Non-invasive ventilation for SARS-CoV-2 acute respiratory failure: a subanalysis from the HOPE COVID-19 registry


ABSTRACT

Background The COVID-19 pandemic has seriously challenged worldwide healthcare systems and limited intensive care facilities, leading to physicians considering the use of non-invasive ventilation (NIV) for managing SARS-CoV-2-related acute respiratory failure (ARF).

Methods We conducted an interim analysis of the international, multicentre HOPE COVID-19 registry including patients admitted for a confirmed or highly suspected SARS-CoV-2 infection until 18 April 2020. Those treated with NIV were considered. The primary endpoint was a composite of death or need for intubation. The components of the composite endpoint were the secondary outcomes. Unadjusted and adjusted predictors of the primary endpoint within those initially treated with NIV were investigated.

Results 1933 patients who were included in the registry during the study period had data on oxygen support type. Among them, 390 patients (20%) were treated with NIV. Compared with those receiving other non-invasive oxygen strategy, patients receiving NIV showed significantly worse clinical and laboratory signs of ARF at presentation. Of the 390 patients treated with NIV, 173 patients (44.4%) met the composite endpoint. In-hospital death was the main determinant (147, 37.7%), while 62 patients (15.9%) needed invasive ventilation. Those requiring invasive ventilation had the lowest survival rate (41.9%). After adjustment, age (adjusted OR (adj(OR)) for 5-year increase: 1.17, 95% CI 1.15 to 1.63, p<0.001), hypertension (adj(OR) 2.95, 95% CI 1.14 to 7.61, p=0.03), room air O2 saturation <92% at presentation (adj(OR) 3.05, 95% CI 1.28 to 7.28, p=0.01), lymphocytopenia (adj(OR) 3.55, 95% CI 1.16 to 10.85, p=0.03) and in-hospital use of antibiotic therapy (adj(OR) 4.91, 95% CI 1.69 to 14.26, p=0.003) were independently associated with the composite endpoint.

Conclusion NIV was used in a significant proportion of patients within our cohort, and more than half of these patients survived without the need for intubation. NIV may represent a viable strategy particularly in case of overcrowded and limited intensive care resources, but prompt identification of failure is mandatory to avoid harm.

Key messages

What is already known on this subject
- Non-invasive efficacy has been clearly validated in the context of cardiogenic pulmonary oedema and chronic obstructive pulmonary disease exacerbation.
- Its role within hypoxaemic acute respiratory failure (ARF) and acute respiratory distress syndrome is still controversial.
- Despite poor evidence supporting its use, during COVID-19 pandemic, a significant proportion of patients admitted for ARF due to SARS-CoV-2 infection were treated with non-invasive ventilation (NIV).

What this study adds
- This interim analysis of the multicentre HOPE COVID-19 registry found that 20% of the patients admitted for COVID-19-related ARF were treated with NIV.
- Among them more than half survived free of the need for intubation, while those failing had very low survival rates.
- NIV may represent a viable strategy particularly in case of overcrowded and limited intensive care resources in this setting, but prompt identification of those failing is mandatory to avoid harm.

INTRODUCTION

The novel coronavirus (SARS-CoV-2) is responsible for the pandemic of respiratory illness named COVID-19. In the majority of cases, the novel virus causes self-limiting respiratory symptoms, but in up
to 10% of patients, it is responsible for severe and progressive
interstitial pneumonia, multiorgan failure and high mortality.1–4

Due to the rapid and massive spread of COVID-19, healthcare
systems have had to face an incredible organisational challenge.
In Italy, the proportion of intensive care unit (ICU) admissions
was reported to be about 12% of confirmed cases, and 16%
within those hospitalised.5 ICU admissions increased continu-
ously and exponentially over the first 2 weeks of the outbreak,
cause governments and healthcare networks to increase ICU
capacity.6 About 11% of patients admitted to the ICU required
non-invasive ventilation (NIV), while 88% were treated with
mechanical invasive ventilation.7 Interestingly, acute respiratory
failure (ARF) and acute respiratory distress syndrome (ARDS)
by SARS-CoV-2 have different characteristics from those previ-
ously described so that pathophysiological assumptions on NIV
use in this scenario could be reconsidered. Furthermore, the
hospital overcrowding due to the present pandemic may cause
many more patients to be treated with it despite poor evidence
supporting it.8 9 In order to better understand the baseline char-
acteristics, the clinical course and outcome of those patients with
COVID-19 treated with NIV, we carried out an interim subanaly-
sis of patients enrolled in the multicentre, cross-sectional HOPE
COVID-19 registry.

METHODS

The HOPE COVID-19 registry is an ongoing international
investigator-initiated observational study involving 7 countries
and 36 hospitals worldwide. It is designed as an ambispec-
tive all-comer cohort without any financial remuneration for
researchers. All patients with a confirmed (ie, consistent clinical
scenario with a positive result to a real-time reverse transcrip-
tase PCR assay for pharyngeal and nasal swab sample) or high
suspicions for COVID-19 case were eligible for enrolment in the
registry as a result of death or discharge from any healthcare-
ensuring centre. There are no exclusion criteria, except for the
patient’s explicit refusal to participate. All clinical decisions
and management are left to the treating physician’s discretion,
according to the local protocol and regular practice. Clinical,
laboratory, instrumental and therapeutic data as well as events
are collected in an electronic dataset in a secure online platform
following prespecified criteria and definitions.

Considering the anonymous characteristics of the registry as
well as the extraordinary health emergency, written informed
consent was not considered mandatory. All local principal
researchers were responsible for the accuracy and veracity of
data. A complete list of hospitals involved, investigators and
collaborators as well as data definitions adopted in the registry
is available on an online platform (www.HopeProjectMD.com).
Neither patients nor the public were involved in the design,
conduct, reporting or dissemination plans of our research.

The following represents an interim analysis on patients
enrolled until 18 April 2020 with complete vital status who
received NIV during admission. Data were analysed for respira-
tory parameters, comorbidities and concomitant therapies. We
noted when mechanical ventilation was implemented, length of
admission, and date of discharge or death.

Endpoints

The primary endpoint was the composite of in-hospital death
or need for orotracheal intubation (OTI). Secondary endpoints
were each component of the primary one. Furthermore, in-hospi-
tal complications such as heart failure, sepsis, relevant bleeding,
embolic events and renal failure deserving clinical attention were
collected as well.

Statistical analysis

Continuous variables are expressed as median and IQR and were
compared by independent samples Student’s t-test, analysis of
variance with Tukey’s test or non-parametric Mann-Whitney U
test when normality or homogeneity of variance assumptions
was not respected (Kolmogorov-Smirnov and homogeneity of
variance tests were used for this purpose). Categorical variables
are presented as counts on available data and relative percent-
ages and were compared by χ2 or Fisher test as appropriate.
Survival analysis was performed with Cox regression using type
of oxygen support as the only covariate. Univariate association
between baseline characteristics, laboratory and imaging find-
ings as well as in-hospital treatment was exploited for both the
composite outcome and in-hospital death alone.

Based on the number of events for variables appraised, a binary
logistic regression analysis was performed to identify indepen-
dent predictors of the primary endpoint.6 Among variables with
a significant univariate association, those with a p value equal
or lower than 0.01 were initially selected. Where variables were
colinear, we selected those with the highest data completeness
rate, the strongest unadjusted association and clinical signifi-
cance. In particular, variables with a missing rate higher than
30% were excluded. The selected covariates were forced in a
binary logistical regression model to find independent predictors
of the primary endpoint. The analyses were carried out using
SPSS V25.0. Statistical significance was set at the two-tailed 0.05
level.

RESULTS

Overall population and subgroup characteristics according to
oxygen support type

A total of 2798 patients were enrolled in HOPE registry from
26 January until 18 April 2020 from all enrolling centres. After
selecting those receiving oxygen therapy and with complete data
on the type of support and vital status at the time of the present
analysis, 1933 patients were considered. A total of 1437 patients
were treated with nasal cannula or high-flow oxygen therapy,
390 were treated with NIV with (n=62) or without (n=328)
consequent need for in-hospital OTI and 106 received invasive
ventilation as initial strategy (see online supplemental figure S1
for study flow chart).

Demographics, comorbidities and clinical course of the
overall population according to type of ventilation are presented
in online supplemental table S1. In the invasive ventilation
population, there were more patients with obesity and/or chronic
kidney disease compared with the other two groups, although
these differences did not reach statistical significance in the
overall comparison. Those needing NIV or invasive ventilation
were more symptomatic for dyspnoea and with desaturation
(O2<92%) at admission when compared with those on oxygen
or high-flow oxygen therapy. Those patients requiring me-
chanical ventilation had more BP abnormalities, higher tempera-
ture, hyposmia and dysgeusia compared with the oxygen group.

Details on laboratory data and in-hospital characteristics and
outcomes for the overall interim cohort are displayed in online
supplemental table S2. The need for invasive ventilation was
associated with worse laboratory data at admission. Furthermore,
when compared with those receiving oxygen, patients receiving
mechanical ventilation (NIV or OTI) experienced higher rates of
complications, requiring more extensive in-hospital therapies


Original research
and a longer length of stay. Finally, using simple oxygen support group as reference, both NIV and OTI groups were associated with an increased risk of short-term death (HR 1.26, 95% CI 1.04 to 1.53 and HR 1.91, 95% CI 1.45 to 2.53, respectively) (figure 1). Those treated with OTI at any point had an increased risk of death more than those who only received NIV (HR 1.52, 95%CI 1.11 to 2.06, p=0.008).

Baseline characteristics of NIV cohort (group 2)
A total of 390 patients with SARS-CoV-2-related ARF initially treated with a NIV strategy were considered for the main analysis. The median age was 70 years old (IQR 58–79), they were predominantly men (65%) and 86 of 390 (22.1%) were treated in the ICU during hospital stay. All demographic characteristics, comorbidities and prior medication used are described in table 1. The most frequent pulmonary diseases at baseline were chronic obstructive pulmonary disease (COPD) (43.5%) and asthma (21.2%), but only 5.2% were treated with chronic oxygen therapy at home. Clinical presentation, laboratory data and in-hospital therapies of group 2 are shown in table 1.

NIV group outcomes
The primary endpoint occurred in 173 (44.4%) patients; there were 147 (37.7%) in-hospital deaths and 62 (15.9%) NIV failures requiring invasive ventilation. In-hospital mortality among the latter group was the highest (36 of 62, 58.1%). Moreover, when compared with those experiencing a successful NIV treatment, patients failing it had increased in-hospital complications rate (see table 1). In univariate analysis, several baseline and in-hospital variables found to be significantly associated with the primary endpoint (see tables 1 and 2). Among in-hospital therapy, the use of corticosteroids and antibiotics had a negative association with composite endpoint (OR 2.95, 95%CI 1.92 to 4.51, p<0.001 and OR 2.52, 95%CI 1.51 to 4.20, p<0.001, respectively).

Associations of baseline characteristics, laboratory and treatment to secondary endpoints are detailed in online supplemental tables S3–S6.

Independent predictors of primary endpoint
Based on the prespecified criteria, 15 covariates (see table 2) were forced into a multivariate binary logistical regression model. Of these, five had a significant independent association with the primary composite endpoint: age, hypertension, room air O₂ saturation below 92% at presentation, lymphocytopenia (ie, lymphocyte count below 1500/mm³) and the use of antibiotic therapy during admission (see table 2 and figure 2).

Due to prior research showing an association with outcomes in COVID-19, a post hoc sensitivity analysis including obesity and smoking in the model was performed (see online supplemental table S7). Neither of these variables demonstrated a significant association with the primary endpoint. Room air oxygen saturation, antibiotic therapy and age remained significant in this analysis; hypertension and lymphocytopenia had borderline association.

DISCUSSION
Our study found that NIV was a useful mode of therapy in patients with ARF due to COVID-19. Of those who received NIV, slightly more than half survived free of intubation. Those who failed NIV and required intubation had a high rate of mortality. Independent predictors of the primary endpoint were age, hypertension, room air O₂ saturation below 92% at presentation, lymphocytopenia and the use of antibiotic therapy during admission.

While NIV efficacy has been clearly validated in the context of cardiogenic pulmonary oedema and COPD exacerbation, its role within hypoxaemic ARF and ARDS is still controversial.10–12 The high rate of treatment failure and subsequent poor prognosis of those treated with NIV when compared with invasive respiratory support justify uncertainty on its use. Indeed, based on previous evidence, guidelines do not recommend the use of NIV in this type of patients with hypoxaemia, and give only a weak recommendation for an initial trial.8 However, several potential confounders may contribute to such negative results and type of interface as well as ventilatory modality (ie, continuous positive airway pressure (CPAP) vs bilevel), and lower or higher positive pressures used are key issues.13–15 Furthermore, COVID-19-related interstitial pneumonia and ARDS have clinical and physiopathological characteristics different from those described in other aetiological contexts.7 16 Little evidence on the effect of NIV therapy in COVID-19-associated ARF has been available up to now.17

In our registry, one-fifth of patients were initially treated with non-invasive positive pressure support. The use of this method of ventilation in previously published reports on COVID-19 ranged between 11% and 56% according to department type (ICU vs other) and severity of included population.18–19 The huge pressure on healthcare systems and limitations in resources may partially explain these high numbers. Interestingly, apart from a higher prevalence of smokers, patients treated with NIV had comparable age and analogous baseline clinical risk profile with that of the group with oxygen support only. However, they had more severe dyspnoea, marked desaturation and lower lymphocyte counts at index evaluation which are probably indicators of an advanced lung involvement, requiring more aggressive ventilatory support during admission.20

A total of 173 patients (44%) in the cohort studied met the primary endpoint, mainly due to death occurrence. Our rate of treatment failure is consistent with that of the small cohort of Pagano et al analysing early ventilatory parameters and lung ultrasound changes to identify those patients who did not improve with NIV strategy.17 Moreover, in our registry, nearly 16% needed rescue OTI and invasive ventilation due to failure of the first non-invasive attempt. This subgroup showed the
### Table 1: HOPE registry subanalysis on patients treated with NIV and according to the primary endpoint

<table>
<thead>
<tr>
<th>Demographic data and baseline characteristics</th>
<th>Overall NIV population (390)</th>
<th>No primary endpoint (217)</th>
<th>Primary endpoint (173)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year median (IQR)</td>
<td>70 (58–79) n=390</td>
<td>62 (52–73) n=217</td>
<td>76 (68–83) n=173</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>133/390 (34.1)</td>
<td>78/217 (35.9)</td>
<td>55/173 (31.8)</td>
<td>0.4</td>
</tr>
<tr>
<td>Obesity, n (%)</td>
<td>70/273 (25.6)</td>
<td>40/156 (25.6)</td>
<td>30/117 (25.6)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>222/383 (58.0)</td>
<td>100/214 (46.7)</td>
<td>122/169 (72.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidaemia, n (%)</td>
<td>141/380 (37.1)</td>
<td>63/213 (29.6)</td>
<td>78/167 (46.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Current or previous smoker, n (%)</td>
<td>103/338 (30.5)</td>
<td>54/185 (29.2)</td>
<td>60/153 (39.2)</td>
<td>0.052</td>
</tr>
<tr>
<td>DM, n (%)</td>
<td>70/354 (19.8)</td>
<td>32/201 (15.9)</td>
<td>38/153 (24.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Prior stroke, n (%)</td>
<td>41/361 (11.4)</td>
<td>18/200 (9.0)</td>
<td>23/161 (14.3)</td>
<td>0.1</td>
</tr>
<tr>
<td>Heart disease, n (%)</td>
<td>113/390 (29)</td>
<td>50/217 (23.0)</td>
<td>63/173 (36.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Lung disease, any, n (%)</td>
<td>85/390 (21.8)</td>
<td>42/217 (19.4)</td>
<td>43/173 (24.9)</td>
<td>0.2</td>
</tr>
<tr>
<td>Asthma, n (%)</td>
<td>18/390 (4.6)</td>
<td>14/217 (6.5)</td>
<td>4/173 (2.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>37/390 (9.5)</td>
<td>16/217 (7.4)</td>
<td>21/173 (12.1)</td>
<td>0.2</td>
</tr>
<tr>
<td>Restrictive lung disease, n (%)</td>
<td>5/390 (1.3)</td>
<td>1/217 (0.5)</td>
<td>4/173 (2.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>任何免疫抑制条件, n (%)</td>
<td>32/320 (10.0)</td>
<td>15/180 (8.3)</td>
<td>17/140 (12.1)</td>
<td>0.3</td>
</tr>
<tr>
<td>Prior therapy</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Anticoagulation, n (%)</td>
<td>61/370 (16.5)</td>
<td>26/206 (12.6)</td>
<td>35/164 (21.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Antplatelet, n (%)</td>
<td>73/372 (19.6)</td>
<td>29/207 (14.0)</td>
<td>44/160 (27.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>ACEi/ARB, n (%)</td>
<td>158/383 (41.3)</td>
<td>75/214 (35.5)</td>
<td>82/169 (48.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>B-blockers, n (%)</td>
<td>82/365 (22.5)</td>
<td>38/205 (18.5)</td>
<td>44/160 (27.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>B-2 agonists, n (%)</td>
<td>59/368 (16)</td>
<td>27/206 (13.1)</td>
<td>32/162 (19.8)</td>
<td>0.09</td>
</tr>
<tr>
<td>Inhaled corticosteroids, n (%)</td>
<td>41 (11.2)</td>
<td>18/204 (8.8)</td>
<td>23/164 (14.1)</td>
<td>0.1</td>
</tr>
<tr>
<td>Home oxygen therapy, n (%)</td>
<td>20/381 (5.2)</td>
<td>8/212 (3.8)</td>
<td>12/169 (7.1)</td>
<td>0.1</td>
</tr>
<tr>
<td>Antidepressant, n (%)</td>
<td>55/371 (14.8)</td>
<td>22/205 (10.7)</td>
<td>33/166 (19.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Fever, n (%)</td>
<td>325/380 (85.5)</td>
<td>185/210 (88.1)</td>
<td>140/170 (82.4)</td>
<td>0.1</td>
</tr>
<tr>
<td>Dyspnoea, any entity, n (%)</td>
<td>259 (66.4)</td>
<td>134/206 (65.0)</td>
<td>125/168 (74.4)</td>
<td>0.051</td>
</tr>
<tr>
<td>O₂ saturation below 92%, n (%)</td>
<td>189/373 (50.7)</td>
<td>75/214 (35.5)</td>
<td>82/169 (48.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diarrhoea, n (%)</td>
<td>52/350 (14.9)</td>
<td>27/206 (13.1)</td>
<td>32/162 (19.8)</td>
<td>0.09</td>
</tr>
<tr>
<td>Anaemia at presentation, n (%)</td>
<td>116/373 (31.1)</td>
<td>52/212 (24.5)</td>
<td>64/161 (49.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>Creatinine (mg/dL), median (IQR)</td>
<td>0.96 (0.75–1.35) n=315</td>
<td>0.9 (0.7–1.16) n=178</td>
<td>1.13 (0.85–1.58) n=137</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High levels of D-dimer, n (%)</td>
<td>141/380 (37.1)</td>
<td>63/213 (29.6)</td>
<td>78/167 (46.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>High levels of CRP, n (%)</td>
<td>366/380 (96.3)</td>
<td>202/212 (95.3)</td>
<td>164/168 (97.6)</td>
<td>0.2</td>
</tr>
<tr>
<td>High levels of troponin, n (%)</td>
<td>66/243 (27.2)</td>
<td>23/137 (16.8)</td>
<td>43/106 (40.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High transaminase level, n (%)</td>
<td>17/343 (5.0)</td>
<td>18/199 (9.0)</td>
<td>5/157 (3.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>High levels of LDH, n (%)</td>
<td>23/342 (6.7)</td>
<td>17/188 (9.0)</td>
<td>6/154 (3.9)</td>
<td>0.06</td>
</tr>
<tr>
<td>High levels of ferritin, n (%)</td>
<td>254/375 (67.7)</td>
<td>145/212 (68.4)</td>
<td>109/163 (66.9)</td>
<td>0.8</td>
</tr>
<tr>
<td>High levels of CRP, n (%)</td>
<td>366/380 (96.3)</td>
<td>202/212 (95.3)</td>
<td>164/168 (97.6)</td>
<td>0.2</td>
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<td>5/157 (3.2)</td>
<td>0.03</td>
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<td>High levels of LDH, n (%)</td>
<td>300/355 (84.5)</td>
<td>163/200 (81.5)</td>
<td>137/155 (88.4)</td>
<td>0.08</td>
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<tr>
<td>High levels of ferritin, n (%)</td>
<td>146/344 (51.3)</td>
<td>91/189 (48.1)</td>
<td>85/154 (55.2)</td>
<td>0.2</td>
</tr>
<tr>
<td>High levels of CRP, n (%)</td>
<td>366/380 (96.3)</td>
<td>202/212 (95.3)</td>
<td>164/168 (97.6)</td>
<td>0.2</td>
</tr>
<tr>
<td>High levels of troponin, n (%)</td>
<td>95/312 (30.4)</td>
<td>43/106 (40.6)</td>
<td>57/141 (40.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Bilateral CXR abnormality, n (%)</td>
<td>263/360 (73.1)</td>
<td>137/201 (68.2)</td>
<td>126/159 (79.2)</td>
<td>0.02</td>
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<tr>
<td>In-hospital therapy</td>
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<tr>
<td>Corticosteroids, n (%)</td>
<td>161/370 (43.5)</td>
<td>64/202 (31.7)</td>
<td>97/168 (57.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chloroquine, n (%)</td>
<td>311/372 (83.6)</td>
<td>178/205 (86.8)</td>
<td>133/167 (79.6)</td>
<td>0.06</td>
</tr>
</tbody>
</table>
worse prognosis with an in-hospital death rate of 58%. Previous very limited evidence of non-invasive support for Middle East respiratory syndrome coronavirus infection showed worse results, while a better success rate (70%) was described for 2003 SARS. Yang et al presented a small report from Wuhan of 52 patients with SARS-CoV-2-related pneumonia admitted to the ICU. Among those receiving non-invasive positive pressure, 72% died. However, the smaller sample size and a more selected population as well as differences in baseline characteristics and comorbidities may explain this divergence in outcome data.

Our study suggests that NIV use was a successful approach for more than half of our COVID-19-related respiratory failure. Adopting a protective CPAP ventilation with helmet interface may allow effective alveolar recruitment, improving oxygenation while limiting risk of ventilatory-induced lung injury. The use of this approach, particularly in case of limited availability for invasive ventilation facilities, may preserve resources, delaying or avoiding intubation. However, prompt identification of those failing with the conservative approach is mandatory to avoid harmful delays and very poor outcome.

Among baseline risk factors, only age and hypertension were independent predictors of the primary endpoint in our cohort. When tested in a sensitivity analysis, neither obesity nor smoking habit reached statistical significance, and hypertension did not maintain a significant association. While it is quite obvious that older patients represent a frailer subset, controversial data on the role of hypertension have been published up to now. A previous meta-analysis described a remarkable prevalence of hypertension in patients with COVID-19, and some observational studies reported hypertension and diabetes along with COPD and cancer history as possible predictors of a more severe in-hospital course. However, limited data with adjusted results on hard endpoints at short-term follow-up have been published, particularly in the setting of those treated with NIV, and more data both on prognostic and pathophysiological mechanisms are probably needed.

### Table 1

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Overall NIV population (390)</th>
<th>No primary endpoint (217)</th>
<th>Primary endpoint (173)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antivirals, n (%)</td>
<td>276/377 (73.2)</td>
<td>162/212 (76.4)</td>
<td>114/165 (69.1)</td>
<td>0.1</td>
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<tr>
<td>Interferon, n (%)</td>
<td>67/366 (18.3)</td>
<td>31/205 (15.1)</td>
<td>36/161 (22.4)</td>
<td>0.08</td>
</tr>
<tr>
<td>Tocilizumab, n (%)</td>
<td>58/363 (16)</td>
<td>28/204 (13.7)</td>
<td>30/159 (18.9)</td>
<td>0.2</td>
</tr>
<tr>
<td>Antibiotic, n (%)</td>
<td>277/368 (75.3)</td>
<td>138/203 (68.0)</td>
<td>139/165 (84.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACEi/ARB, n (%)</td>
<td>63/368 (17.1)</td>
<td>37/209 (17.7)</td>
<td>26/159 (16.4)</td>
<td>0.7</td>
</tr>
<tr>
<td>Pronation in NIV, n (%)</td>
<td>63/372 (16.9)</td>
<td>30/206 (14.6)</td>
<td>33/166 (19.9)</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>In-hospital complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis, n (%)</td>
<td>143/375 (38.1)</td>
<td>60/210 (28.6)</td>
<td>83/165 (50.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relevant bleeding, n (%)</td>
<td>15/354 (4.2)</td>
<td>6/198 (3.0)</td>
<td>9/156 (5.8)</td>
<td>0.2</td>
</tr>
<tr>
<td>Embolic event, n (%)</td>
<td>12/361 (3.3)</td>
<td>6/205 (2.9)</td>
<td>6/156 (3.8)</td>
<td>0.6</td>
</tr>
<tr>
<td>Renal failure during admission, n (%)</td>
<td>113/376 (30.1)</td>
<td>34/208 (16.3)</td>
<td>79/168 (47.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart failure during admission, n (%)</td>
<td>43/373 (11.5)</td>
<td>12/211 (5.7)</td>
<td>31/162 (19.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Circulatory or ECMO support, n (%)</td>
<td>33/361 (9.1)</td>
<td>2/201 (1.0)</td>
<td>31/160 (19.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of in-hospital stay in days, median (IQR)</td>
<td>8 (4–15) n=338</td>
<td>10 (5–16) n=178</td>
<td>7 (3–12) n=160</td>
<td>0.006</td>
</tr>
</tbody>
</table>

ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; CL, Creatinine clearance; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation; LDH, lactic dehydrogenase; NIV, non-invasive ventilation.

### Table 2

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Univariate OR</th>
<th>95% CI</th>
<th>P value</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (OR per 5-year increase)</td>
<td>1.37</td>
<td>1.26 to 1.49</td>
<td>&lt;0.001</td>
<td>1.37</td>
<td>1.15 to 1.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>2.09</td>
<td>1.37 to 3.19</td>
<td>0.001</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.96</td>
<td>1.92 to 4.55</td>
<td>&lt;0.001</td>
<td>2.95</td>
<td>1.14 to 7.61</td>
<td>0.03</td>
</tr>
<tr>
<td>Heart disease</td>
<td>1.91</td>
<td>1.23 to 2.98</td>
<td>0.004</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CKD history</td>
<td>4.97</td>
<td>2.08 to 11.88</td>
<td>&lt;0.001</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Previous aspirin therapy</td>
<td>2.23</td>
<td>1.32 to 3.76</td>
<td>0.002</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Previous antithrombotic therapy</td>
<td>2.06</td>
<td>1.15 to 3.70</td>
<td>0.01</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>O₂ saturation below 92% at index evaluation</td>
<td>5.16</td>
<td>3.31 to 8.04</td>
<td>&lt;0.001</td>
<td>3.05</td>
<td>1.28 to 7.28</td>
<td>0.01</td>
</tr>
<tr>
<td>Anaemia</td>
<td>2.03</td>
<td>1.30 to 3.17</td>
<td>0.002</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Elevated D-dimer</td>
<td>2.25</td>
<td>1.34 to 3.79</td>
<td>0.002</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Elevated troponin</td>
<td>3.38</td>
<td>1.87 to 6.12</td>
<td>&lt;0.001</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Elevated procalcitonin</td>
<td>2.38</td>
<td>1.45 to 3.89</td>
<td>0.001</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lymphocytopenia (&lt;1500/mm³)</td>
<td>3.91</td>
<td>2.05 to 7.48</td>
<td>&lt;0.001</td>
<td>3.55</td>
<td>1.16 to 10.85</td>
<td>0.03</td>
</tr>
<tr>
<td>In-hospital corticosteroid use</td>
<td>2.95</td>
<td>1.92 to 4.51</td>
<td>&lt;0.001</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>In-hospital antibiotic use</td>
<td>2.52</td>
<td>1.51 to 4.20</td>
<td>&lt;0.001</td>
<td>4.91</td>
<td>1.69 to 14.26</td>
<td>0.003</td>
</tr>
</tbody>
</table>

ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; NIV, non-invasive ventilation.
of variables included in our dataset, the relatively small sample size and event counts may contribute to a certain degree of bias persistence on primary endpoint associations. To account for potential clinically relevant interfering covariates such as obesity and smoking habit, we performed a sensitivity analysis forcing them in a multivariate model that did not show a significant association. However, the substantial proportion of missing values on obesity data as well as the already mentioned limited sample size and number of events may limit reliability of this exploratory analysis.

CONCLUSION

NIV may have a significant role in supporting patients with COVID-19-related respiratory failure. It effectively supported and prevented the need for intubation of more than one-half of those treated. Those failing had a very poor in-hospital survival rate. Negative predictors were older age, history of hypertension, a more severe desaturation and lymphocytopenia at index evaluation, and the need for antibiotic therapy during admission. Randomised studies are needed to help to identify those who may benefit from this type of ventilatory support.

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Contributors MB, IJN-G and LF initially planned the study, conducted and checked the statistical analysis on the dataset, and wrote the first draft of the paper. All the other authors were involved in the improvement of the study design and contributed significantly to the interpretation of data, revision of the paper’s drafts and approved the final version of the manuscript.

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REFERENCES