to the limited accuracy of the SpO2 measurement in the presence of very low values (< 80%), with consequent impossibility to distinguish true and false low SpO2 [25, 26]. ROX index has already been employed in subjects with COVID-19 treated with HFNC as well as with NIV, to early identify those at high risk of failure, with good results [27–29] but different cut-offs have been adopted by different studies. In this population, a value < 4.88, the usual suggested cut-off, was significantly more common among those with an adverse prognosis from Day +2, but it did not show an independent association with an increased mortality rate.

The HACOR score [11] and the nomogram elaborated by Liu and coll. [13] are both based on parameters easily obtainable at the bedside. The prognostic performance of the HACOR score has already been tested among COVID subjects, but it was tested only in the first hours after the beginning of the treatment with NIV and its prognostic value has been confirmed [30, 31]. Its good prognostic stratification ability could be ascribed to the combination of parameters expressing oxygenation status, the degree of respiratory distress and the global clinical severity. However, the novelty of the present study was the observation of the trend of the score over a long period, encompassing the days immediately before and after the beginning of the treatment with NIV. We could show that respiratory parameters collected before the initiation of NIV and the score calculated at that moment did not allow the identification of patients at risk of both NIV failure and mortality. This means that, in the presence of COVID, even patients with severe respiratory failure can undergo a trial of NIV and what really predicts an unfavorable prognosis is the lack of improvement of respiratory parameters with the ventilatory support. In fact, for the first time we demonstrated that, after the beginning of NIV, a value of HACOR score > 5 was significantly associated with an adverse outcome, independent to the age and the presence of comorbidities. Alongside, this was the first attempt to test the nomogram elaborated by Liu and coll. in a different population. Its appealing characteristics could allow us to identify subjects earlier at risk of an adverse prognosis. However, it did not cope up with expectations and, in the earliest phases of the treatment, its discriminative ability was fair.

The ultrasonographic findings did not add useful prognostic information. The values of LUS score found in this study population are consistent with previous papers [17, 32]. The absence of significant differences between subjects with favorable and adverse prognosis could find two main reasons. As for respiratory parameters, a single evaluation performed at the beginning of the treatment could not be able to distinguish between subjects who will respond to the treatment with NIV and those who will not, as, again, the response to the treatment plays a pivotal role over the baseline conditions. From an epidemiological point of view, most of the previous papers which evaluated the prognostic value of LUS score, included subjects encompassing a wide range of severity of COVID-19, from nearly asymptomatic to severe ARF. In this study population, which included only subjects with severe ARF, serial ultrasonographic evaluations could give more relevant prognostic information than a single assessment.

A separate mention deserves the disproportionally high mortality among those, who underwent NIV as ceiling treatment. We decided to include these patients in the analysis of parameters, which predicted the mortality rate, as they represented a significant proportion of subjects treated with NIV and identifying parameters for their early prognostic stratification could be useful for clinicians. Their exclusion from that analysis did not significantly modify the results, especially regarding the HACOR score. Therefore, the prognostic value of the scores we observed was not primarily due to these patients, but was valid for the whole study population.

This study has several limitations. The retrospective, single-center design may limit its applicability. We decided to observe subjects for a long period and we considered, for every evaluation, the worse parameters. We cannot exclude that different criteria could modify our results, but this choice was motivated by the need to be consistent in all subjects and during the whole period.
From the beginning of the ventilatory support, most of our patients alternated NIV and HFNC. These patients required very long treatment with NIV, so that interruptions of NIV were allowed during daytime, if they were able to maintain an SO2 > 94% without respiratory distress for brief periods. We did not systematically annotate the length of the interruptions and we cannot assess a possible prognostic weight of this modality to use NIV, but it was the norm for most of our patients. We did not systematically perform an ultrasound cardiac examination or chest CT scan and we were not able to consider the possible prognostic value of the presence of new-onset right ventricular systolic dysfunction or thromboembolic events [33]. To what extent these alterations affect the response to the treatment with NIV has not been definitively evaluated and needs to be explored in future studies.

Conclusion

We observed that the treatment with NIV was successful in a relevant proportion of subjects. This could be a support to perform a trial of NIV in all the subjects with COVID-19, who do not have clear contraindication to this kind of support. The assessment after 24–48 h of treatment with NIV gave the best prognostic information in these subjects, while the evaluations before and concomitant with the NIV initiation did not allow the identification of subjects at high risk of adverse prognosis. An HACOR score > 5 after the initiation of NIV was independently associated with an increased mortality rate and a high prevalence of NIV failure, independently to age and the presence of previous medical conditions.

Author contributions FI and FP gave substantial contributions to the conception and design of the work. FG, PA, LC, MB, GG, AM, LL and LM gave substantial contributions in the acquisition, and analysis of data for the work. CL, EP, ADP, AL gave their contribution for the interpretation of data. FI, FL and LS, drafted the manuscript; FC and MZ revised it critically for important intellectual content. FL and RP gave the final approval of the version to be published.

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Data Availability Material The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest No conflict of interest to declare.

References

1. Rochwerg B, Brochard L, Elliott MW et al (2017) Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. https://doi.org/10.1183/13993003.02426-2016
2. Alhazzani W, Moller MH, Arabi YM et al (2020) Surviving sepsis campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med 46(5):854–887. https://doi.org/10.1007/s00134-020-00622-5
3. Grieco DL, Menga LS, Eleuteri D, Antonelli M (2019) Patient self-inflicted lung injury: implications for acute hypoxic respiratory failure and ARDS patients on non-invasive support. Minerva Anestesiologica 85(9):1014–1023. https://doi.org/10.23736/S0375-9393.19.13418-9
4. Brochard L, Lefebvre JC, Cordioli RL, Akoumianaki E, Richard JC (2014) Noninvasive ventilation for patients with hypoxic acute respiratory failure. Semin Respir Crit Care Med 35(4):492–500. https://doi.org/10.1055/s-0034-1383863
5. Slutsky AS, Ranieri VM (2013) Ventilator-induced lung injury. N Engl J Med 369(22):2126–2136. https://doi.org/10.1056/NEJMr1208707
6. Alraddadi BM, Qushmaq I, Al-Hameed FM et al (2019) Noninvasive ventilation in critically ill patients with the Middle East respiratory syndrome. Influenza Other Respir Viruses 13(4):382–390. https://doi.org/10.1111/irv.12635
7. Duca A, Memaj I, Zanardi F et al (2020) Severity of respiratory failure and outcome of patients needing a ventilatory support in the Emergency Department during Italian novel coronavirus SARS-CoV2 outbreak: preliminary data on the role of Helmet CPAP and Non-Invasive Positive Pressure Ventilation. EClinicalMedicine 24:100419. https://doi.org/10.1016/j.eclinm.2020.100419
8. Brusasco C, Corradi F, Di Domenico A et al (2020) Continuous positive airway pressure in Covid-19 patients with moderate-to-severe respiratory failure. Eur Respir J. https://doi.org/10.1183/13993003.02524-2020
9. Grieco DL, Menga LS, Cesaroni M et al (2021) Effect of helmet noninvasive ventilation vs high-flow nasal oxygen on days free of respiratory support in patients with COVID-19 and moderate to severe hypoxemic respiratory failure: the HENIVOT Randomized
Clinical Trial. JAMA 325(17):1731–1743. https://doi.org/10.1001/jama.2021.4682
10. Roca O, Caralt B, Messika J et al (2019) An index combining respiratory rate and oxygenation to predict outcome of nasal high-flow therapy. Am J Respir Crit Care Med 199(11):1368–1376. https://doi.org/10.1164/rcrm.201803-0589OC
11. Duan J, Han X, Bai L, Zhou L, Huang S (2017) Assessment of heart rate, acidosis, consciousness, oxygenation, and respiratory rate to predict noninvasive ventilation failure in hypoxic patients. Intensive Care Med 43(2):192–199. https://doi.org/10.1007/s00134-016-4601-3
12. Innocenti F, Giordano L, Gualtieri S et al (2020) Prediction of mortality with the use of noninvasive ventilation for acute respiratory failure. Respir Care. https://doi.org/10.4187/respcare.07464
13. Liu L, Xie J, Wu W et al (2021) A simple nomogram for predicting failure of non-invasive respiratory strategies in adults with COVID-19: a retrospective multicentre study. Lancet Digit Health 3(3):e166–e174. https://doi.org/10.1016/S2589-7500(20)30316-2
14. Davies M, Allen M, Bentley A et al (2018) British Thoracic Society Quality Standards for acute non-invasive ventilation in adults. Bmj Open Respir Res 5(1):e000283. https://doi.org/10.1136/bmjresp-2018-000283
15. Volpicelli G, Elbarbary M, Blaivas M et al (2012) International evidence-based recommendations for point-of-care lung ultrasound. Intensive Care Med 38(4):577–591. https://doi.org/10.1007/s00134-012-2513-4
16. Mojoli F, Bouhemad B, Mongodi S, Lichtenstein D (2019) Lung ultrasound for critically Ill patients. Am J Respir Crit Care Med 199(6):701–714. https://doi.org/10.1164/rcrm.201802-0236CI
17. Ji L, Cao C, Gao Y et al (2020) Prognostic value of bedside lung ultrasound score in patients with COVID-19. Crit Care 24(1):700. https://doi.org/10.1186/s13054-020-03416-1
18. Aliberti S, Radovanovic D, Billi F et al (2020) Helmet CPAP treatment in patients with COVID-19 pneumonia: a multicenter, cohort study. Eur Respir J. https://doi.org/10.1183/13993003.01935-2020
19. Bellani G, Laffey JG, Pham T et al (2016) Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 315(8):788–800. https://doi.org/10.1001/jama.2016.0291
20. Brambilla AM, Aliberti S, Prina E et al (2014) Helmet CPAP vs. oxygen therapy in severe hypoxemic respiratory failure due to pneumonia. Intensive Care Med 40(7):942–949. https://doi.org/10.1007/s00134-014-3325-5
21. Tobin MJ, Jubran A, Laghi F (2020) PSI-LILI as justification for intubation in COVID-19: readers as arbiters. Ann Intensive Care 10(1):156. https://doi.org/10.1186/s13633-020-00774-5
22. Gattinoni L, Coppola S, Cressoni M et al (2020) COVID does not lead to a “typical" acute respiratory distress syndrome. Am J Respir Crit Care Med 201(10):1299–1300. https://doi.org/10.1164/rcrm.202003-0817LE
23. Tobin MJ, Laghi F, Jubran A (2020) Why COVID-19 silent hypoxemia is baffling to physicians. Am J Respir Crit Care Med 202(3):356–360. https://doi.org/10.1164/rcrm.202006-2157CP
24. Marini JJ, Gattinoni L (2020) Management of COVID-19 respiratory distress. JAMA. https://doi.org/10.1001/jama.2020.6825
25. Tobin MJ, Jubran A, Laghi F (2020) Misconceptions of pathophysiology of happy hypoxemia and implications for management of COVID-19. Respir Res 21(1):249. https://doi.org/10.1186/s12931-020-01520-y
26. Yousuf A, Gottlieb DS, Aggarwal A, Peacock B, Konda S (2022) An observational longitudinal study of the use of ROX index to predict treatment failure in patients receiving continuous positive airway pressure for COVID-19. Health Sci Rep 5(1):e482. https://doi.org/10.1002/hsr2.482
27. Calligaro GL, Lalla U, Audley G et al (2020) The utility of high-flow nasal oxygen for severe COVID-19 pneumonia in a resource-constrained setting: a multi-centre prospective observational study. EClinicalMedicine 28:100570. https://doi.org/10.1016/j.eclinm.2020.100570
28. Zucman N, Mullaert J, Roux D et al (2020) Prediction of outcome of nasal high-flow use during COVID-19-related acute hypoxic respiratory failure. Intensive Care Med 46(10):1924–1926. https://doi.org/10.1007/s00134-020-06177-1
29. Leszek A, Wozniak H, Giudicelli-Bailly A et al (2022) Early measurement of ROX index in intermediary care unit is associated with mortality in intubated COVID-19 patients: a retrospective study. J Clin Med. https://doi.org/10.3390/jcm11020365
30. Santus P, Pini S, Amati F et al (2022) Predictors of helmet CPAP failure in COVID-19 pneumonia: a prospective, multicenter, and observational cohort study. Can Respir J 2022:1499690. https://doi.org/10.1155/2022/1499690
31. Guia MF, Boleo-Tome JP, Imitazione P et al (2021) Usefulness of the HACOR score in predicting success of CPAP in COVID-19-related hypoxemia. Respir Med 187:106550. https://doi.org/10.1016/j.rmed.2021.106550
32. Lichter Y, Topilsky Y, Taieb P et al (2020) Lung ultrasound predicts clinical course and outcomes in COVID-19 patients. Intensive Care Med 46(10):1873–1883. https://doi.org/10.1007/s00134-020-06212-1
33. Corica B, Marra AM, Basili S et al (2021) Prevalence of right ventricular dysfunction and impact on all-cause death in hospitalized patients with COVID-19: a systematic review and meta-analysis. Sci Rep 11(1):17774. https://doi.org/10.1038/s41598-021-96955-8

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