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

Maurizio Bertaina ,[1,2] Ivan J Nuñez-Gil,[3] Luca Franchin,[2,4] Inmaculada Fernández Rozas,[5] Ramón Arroyo-Espliguero,[6] María C Viana-Llamas,[6] Rodolfo Romero,[7] Charbel Maroun Eid,[8] Aitor Uribarri,[9] Víctor Manuel Becerra-Muñoz,[10] Jia Huang,[11] Emilio Alfonso,[12] Fernando Marmol-Mosquera,[13] Fabrizio Ugo,[14] Enrico Cerrato,[15] Lucia Fernandez-Presa,[16] Sergio Raposeiras Roubin,[17] Gisela Feltes Guzman,[18] Adelina Gonzalez,[19] Mohammad Abumayyaleh,[20] Antonio Fernandez-Ortiz,[3] Carlos Macaya,[3] Vicente Estrada,[3] On behalf of HOPE COVID-19 investigators

Handling editor Lara Nicole Goldstein

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/emermed-2020-210411).

For numbered affiliations see end of article.

Correspondence to
Dr Maurizio Bertaina, Department of Cardiology, San Giovanni Bosco Hospital, Torino, Piemonte 10154, Italy; maurizio.bertaina@gmail.com

Received 15 July 2020
Revised 26 January 2021
Accepted 1 February 2021

To cite: Bertaina M, Nuñez-Gil IJ, Franchin L, *et al*. *Emerg Med J* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/emermed-2020-210411

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: 1.37, 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 O_2 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. Further studies are required to better clarify our hypothesis.

Trial registration numbers NCT04334291/EUPAS34399.

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 continuously and exponentially over the first 2 weeks of the outbreak, causing governments and healthcare networks to increase ICU capacity.[5] About 11% of patients admitted to the ICU required non-invasive ventilation (NIV), while 88% were treated with mechanical invasive ventilation.[6] Interestingly, acute respiratory failure (ARF) and acute respiratory distress syndrome (ARDS) by SARS-CoV-2 have different characteristics from those previously 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.[7 8] In order to better understand the baseline characteristics, the clinical course and outcome of those patients with COVID-19 treated with NIV, we carried out an interim subanalysis 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 ambispective 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 transcriptase PCR assay for pharyngeal and nasal swab sample) or high suspicion for COVID-19 case were eligible for enrolment in the registry as a result of death or discharge from any healthcare-enrolling 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 respiratory 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-hospital 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 percentages and were compared by $\chi 2$ 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 findings 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 independent predictors of the primary endpoint.[9] 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 significance. 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 V.25.0. 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 group, 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 (O_2<92%) at admission when compared with those on oxygen or high-flow oxygen therapy. Those patients requiring mechanical ventilation had more BP abnormalities, higher temperature, 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

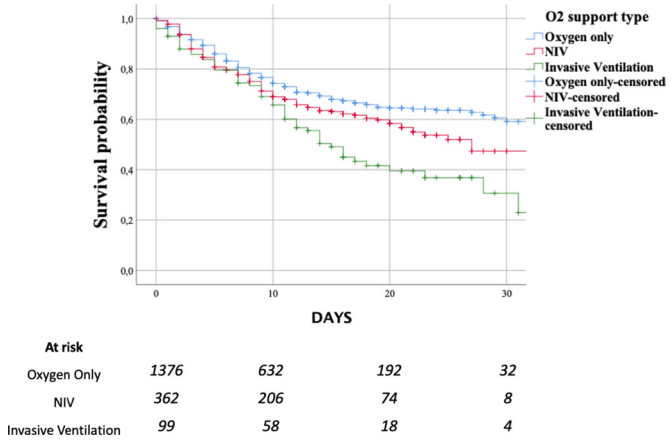

Figure 1 In-hospital survival according to O_2 support type. Cox regression for survival analysis' p values are 0.02 for oxygen only versus NIV and 0.008 for NIV versus invasive ventilation. NIV, non-invasive ventilation.

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 were 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 O_2 saturation below 92% at presentation, lymphocytopenia (ie, lymphocyte count below 1500/mm^3) 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 O_2 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.[3 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

	Overall NIV population (390)	No primary endpoint (217)	Primary endpoint (173)	P value
Demographic data and baseline characteristics				
Age, year median (IQR)	70 (58–79) n=390	62 (52–73) n=217)	76 (68–83) n=173	<0.001
Female sex, n (%)	133/390 (34.1)	78/217 (35.9)	55/173 (31.8)	0.4
Obesity, n (%)	70/273 (25.6)	40/156 (25.6)	30/117 (25.6)	1.0
Hypertension, n (%)	222/383 (58.0)	100/214 (46.7)	122/169 (72.2)	<0.001
Dyslipidaemia, n (%)	141/380 (37.1)	63/213 (29.6)	78/167 (46.7)	0.001
Current or previous smoker, n (%)	103/338 (30.5)	54/185 (29.2)	60/153 (39.2)	0.052
DM, n (%)	70/354 (19.8)	32/201 (15.9)	38/153 (24.8)	0.04
Prior stroke, n (%)	41/361 (11.4)	18/200 (9.0)	23/161 (14.3)	0.1
Heart disease, n (%)	113/390 (29)	50/217 (23.0)	63/173 (36.4)	0.004
Lung disease, any n (%)	85/390 (21.8)	42/217 (19.4)	43/173 (24.9)	0.2
Asthma, n (%)	18/390 (4.6)	14/217 (6.5)	4/173 (2.3)	0.09
COPD, n (%)	37/390 (9.5)	16/217 (7.4)	21/173 (12.1)	0.1
Restrictive lung disease, n (%)	5/390 (1.3)	1/217 (0.5)	4/173 (2.3)	0.2
Liver disease, n (%)	16/347 (4.6)	9/192 (4.7)	7/155 (4.5)	0.9
Chronic kidney disease CL <30, n (%)	31/352 (8.8)	7/197 (3.6)	24/155 (15.5)	<0.001
Cancer history, n (%)	62/366 (16.9)	32/206 (15.5)	30/160 (18.8)	0.5
Connective disease, n (%)	17/361 (4.7)	6/200 (3.0)	11/161 (6.8)	0.09
Any immunosuppressive condition, n (%)	32/320 (10.0)	15/180 (8.3)	17/140 (12.1)	0.3
Prior therapy				
Anticoagulation, n (%)	61/370 (16.5)	26/206 (12.6)	35/164 (21.3)	0.03
Antiplatelet, n (%)	73/372 (19.6)	29/207 (14.0)	44/165 (26.7)	0.002
ACEi/ARB, n (%)	158/383 (41.3)	75/214 (35.5)	82/169 (48.5)	0.01
B-blockers, n (%)	82/365 (22.5)	38/205 (18.5)	44/160 (27.5)	0.04
B-2 agonists, n (%)	59/368 (16)	27/206 (13.1)	32/162 (19.8)	0.09
Inhaled corticosteroids, n (%)	41 (11.2)	18/204 (8.8)	23/163 (14.1)	0.1
Home oxygen therapy, n (%)	20/381 (5.2)	8/212 (3.8)	12/169 (7.1)	0.1
Antidepressant, n (%)	55/371 (14.8)	22/205 (10.7)	33/166 (19.9)	0.01
Clinical presentation				
Fever, n (%)	325/380 (85.5)	185/210 (88.1)	140/170 (82.4)	0.1
Dyspnoea, any entity n (%)	259 (66.4)	134/206 (65.0)	125/168 (74.4)	0.051
Tachypnoea, n (%)	143/354 (40.4)	64/193 (33.2)	79/161 (49.1)	0.002
O_2 saturation below 92%, n (%)	189/373 (50.7)	67/203 (33.0)	122/170 (71.8)	<0.001
Diarrhoea, n (%)	52/350 (14.9)	36/194 (18.6)	16/156 (10.3)	0.03
Vomiting, n (%)	23/356 (6.5)	18/199 (9.0)	5/157 (3.2)	0.03
Hyposmia/anosmia, n (%)	17/343 (5.0)	14/190 (7.4)	3/153 (2.0)	0.02
Dysgeusia, n (%)	23/342 (6.7)	17/188 (9.0)	6/154 (3.9)	0.06
Cough, n (%)	254/375 (67.7)	145/212 (68.4)	109/163 (66.9)	0.8
Max temperature at presentation (°C), median (IQR)	37.7 (36.9–38.4) n=180	37.6 (36.8–38.5) n=95	37.7 (37–38.5) n=85	0.4
BP abnormality, n (%)	43/383 (11.2)	17/216 (7.9)	26/167 (15.6)	0.02
Laboratory data				
Lymphocytopenia (<1.5×10^9/L), n (%)	292/358 (81.6)	149/202 (73.8)	143/156 (91.7)	<0.001
Thrombocytopenia (<150 k), n (%)	98/372 (26.3)	53/213 (24.9)	45/159 (28.3)	0.5
Anaemia at presentation, n (%)	116/373 (31.1)	52/212 (24.5)	64/161 (39.8)	0.002
Creatinine (mg/dL), median (IQR)	0.96 (0.75–1.35) n=315	0.9 (0.7–1.16) n=178	1.13 (0.85–1.58) n=137	<0.001
High levels of D-dimer, n (%)	245/335 (73.1)	128/192 (66.7)	117/143 (81.8)	0.002
High levels of troponin, n (%)	66/243 (27.2)	23/137 (16.8)	43/106 (40.6)	<0.001
High transaminase level, n (%)	176/343 (51.3)	91/189 (48.1)	85/154 (55.2)	0.2
High levels of LDH, n (%)	300/355 (84.5)	163/200 (81.5)	137/155 (88.4)	0.08
High levels of ferritin, n (%)	146/244 (59.8)	89/140 (63.6)	57/104 (54.8)	0.2
High levels of CRP, n (%)	366/380 (96.3)	202/212 (95.3)	164/168 (97.6)	0.2
High levels of procalcitonin, n (%)	95/312 (30.4)	38/171 (22.2)	57/141 (40.4)	0.001
Bilateral CXR abnormality, n (%)	263/360 (73.1)	137/201 (68.2)	126/159 (79.2)	0.02
In-hospital therapy				
Corticosteroids, n (%)	161/370 (43.5)	64/202 (31.7)	97/168 (57.7)	<0.001
Chloroquine, n (%)	311/372 (83.6)	178/205 (86.8)	133/167 (79.6)	0.06

Continued

Table 1 Continued

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

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.

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.[21] The use of this approach, particularly in case of limited availability for invasive ventilation facilities, may preserve resources, delaying or avoiding intubation.[22] 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,[23 24] and some observational studies reported hypertension and diabetes along with COPD and cancer history as possible predictors of a more severe in-hospital course.[20 25] 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 2 Unadjusted and adjusted ORs for primary endpoint within NIV subgroup; baseline creatinine levels, previous therapy with ACEi/ARB and tachypnoea were excluded due to collinearity with CKD history, hypertension and O_2 saturation below 92%, respectively

	Univariate OR	95% CI	P value	Adjusted OR	95% CI	P value
Age (OR per 5-year increase)	1.37	1.26 to 1.49	<0.001	1.37	1.15 to 1.63	<0.001
Dyslipidaemia	2.09	1.37 to 3.19	0.001	–	–	–
Hypertension	2.96	1.92 to 4.55	<0.001	2.95	1.14 to 7.61	0.03
Heart disease	1.91	1.23 to 2.98	0.004	–	–	–
CKD history	4.97	2.08 to 11.88	<0.001	–	–	–
Previous aspirin therapy	2.23	1.32 to 3.76	0.002	–	–	–
Previous antidepressant therapy	2.06	1.15 to 3.70	0.01	–	–	–
O_2 saturation below 92% at index evaluation	5.16	3.31 to 8.04	<0.001	3.05	1.28 to 7.28	0.01
Anaemia	2.03	1.30 to 3.17	0.002	–	–	–
Elevated D-dimer	2.25	1.34 to 3.79	0.002	–	–	–
Elevated troponin	3.38	1.87 to 6.12	<0.001	–	–	–
Elevated procalcitonin	2.38	1.45 to 3.89	0.001	–	–	–
Lymphocytopenia (<1500/mm^3)	3.91	2.05 to 7.48	<0.001	3.55	1.16 to 10.85	0.03
In-hospital corticosteroid use	2.95	1.92 to 4.51	<0.001	–	–	–
In-hospital antibiotic use	2.52	1.51 to 4.20	<0.001	4.91	1.69 to 14.26	0.003

ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; NIV, non-invasive ventilation.

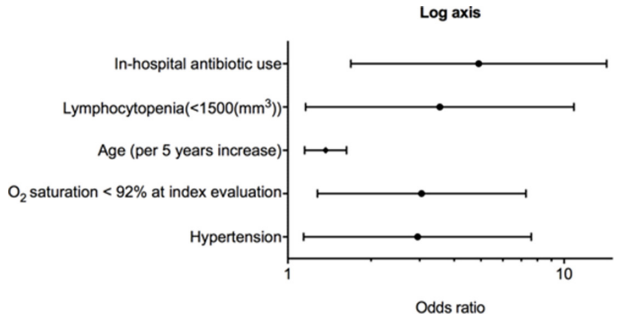

Figure 2 Multivariate OR for primary endpoint. Baseline creatinine levels, previous therapy with ACEi/ARB and tachypnoea were excluded due to collinearity with CKD history, hypertension and $O_2S<92\%$, respectively. ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease.

Among those elements collected during index evaluation, low lymphocyte levels were associated with the primary endpoint. Direct viral infection of T and B cells and consequent immune system dysregulation and cytokine storm may underlie this negative prognostic association.[26] Although not independent predictors of outcome, laboratory markers of other organs' dysfunction at presentation were more frequently present in those with the need for more intensive ventilatory support and a worse clinical outcome. These findings underline the relevant role of multiorgan involvement as a prognostic determinant of COVID-19. Myocardial injury and thrombotic complications may be relevant events associated with a severe clinical course.[27 28]

An increase in medical and physical (ie, pronation) therapeutic interventions was registered among those experiencing a worse clinical course. Nevertheless, no significant protective association between any of these interventions and survival emerged from our analysis. In particular, while an association with an increased risk of the primary endpoint and the use of corticosteroids during admission emerged at univariate analysis, it lost significance after multivariate adjustment. This result is consistent with the preferential use of these drugs in more compromised and severe patients as recommended by many local therapeutic protocols during the initial spread of the pandemic and is not to be seen as a contradiction when compared with evidence coming from randomised controlled trials suggesting a survival benefit.[29 30] The observational design, the limited sample size, the focus on NIV along with absence of standardised management protocol in our study may explain the absence of benefit with steroid use.

An increased risk for in-hospital treatment failure emerged among those treated with antibiotic therapy. This report seems to strengthen previous evidence on the uselessness of systematic administration of azithromycin for patients with COVID-19, but probably underlies a proportion of patients experiencing a worse clinical course and superimposed bacterial infections.[31]

Limitations

Our study must acknowledge several limitations. First of all, the observational design and the extraordinary emergency setting of data collection inevitably led to missing or uncollected information. Particularly, NIV modalities and setting values are lacking and may have played a prognostic role themselves. Furthermore, by depicting a real-life pandemic scenario, our study must acknowledge all the inherent heterogeneity in therapeutic management between enrolling centres. Finally, even if multivariate adjustment was performed, the limited number 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.

Author affiliations
[1]Department of Cardiology, San Giovanni Bosco Hospital, Turin, Piemonte, Italy
[2]Emergency Medicine Department, Martini Hospital Centre, Torino, Piemonte, Italy
[3]Cardiovascular Institute, Hospital Clinico San Carlos, Madrid, Community of Madrid, Spain
[4]Division of Cardiology, Cardiovascular and Thoracic Department, University Hospital Città della Salute e della Scienza, Turin, Italy
[5]Cardiology Department, Severo Ochoa University Hospital, Leganes, Madrid, Spain
[6]Department of Cardiology, General University Hospital of Guadalajara, Guadalajara, Castilla-La Mancha, Spain
[7]Servicio de Urgencias, Getafe University Hospital, Getafe, Community of Madrid, Spain
[8]Emergency Department, La Paz University Hospital, Madrid, Spain
[9]Division of Cardiology, Valladolid University Clinical Hospital, Valladolid, Castilla y León, Spain
[10]Division of Cardiology, Virgen de la Victoria University Hospital, Malaga, Andalucía, Spain
[11]Department of Critical Care Medicine, Shenzhen Second People's Hospital, Shenzhen, Guangdong, China
[12]Division of Cardiology, Institute of Cardiology and Cardiovascular Surgery, Havana, Cuba
[13]Internal Medicine Department, Hospital General del norte de Guayaquil IESS Los Ceibos, Guayaquil, Ecuador
[14]Division of Cardiology, Sant'Andrea di Vercelli Hospital, Vercelli, Piedmont, Italy
[15]Division of Cardiology, San Luigi Gonzaga University Hospital, Orbassano, Italy
[16]Pulmonary Department, Hospital Clinico, Valencia, Spain
[17]Division of Cardiology, University Hospital Alvaro Cunqueiro, Vigo, Galicia, Spain
[18]Division of Cardiology, Hospital Nuestra Señora de América Madrid, Madrid, Spain
[19]Infanta Sofia University Hospital, San Sebastian de los Reyes, Community of Madrid, Spain
[20]University Medical Centre Mannheim, Heidelberg University, Mannheim, Germany

Twitter Maurizio Bertaina @maurib89 and Fernando Marmol-Mosquera @FernanMarmol

Acknowledgements The authors thank Cardiovascular Excellence SL for their essential support in the database and HOPE webpage, all HOPE researchers and Elena Kneip for her support in the English language review.

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.

Funding The HOPE COVID-19 registry was supported by a not-conditioning promoter (Fundación interhospitalaria para la Investigación cardiovascular, FIC. Paseo del Pintor Rosales, Madrid, Spain; CIF: G-81563801).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The HOPE COVID-19 registry was approved by the ethics committee of the promoting centre (Hospital Clinico San Carlos, Madrid, Spain; internal code: 20/241-E) and accepted by institutional boards or local committees.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iD

Maurizio Bertaina http://orcid.org/0000-0001-5727-4107

REFERENCES

1 Huang C, Wang Y, Li X, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506.
2 Chen N, Zhou M, Dong X, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395:507–13.
3 Wang D, Hu B, Hu C, *et al*. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020;323:1061.
4 Liu K, Fang Y-Y, Deng Y, *et al*. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chin Med J* 2020;133:1025–31.
5 Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: early experience and forecast during an emergency response. *JAMA* 2020;323:1545–6.
6 Grasselli G, Zangrillo A, Zanella A, *et al*. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. *JAMA* 2020;323:1574.
7 Gattinoni L, Coppola S, Cressoni M, *et al*. COVID-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med* 2020;201:1299–300.
8 Alhazzani W, Møller MH, Arabi YM, *et al*. Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Intensive Care Med* 2020;46:854–87.
9 D'Ascenzo F, Cavallero E, Biondi-Zoccai G, *et al*. Use and misuse of multivariable approaches in interventional cardiology studies on drug-eluting stents: a systematic review. *J Interv Cardiol* 2012;25:611–21.
10 Nava S, Hill N. Non-Invasive ventilation in acute respiratory failure. *The Lancet* 2009;374:250–9.
11 Antonelli M, Conti G, Moro ML, *et al*. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. *Intensive Care Med* 2001;27:1718–28.
12 Antonelli M, Conti G, Esquinas A, *et al*. A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. *Crit Care Med* 2007;35:18–25.
13 Amato MBP, Meade MO, Slutsky AS, *et al*. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med Overseas Ed* 2015;372:747–55.
14 Patel BK, Wolfe KS, Pohlman AS, *et al*. Effect of noninvasive ventilation delivered by helmet vs face mask on the rate of endotracheal intubation in patients with acute respiratory distress syndrome: a randomized clinical trial. *JAMA* 2016;315:2435–41.
15 Beitler JR, Owens RL, Malhotra A. Unmasking a role for noninvasive ventilation in early acute respiratory distress syndrome. *JAMA* 2016;315:2401–3.
16 Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not? *Crit Care* 2020;24:154.
17 Pagano A, Porta G, Bosso G, *et al*. Non-invasive CPAP in mild and moderate ARDS secondary to SARS-CoV-2. *Respir Physiol Neurobiol* 2020;280:103489.
18 Grasselli G, Zangrillo A, Zanella A, *et al*. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. *JAMA* 2020;323:1574–81.
19 Yang X, Yu Y, Xu J, *et al*. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020;8:475–81.
20 Wu C, Chen X, Cai Y, *et al*. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020;180:934–43.
21 Whittle JS, Pavlov I, Sacchetti AD, *et al*. Respiratory support for adult patients with COVID-19. *J Am Coll Emerg Physicians Open* 2020;1:95–101.
22 Oranger M, Gonzalez-Bermejo J, Dacosta-Noble P, *et al*. Continuous positive airway pressure to avoid intubation in SARS-CoV-2 pneumonia: a two-period retrospective case-control study. *Eur Respir J* 2020;56:2001692. doi:10.1183/13993003.01692-2020
23 Emami A, Javanmardi F, Pirbonyeh N, *et al*. Prevalence of underlying diseases in hospitalized patients with COVID-19: a systematic review and meta-analysis. *Arch Acad Emerg Med* 2020;8:e35.
24 Yang J, Zheng Y, Gou X, *et al*. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *Int J Infect Dis* 2020;94:91–5. doi:10.1016/j.ijid.2020.03.017
25 Guan W-J, Liang W-H, Zhao Y, *et al*. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J* 2020;55:2000547.
26 Azkur AK, Akdis M, Azkur D, *et al*. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. *Allergy* 2020;75:1564–81.
27 Ni W, Yang X, Liu J, *et al*. Acute Myocardial Injury at Hospital Admission Is Associated With All-Cause Mortality in COVID-19. *J Am Coll Cardiol* 2020;76:124–5.
28 Lodigiani C, Iapichino G, Carenzo L, *et al*. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res* 2020;191:9–14.
29 RECOVERY Collaborative Group, Horby P, Lim WS, *et al*. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021;384:693–704.
30 Angus DC, Derde L, Al-Beidh F, *et al*. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA* 2020;324:1317–29.
31 Rosenberg ES, Dufort EM, Udo T, *et al*. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. *JAMA* 2020;323:2493.

Non-invasive ventilation for SARS-COV2 related acute respiratory failure: a sub-analysis from the HOPE COVID-19 registry

SUPPLEMENTAL MATERIAL

Index

	Overall population (1933)	Oxygen only (1437)	NIV w/wo intubation (390)	Invasive ventilation (106)	p-value
Demographic data and baseline characteristics					
Age, year median (IQR)	71 (58-80) n= 1928	71 (58-81) n=1435	70 (58-79) n= 390	67 (57-73) n= 102	0.18
Female sex n (%)	703 (36.4)	538 (37.4%)	133 (34.1)	32 (30.2)	0.19
Obesity n (%)	365/1429 (25.5)	263/1067 (24.6)	70/273 (25.6)	32/89 (36)	0.06
Hypertension n (%)	1070/1924 (55.6)	784/1435 (56.4)	222/383 (58.0)	64 (60.4%)	0.3
Dyslipidemia n (%)	757/1911 (39.6)	574/1425 (40.3)	141/380 (37.1)	42 (39.6)	0.53
Current or previous Smoker n (%)	471/1721 (27.4)	330/1286 (25.7) *	113/338 (33.4) *	28/97 (28.9)	**0.02**
DM n (%)	389/1831 (21.2)	292/1378 (21.2)	70/354 (19.8)	27/99 (27.3)	0.27
Prior stroke n (%)	188/1867 (10.1)	142/1402 (10.1)	41/361 (11.4)	5/104 (4.8%)	0.15
Heart disease, any n (%)	548 (28.3)	407 (28.3)	113 (29)	28 (26.4)	0.87
Lung Disease, any n (%)	428 (22.1)	318 (22.1)	85/390 (21.8)	25 (23.6)	0.93
Asma n (%)	97 (5)	73 (5.1)	18 (4.6)	6 (5.7)	0.98
COPD n (%)	172 (8.9)	124 (8.6)	37 (9.5)	11 (10.4)	0.75
Restrictive n (%)	21 (1)	15 (1)	5 (1.3)	1(0.9)	0.98
Liver disease n (%)	64/1842 (3.5)	44/1391 (3.2)	16/347 (4.6)	4/104 (3.8)	0.41
Chronic kidney disease CL<30 n (%)	154/1833 (8.4)	109/1378 (7.9)	31/352 (8.8)	14/103 (13.6)	0.13
Cancer history n (%)	280/1866 (15)	207/1397 (14.8)	62/366 (16.9)	11/103 (10.7)	0.27
Connective disease n (%)	67/1867 (3.6)	48/1402 (3.4)	17/361 (4.7)	2/104 1.9)	0.32
Any immunosuppressive condition n (%)	145/1707 (8.5)	102/1290 (7.9)	32/320 (10.0)	11/97 (11.3)	0.28
Prior therapies					

Anticoagulation n (%)	267/1885 (14.2)	192/1411 (13.6)	61/370 (16.5)	14/104 (13,5)	0.36
Antiplatelet n (%)	349/1894 (18.4)	254/1417 (17.9)	73/372 (19.6)	22/105 (21)	0.6
ACEI/ARB n (%)	765/1907 (40.1)	554/1418 (39.1)	158/383 (41.3)	53 (50)	0.08
Beta-blockers n (%)	392/1889 (20.8)	289/1419 (20.4)	82/365 (22.5)	21/105 (20)	0.67
Beta-2 agonists n (%)	241/1884 (12.8)	170/1413 (12)	59/368 (16)	12/103 (11.7)	0.12
Inhaled Corticosteroids n (%)	207/1889 (11)	150/1417 (10.6)	41/367 (11.2)	16/105 (15.2)	0.34
Home Oxygen therapy n (%)	87/1909 (4.6)	6/14242 (4.3)	20/381 (5.2)	5/104 (4.8)	0.75
Antidepressant n (%)	276/1886 (14.6)	213/1410 (15.1)	55/371 (14.8)	8/105 (7.6)	0.11
Clinical presentation					
Fever n (%)	1600/1912 (83.7)	1182/1426 (82.9)	325/380 (85.5)	93 (87.7)	0.24
Dyspnea, any entity n (%)	1204/1889 (63.7)	856/1410 (60.7) *	259/374 (66.4) *	89/105 (84.8) *	**<0.001**
Tachypnea n (%)	609/1814 (33.6)	404/1356 (29.8) *	143/354 (40.4) *	62/104 (59.6) *	**<0.001**
O2 saturation < 92% n (%)	851/1876 (45.4)	584/1399 (41.7) *	189/373 (50.7) *	78/104 (75) *	**<0.001**
Diarrhea n (%)	342/1811 (18.9)	269/1362 (19.8)	52/350 (14.9)	21/99 (21.2)	0.09
Vomiting n (%)	140/1811 (7.7)	11/1355 (8.2)	23/356 (6.5)	6/100 (6)	0.44
Hypo/anosmia n (%)	99/1724 (5.7)	68/1285 (5.3) *	17/343 (5.0) °	14/96 (14.6) *°	**0.001**
Dysgeusia n (%)	118/1723 (6.8)	81/1286 (6.3) °	23/342 (6.7) *	14/95 (14.7) *°	**0.007**
Cough n (%)	1336/1891 (70.7)	999/1412 (10.8)	254/375 (67.7)	83/104 (79.8)	0.06
Max temperature at presentation (°C) median(IQR)	37,7 (36.8-38.5) n=930	37.6 (36.8-38.5) * n=705	37.7 (36.9-38.4) ° n = 180	38.2 (37.6-38.6) *° n=45	**0.002**
Blood pressure abnormality n (%)	166/1909 (8.7)	107/1420 (7.5) *	43/383 (11.2)	16 (15.1) *	**0.004**

Table S1. Overall HOPE REGISTRY population baseline characteristics according to ventilation and oxygen support type. ACEi: Angiotensin converting enzymes inhibitors, ARB: angiotensin receptor blocker, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease.
* and ° mark the groups with a statistically significant difference

	Overall population (1933)	Oxygen only (1437)	NIV w/wo intubation (390)	Invasive ventilation (106)	p-value
			Laboratory data		
Leucocytes, 10^9/L median (IQR)	6.2 (4.7-8.7) n=1883	6.1(4.5-8.5) * n= 1405	6.5 (5-9.3) ° n=376	7.3 (5.3-12) *° n =102	**0.02**
Lymphocytopenia (<1.5 109/L) n (%)	1472/1824 (80.7)	1107/1366 (81)	292/358 (81.6)	74/100 (74)	0.22
Thrombocytopenia (<150k) n (%)	544/1877 (29)	414/1401 (29.6)	98/372 (26.3)	32/104 (30.8)	0.44
Anemia at presentation n (%)	485/1868 (26)	339/1393 (24.3) *	116/373 (31.1) *	30/102 (29.4)	**0.022**
Creatinine (mg/dl) median (IQR)	0.95 (0.75-1.24) n=1592	0.94 (0.75-1.21) * n=1198	0.96 (0.75-1.35) n=315	1.08 (0.8-1.6) * n=79	**0.01**
High levels of D-dimer n (%)	1167/1641 (71.1)	847/1217 (69.6) *	245/335 (73.1)	75/89 (84.3) *	**0.009**
High levels of troponin n (%)	180//918 (19.6)	86/602 (14.3) *°	66/243 (27.2) *	28/73 (38.4) °	**<0.001**
High transaminase level n (%)	849/1756 (48.3)	603/1315 (45.9) *	176/343 (51.3) °	70/98 (71.4) *°	**<0.001**
High levels of LDH n (%)	1403/1724 (81.4)	1028/1283 (80.1)	300/355 (84.5)	75/86 (87.2)	0.06
High levels of ferritin n (%)	686/1073 (63.9)	486/756 (64.3)	146/244 (59.8)	54/72 (74)	0.08
High levels of CRP n (%)	1799/1893 (95)	1333/1411(94.5)	366/380 (96.3)	100/102 (98)	0.12
High levels of procalcitonin n (%)	407/1480 (27.5)	270/1077 (25.1) *	95/312 (30.4) °	42/91 (46.2) *°	**<0.001**
			Imaging		
Bilateral chest x-rays abnormality n (%)	1260 (65.2)	923 (64.2)	263 (67.4)	74 (69.8)	0.14
			In-hospital therapy		
Corticosteroids n (%)	555/1869 (29.7)	351/1403 (25) *°	161/370 (43.5) °	43/96 (44.9) *	**<0.001**
Chloroquine n (%)	1594/1893 (84.2)	1192/1417 (84.1)	311/372 (83.6)	91/104 (87.5)	0.62
Antivirals n (%)	1299/1898 (68.4)	936/1416 (66.1) *°	276/377 (73.2) *	87/105 (82.9) °	**<0.001**
Interferon n (%)	320/1857 (17.2)	206/1389 (14.8) °	67/366 (18.3) *	47/102 (46.1) *°	**<0.001**

Tocilizumab n (%)	174/1858 (9.4)	82/1391 (5.9) *	58/363 (16) *	34/104 (32.7) *	**<0.001**
Antibiotic n (%)	1457/1833 (79.5)	1085/1361 (79.7) *	277/368 (75.3) °	95/104 (91.3) *°	**0.001**
ACEI/ARB n (%)	341/1800 (18.9)	261/1334 (19.6)	63/368 (17.1)	17/98 (17.3)	0.52
Pronation during admission n (%)	244/1854 (13.2)	102/1386 (7.4) *	87/372 (23.4) *	55/96 (57.3) *	**<0.001**
In-hospital Complications					
Sepsis n (%)	332/1866 (17.8)	138/1394 (9.9) *	143/375 (38.1) *	51/97 (52.6) *	**<0.001**
Relevant bleedings n (%)	43/1826 (2.4)	21/1378 (1.5) *°	15/354 (4.2) *	7/94 (7.4) °	**<0.001**
Embolic event n (%)	34/1833 (1.9)	18/1376 (1.3) *°	12/361 (3.3) *	4/96 (4.2) °	**0.009**
Renal failure during admission n (%)	414/1880 (22)	245/1405 (17.4) *	113/376 (30.1) *	56/99 (56.6) *	**<0.001**
Heart failure during admission n (%)	170/1870 (9.1)	97/1398 (6.9) *	43/373 (11.5) *	30/99 (30.3) *	**<0.001**
Circulatory or ECMO support n (%)	61/1850 (3.3)	1/468 (0.2) *	33/361 (9.1) *	27/97 (27.8) *	**<0.001**
Length of hospital stay (days) mean ±SD	9.19 ±6.7, n=1741	8.9 ±6.4, n=1329*	9.9 ± 7.3, n=331	11.5 ± 8.0, n=81*	**<0.001**

Table S2. Overall HOPE REGISTRY population laboratory characteristics and in-hospital outcomes according to ventilation and oxygen support type.
ACEi: Angiotensin converting enzymes inhibitors, ARB: angiotensin receptor blocker, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease. CRP: C-reactive protein, LDH: lactic dehydrogenase, ECMO: Extracorporeal membrane oxygenation
* and ° mark the groups with a statistically significant difference

	Overall NIV population (390)	**Alive (243)**	**Dead (147)**	**p-value**
Demographic data and baseline characteristics				
Age, year median (IQR)	70 (58-79) n= 390	63 (53-73) n=243	78 (70-85) n=147	**<0.001**
Female sex n (%)	133/390 (34.1)	86/243 (35.4)	47/147 (32.0)	0.5
BMI n (%)	27 (25-31) n=219	27 (25-31) n=142	27 (25-31) n=77	0.1
Obesity n (%)	70/273 (25.6)	45/179 (25.1)	25/94 (26.6)	0.9
Hypertension n (%)	222/383 (58.0)	117/239 (49.0)	105/144 (72.9)	**<0.001**
Dyslipidemia n (%)	141/380 (37.1)	71/238 (29.8)	70/142 (49.3)	**<0.001**
Current or previous Smoker n (%)	103/338 (30.5)	51/210 (29.1)	52/128 (40.7)	**0.004**
DM n (%)	70/354 (19.8)	39/225 (17.3)	31/129 (24.0)	0.1
Prior stroke n (%)	41/361 (11.4)	19/225 (8.4)	22/136 (16.2)	**0.04**

Heart disease, any n (%)	113/390 (29)	57/243 (23.5)	56/147 (38.1)	**0.002**
Lung Disease, any n (%)	85/390 (21.8)	48/243 (19.8)	37/147 (25.2)	0.3
Asma n (%)	18/390 (4.6)	14/243 (5.8)	4/147 (2.7)	0.3
COPD n (%)	37/390 (9.5)	16/243 (6.6)	21/147 (14.3)	**0.02**
Restrictive lung disease n (%)	5/390 (1.3)	4/243 (1.6)	1/147 (0.7)	0.7
Liver disease n (%)	16/347 (4.6)	9/217 (4.1)	7/130 (5.4)	0.6
Chronic kidney disease CL<30 n (%)	31/352 (8.8)	7/220 (3.2)	24/132 (18.2)	**<0.001**
Cancer history n (%)	62/366 (16.9)	34/229 (14.8)	28/137 (20.4)	0.2
Connective disease n (%)	17/361 (4.7)	6/225 (2.7)	11/136 (8.1)	**0.02**
Any immunosuppressive condition n (%)	32/320 (10.0)	16/202 (7.9)	16/118 (13.6)	0.1
Prior therapies				
Anticoagulation n (%)	61/370 (16.5)	30/231 (13.0)	31/139 (22.3)	**0.02**
Antiplatelet n (%)	73/372 (19.6)	32/232 (13.8)	41/140 (29.3)	**<0.001**
ACEI/ARB n (%)	158/383 (41.3)	85/239 (35.6)	73/144 (50.7)	**0.004**
B-blockers n (%)	82/365 (22.5)	42/229 (18.3)	40/136 (29.4)	**0.01**
B-2 agonists n (%)	59/368 (16)	28/230 (12.2)	31/138 (22.5)	**0.01**
Inhaled Corticosteroids n (%)	41 (11.2)	20/229 (8.7)	21/138 (15.2)	0.06
Home Oxygen therapy n (%)	20/381 (5.2)	10/236 (4.2)	10/145 (6.9)	0.3
Antidepressant n (%)	55/371 (14.8)	25/230 (10.9)	30/141 (21.3)	**0.01**
Clinical presentation				
Fever n (%)	325/380 (85.5)	209/236 (88.6)	116/144 (80.6)	**0.03**
Dyspnea, any entity n (%)	259 (66.4)	155/232 (64.8)	104/142 (73.0)	0.2
Tachypnea n (%)	143/354 (40.4)	74/219 (33.8)	69/135 (51.1)	**0.001**
O2 saturation below 92% n (%)	189/373 (50.7)	86/229 (37.6)	103/144 (71.5)	**<0.001**
Diarrhea n (%)	52/350 (14.9)	39/220 (17.7)	13/130 (10.0)	**0.05**
Vomiting n (%)	23/356 (6.5)	19/225 (8.4)	4/131 (3.1)	**0.05**
Hypo/anosmia n (%)	17/343 (5.0)	15/216 (6.9)	2/127 (1.6)	**0.03**
Dysgeusia n (%)	23/342 (6.7)	22/214 (10.3)	1/128 (0.8)	**0.001**
Cough n (%)	254/375 (67.7)	162/238 (68.1)	92/137 (67.2)	0.9
Max temperature at presentation (°C) n (%)	37.7 (36.9-38.4) n = 180	37.6 (36.9-38.5) n=107	37.7 (36.9-38.4) n=73	0.9
Blood pressure abnormality n (%)	43/383 (11.2)	17/242 (7.0)	26/141 (18.4)	**0.001**
Laboratory data				
Leucocytes, 10^9/L median (IQR)	6.5 (5-9.3) n=376	6.6 (4.9-9.4) n=237	7.2 (5.2-9.9) n=139	0.2
Platelets count (<1.5 109/L) n (%)	292/358 (81.6)	171/227 (75.3)	121/131 (92.4)	**<0.001**
Thrombocytopenia (<150k) n (%)	98/372 (26.3)	58/238 (24.4)	40/134 (29.9)	0.3
Anemia at presentation n (%)	116/373 (31.1)	60/238 (25.2)	56/135 (41.5)	**0.001**
Creatinine (mg/dl) median (IQR)	0.96 (0.75-1.35) n=315	0,9 (0,7-1.19) n=193	1.13 (0.85-1.58) n=122	**0.01**
High levels of D-dimer n (%)	245/335 (73.1)	150/216 (69.4)	95/119 (79.8)	**0.04**
High levels of troponin n (%)	66/243 (27.2)	29/152 (19.1)	37/91 (40.7)	**<0.001**
High transaminase level n (%)	176/343 (51.3)	105/215 (48.8)	71/128 (55.5)	0.2
High levels of LDH n (%)	300/355 (84.5)	183/223 (82.1)	117/132 (88.6)	0.1

High levels of ferritin n (%)	146/244 (59.8)	100/156 (64.1)	46/88 (52.3)	0.07
High levels of CRP n (%)	366/380 (96.3)	226/238 (95.0)	140/142 (98.6)	0.07
High levels of procalcitonin n (%)	95/312 (30.4)	42/196 (21.4)	53/116 (45.7)	**<0.001**
Imaging				
Bilateral chest XR abnormality n (%)	263/360 (73.1)	156/227 (68.7)	107/133 (80.5)	**0.02**
In-hospital therapies				
Corticosteroids n (%)	161/370 (43.5)	79/226 (35.0)	82/144 (56.9)	**<0.001**
Chloroquine n (%)	311/372 (83.6)	200/230 (87.0)	111/142 (78.2)	**0.03**
Antivirals n (%)	276/377 (73.2)	180/237 (75.9)	96/140 (68.6)	0.1
Interferon n (%)	67/366 (18.3)	42/228 (18.4)	25/138 (18.1)	1.0
Tocilizumab n (%)	58/363 (16)	34/228 (14.9)	24/135 (17.8)	0.5
Antibiotic n (%)	277/368 (75.3)	161/228 (70.6)	116/140 (82.9)	**0.008**
ACEI/ARB n (%)	63/368 (17.1)	42/234 (17.9)	21/134 (15.7)	0.7
Ventilation therapy				
Need for invasive mechanical ventilation n (%)	62/390 (15.9)	26/243 (10.7)	36/147 (24.5)	**0.001**
Pronation in NIV n (%)	63/372 (16.9)	30/230 (13.0)	33/142 (23.2)	**0.011**
In-hospital complications				
Sepsis n (%)	143/375 (38.1)	67/236 (28.4)	76 /139 (54.7)	**<0.001**
Relevant bleedings n (%)	15/354 (4.2)	8/223 (3.6)	7/131 (5.3)	0.4
Embolic event n (%)	12/361 (3.3)	7/230 (3.0)	5/131 (3.8)	0.7
Renal failure during admission n (%)	113/376 (30.1)	39/234 (16.7)	74/142 (52.1)	**<0.001**
Heart failure during admission n (%)	43/373 (11.5)	14/236 (5.9)	29/137 (21.2)	**<0.001**
Circulatory or ECMO support n (%)	33/361 (9.1)	8/227 (3.5)	25/134 (18.7)	**<0.001**
Length of in-hospital stay median (IQR)	8 (4-15) n=338	10 (6-16) n=232	6 (3-10) n=147	**<0.001**

Table S3. HOPE REGISTRY Cohort of patients treated with NIV according to death status.
ACEi: Angiotensin converting enzymes inhibitors, ARB: angiotensin receptor blocker, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease. CRP: C-reactive protein, LDH: lactic dehydrogenase, ECMO: Extracorporeal membrane oxygenation

	Univariate OR	95% CI		p-value
Age (OR per 5-year increase)	1.46	1.33	1.61	<0.001
Dyslipidemia	2.29	1.49	3.52	<0.001
Hypertension	2.81	1.80	4.39	<0.001
Heart Disease, any	2.0	1.29	3.14	0.002
CKD history	6.76	2.83	16.19	<0.001
Previous antiplatelet therapy	2.59	1.54	4.36	<0.001
Previous ACEI/ARB therapy	1.86	1.22	2.84	0.004
Previous Inhaled Beta-agonist Therapy	2.09	1.19	3.67	0.009
Previous Antidepressant therapy	2.22	1.24	3.95	0.006
O2 saturation below 92% at index evaluation	4.18	2.66	6.55	<0.001
Dysgeusia	0.07	0.01	0.52	<0.001
Blood pressure abnormalities	2.99	1.56	5.74	<0.001
Anemia	2.10	1.34	3.30	0.001
Elevated Troponin	2.90	1.63	5.20	<0.001
Lymphocytopenia (<1500/mm3)	3.96	1.94	8.08	<0.001
In hospital corticosteroid use	2.46	1.60	3.78	<0.001
In hospital antibiotic use	2.01	1.19	3.40	0.008

Table S4. Unadjusted OR for death within NIV subgroup.
ACEi: Angiotensin converting enzymes inhibitors, ARB: angiotensin receptor blocker, CKD: chronic kidney disease.

	Overall NIV population (390)	No orotracheal intubation (328)	Orotracheal intubation (62)	p-value
Ventilation therapy				
Age, year	70 (58-79) n= 390	71 (57-80) n=328	68 (60-73) n=62	68 (60-73) n=62
Female sex	133/390 (34.1)	16/62 (25.8)	117/328 (35.7)	0.1
Obesity	70/273 (25.6)	11/55 (20.0)	59/218 (27.1)	0.3
Hypertension	222/383 (58.0)	182/322 (56.5)	40/61 (65.6)	0.2
Dyslipidemia	141/380 (37.1)	119/319 (37.3)	22/61 (36.1)	0.9
Current or previous Smoker	103/338 (30.5)	95/279 (34.1)	19/59 (32.2)	0.8
DM	70/354 (19.8)	56/295 (19.0)	14/59 (23.7)	0.4
Prior stroke	41/361 (11.4)	39/302 (12.9)	2/59 (3.4)	0.05
Heart disease	113/390 (29)	100/328 (30.5)	13/62 (21.0)	0.1
Lung Disease, any	85/390 (21.8)	72/328 (22.0)	13/62 (21.0)	0.9
Asma	18/390 (4.6)	17/328 (5.2)	17/328 (5.2)	0.3
COPD	37/390 (9.5)	33/328 (10.1)	4/62 (6.5)	0.4
Restrictive lung disease	5/390 (1.3)	17/328 (5.2)	17/328 (5.2)	0.03
Liver disease	16/347 (4.6)	14/289 (4.8)	2/58 (3.4)	0.6
Chronic kidney disease CL<30	31/352 (8.8)	23/293 (7.8)	8/59 (13.6)	0.16
Cancer history	62/366 (16.9)	57/308 (18.5)	5/58 (8.6)	0.07
Connective disease	17/361 (4.7)	17/303 (5.6)	0/58 (0.0)	0.09
Any immunosuppressive condition	32/320 (10.0)	30/264 (11.4)	2/56 (3.6)	0.08
Previous therapies				
Anticoagulation	61/370 (16.5)	52/310 (16.8)	9/60 (15.0)	0.7
Antiplatelet	73/372 (19.6)	61/312 (19.6)	12/60 (20.0)	0.9
ACEI/ARB	158/383 (41.3)	133/323 (41.2)	25/60 (41.7)	0.9
B-blockers	82/365 (22.5)	73/306 (23.9)	9/59 (15.3)	0.15
B-2 agonists	59/368 (16)	54/309 (17.5)	5/59 (8.5)	0.08
Inhaled Corticosteroids	41 (11.2)	34/307 (11.1)	7/60 (11.7)	0.9
Home Oxygen therapy	20/381 (5.2)	17/322 (5.3)	3/59 (5.1)	1.0
Antidepressant	55/371 (14.8)	46/311 (14.8)	9/60 (15.0)	1.0
Clinical presentation				
Fever	325/380 (85.5)	270/320 (84.4)	55/60 (91.7)	0.1
Dyspnea, any entity	259 (66.4)	214/313 (68.4)	45/61 (73.8)	0.4
Tachypnea	143/354 (40.4)	115/293 (39.2)	28/61 (45.9)	0.3
O2 saturation below 92%	189/373 (50.7)	150/312 (48.1)	39/61 (63.9)	0.02
Diarrhea	52/350 (14.9)	47/290 (16.2)	5/60 (8.3)	0.1
Vomiting	23/356 (6.5)	22/296 (7.4)	1/60 (1.7)	0.1
Hypo/anosmia	17/343 (5.0)	16/283 (5.7)	1/60 (1.7)	0.2
Dysgeusia	23/342 (6.7)	18/282 (6.4)	5/60 (8.3)	0.6
Cough	254/375 (67.7)	214/315 (67.9)	40/60 (66.7)	0.9
Max temperature at presentation (°C)	37.7 (36.9-38.4) n = 180	37.7 (36.8-38.4) n=149	37.9 (37.4-38.6)	0.2

Blood pressure abnormality	43/383 (11.2)	33/321 (10.3)	10/62 (16.1)	0.18
Laboratory data				
Leucocytes, 10^9/L	6.5 (5-9.3) n=376	0.95 (0.74-1.33) n=275	0.95 (0.74-1.33) n=275	0.1
Lymphocytopenia (<1.5 109/L)	292/358 (81.6)	239/300 (79.7)	53/58 (91.4)	0.04
Thrombocytopenia (<150k)	98/372 (26.3)	81/316 (25.6)	17/56 (30.4)	0.5
Anemia at presentation	116/373 (31.1)	95/312 (30.4)	21/61 (34.4)	0.5
Creatinine (mg/dl)	0.96 (0.75-1.35) n=315	0.95 (0.74-1.33) n=275	0.95 (0.74-1.33) n=275	0.07
High levels of D-dimer	245/335 (73.1)	194/278 (69.8)	51/57 (89.5)	0.002
High levels of troponin	66/243 (27.2)	50/201 (24.9)	16/42 (38.1)	0.08
High transaminase level	176/343 (51.3)	141/283 (49.8)	35/60 (58.3)	0.2
High levels of LDH	300/355 (84.5)	248/298 (83.2)	52/57 (91.2)	0.1
High levels of ferritin	146/244 (59.8)	126/199 (63.3)	20/45 (44.4)	0.02
High levels of CRP	366/380 (96.3)	307/319 (96.2)	59/61 (96.7)	0.9
High levels of procalcitonin	95/312 (30.4)	71/252 (28.2)	24/60 (40.0)	0.07
Imaging				
Bilateral chest XR abnormality	263/360 (73.1)	212/300 (70.7)	51/60 (85.0)	0.02
In-hospital therapies				
Corticosteroids	161/370 (43.5)	122/310 (39.4)	39/60 (65.0)	<0.001
Chloroquine	311/372 (83.6)	254/311 (81.7)	57/61 (93.4)	0.02
Antivirals	276/377 (73.2)	223/316 (70.6)	53/61 (86.9)	0.008
Interferon	67/366 (18.3)	46/307 (15.0)	21/59 (35.6)	<0.001
Tocilizumab	58/363 (16)	38/303 (12.5)	20/60 (33.3)	<0.001
Antibiotic	277/368 (75.3)	219/307 (71.3)	58/61 (95.1)	<0.001
ACEI/ARB	63/368 (17.1)	56/307 (18.2)	7/61 (11.5)	0.2
Pronation during hospitalization	87/372 (23.4)	63/313 (20.1)	24/59 (40.7)	0.001
In-hospital complications				
Sepsis	143/375 (38.1)	111/315 (35.2)	32/60 (53.3)	0.008
Relevant bleedings	15/354 (4.2)	9/294 (3.1)	6/60 (10.0)	0.02
Embolic event	12/361 (3.3)	7/301 (2.3)	5/60 (8.3)	0.02
Renal failure during admission	113/376 (30.1)	80/314 (25.5)	33/62 (53.2)	<0.001
Heart failure during admission	43/373 (11.5)	35/312 (11.2)	8/61 (13.1)	0.7
Circulatory or ECMO support	33/361 (9.1)	2/301 (0.7)	31760 (51.7)	<0.001
TIME of in hospital stay	8 (4-15) n=338	10 (5-16) n=178	7 (3-12) n=160	0.006

Table S5. HOPE REGISTRY sub-analysis on patients treated with NIV and according to OTI.
ACEi: Angiotensin converting enzymes inhibitors, ARB: angiotensin receptor blocker, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease. CRP: C-reactive protein, LDH: lactic dehydrogenase, ECMO: Extracorporeal membrane oxygenation

	Univariate OR	95% CI		P value
Prior Stroke	0.24	0.06	1.00	0.05
O2 saturation below 92% at index evaluation	1.92	1.09	3.38	0.02
Elevated D-Dimer	3.68	1.52	8.91	0.002
Elevated ferritin	0.46	0.24	0.82	0.02
Lymphocytopenia (<1500/mm3)	2.71	1.04	7.06	0.04
Bilateral Chest x-rays abnormalities	2.35	1.11	4.99	0.02
In-hospital corticosteroid use	2.86	1.61	5.09	<0.001
In-hospital Chloroquine use	3.20	1.11	9.17	0.02
In hospital antiviral use	2.76	1.26	6.04	0.008
In hospital Interferon use	3.14	1.69	5.82	<0.001
In hospital use of Tocilizumab	3.49	1.85	6.58	<0.001
In hospital antibiotic use	7.77	2.37	25.45	<0.001
Pronation during hospitalization	2.72	1.51	4.90	0.001

Table S6. Unadjusted OR for orotracheal intubation within NIV subgroup.

	Adjusted OR	95% CI		p-value
Age (OR per 5-year increase)	1.36	1.12	1.67	0.002
Dyslipidemia	-	-	-	-
Hypertension	2.49	0.78	8.01	0.13
Heart Disease	-	-	-	-
CKD history	-	-	-	-
Previous aspirin therapy	-	-	-	-
Previous Antidepressant therapy	-	-	-	-
O2 saturation below 92% at index evaluation	3.72	1.38	10.03	0.01
Anemia	-	-	-	-
Elevated D-Dimer	-	-	-	-
Elevated Troponin	-	-	-	-
Elevated Procalcitonin	-	-	-	-
Lymphocytopenia (<1500/mm3)	3.60	0.97	13.4	0.055
In hospital corticosteroid use	-	-	-	-
In hospital antibiotic use	4.9	1.1	21.76	0.037
Obesity	1.87	0.58	6.04	0.29
Previous or current smoker	0.91	0.32	2.59	0.86

Table S7. Sensitivity multivariate logistic regression analysis forcing "obesity" and "Smoke habits" (previous or current smokers) in the model. Where not shown (i.e. "-") p value is higher than 0.05.

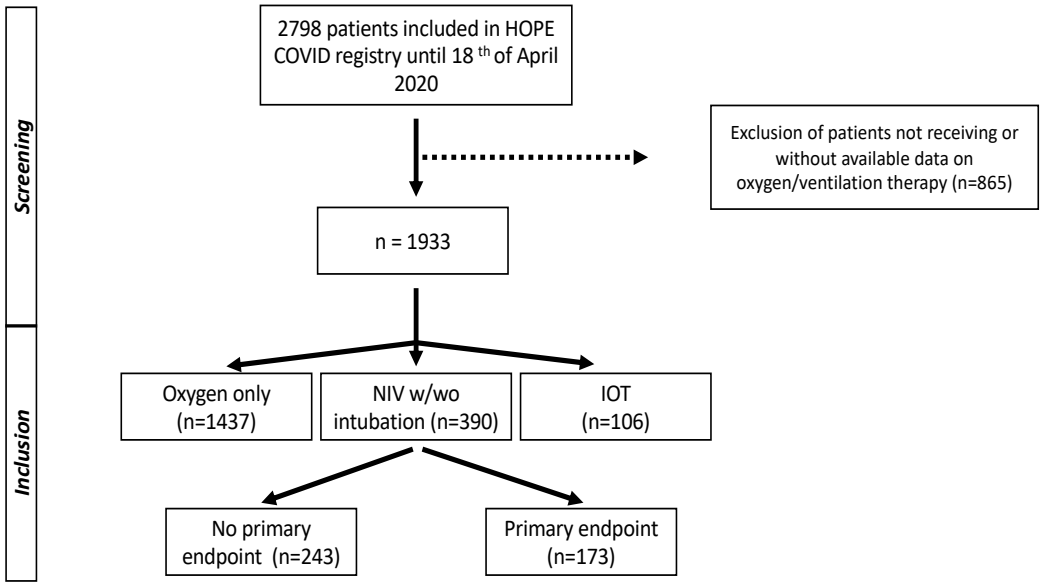

Figure S1. HOPE COVID sub-study flow-chart.