Infection (2021) 49:989–997
https://doi.org/10.1007/s15010-021-01633-6

ORIGINAL PAPER

Non-invasive ventilation versus mechanical ventilation in hypoxemic patients with COVID-19

Iain S. Forrest[1,2,3,4] · Suraj K. Jaladanki[1,3,5,6] · Ishan Paranjpe[1,3,5,6] · Benjamin S. Glicksberg[4,5,6] · Girish N. Nadkarni[1,3,4,5,6,7] · Ron Do[1,3,4]

Received: 24 February 2021 / Accepted: 25 May 2021 / Published online: 5 June 2021

Abstract

Purpose Limited mechanical ventilators (MV) during the Coronavirus disease (COVID-19) pandemic have led to the use of non-invasive ventilation (NIV) in hypoxemic patients, which has not been studied well. We aimed to assess the association of NIV versus MV with mortality and morbidity during respiratory intervention among hypoxemic patients admitted with COVID-19.

Methods We performed a retrospective multi-center cohort study across 5 hospitals during March–April 2020. Outcomes included mortality, severe COVID-19-related symptoms, time to discharge, and final oxygen saturation (SpO2) at the conclusion of the respiratory intervention. Multivariable regression of outcomes was conducted in all hypoxemic participants, 4 subgroups, and propensity-matched analysis.

Results Of 2381 participants with laboratory-confirmed SARS-CoV-2, 688 were included in the study who were hypoxemic upon initiation of respiratory intervention. During the study period, 299 participants died (43%), 163 were admitted to the ICU (24%), and 121 experienced severe COVID-19-related symptoms (18%). Participants on MV had increased mortality than those on NIV (128/154 [83%] versus 171/534 [32%], OR = 30, 95% CI 16–60) with a mean survival of 6 versus 15 days, respectively. The MV group experienced more severe COVID-19-related symptoms [55/154 (36%) versus 66/534 (12%), OR = 4.3, 95% CI 2.7–6.8], longer time to discharge (mean 17 versus 7.1 days), and lower final SpO2 (92 versus 94%). Across all subgroups and propensity-matched analysis, MV was associated with a greater OR of death than NIV.

Conclusions NIV was associated with lower respiratory intervention mortality and morbidity than MV. However, findings may be liable to unmeasured confounding and further study from randomized controlled trials is needed to definitively determine the role of NIV in hypoxemic patients with COVID-19.

Keywords COVID-19 · SARS-CoV-2 · Non-invasive ventilation · Mechanical ventilation · Critical care outcomes

Abbreviations

ICU	Intensive care unit
MV	Mechanical ventilation
NIV	Non-invasive ventilation
SD	Standard deviation
COVID-19	Coronavirus disease
OR	Odds ratio
RCT	Randomized controlled trial

✉ Ron Do
ron.do@mssm.edu

[1] The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, Annenberg Building, Floor 18 Room 80A, 1468 Madison Ave, New York, NY 10029, USA

[2] Medical Scientist Training Program, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[3] The BioMe Phenomics Center, Icahn School of Medicine at Mount Sinai, Annenberg Building, Floor 18 Room 80A, 1468 Madison Ave, New York, NY 10029, USA

[4] Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, Annenberg Building, Floor 18 Room 80A, 1468 Madison Ave, New York, NY 10029, USA

[5] The Hasso Plattner Institute for Digital Health at Mount Sinai, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[6] The Mount Sinai Clinical Intelligence Center, New York, NY, USA

[7] Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SE	Standard error
SpO2	Oxygen saturation
β	Effect size estimate
95% CI	95% Confidence interval

Introduction

The ongoing coronavirus disease 2019 (COVID-19) pandemic, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus, has pushed healthcare systems to act against a novel pathogen that can leave patients hypoxemic with concomitant respiratory distress [1, 2]. Supplying adequate oxygen to these patients is a mainstay of treatment, yet fatality rates around 50% have been reported in mechanically ventilated (MV) patients [3]. Due in part to the limited supply of mechanical ventilators during surges of COVID-19 cases, non-invasive ventilation (NIV) has been employed as an alternative method for delivering oxygen to hypoxemic patients with COVID-19 [4, 5]; yet this remains controversial with little empirical evidence for efficacy thus far [6, 7]. In some cases, MV is completely forgone for "happy hypoxic" patients who exhibit silent hypoxemia [8, 9]. Given that the current respiratory treatment of COVID-19 varies greatly by modality and mortality, an analysis of clinical outcomes in patients with different pulmonary interventions is needed.

Understanding the effectiveness of NIV relative to MV is critical as different regions of the United States and the world contend with record levels of COVID-19 cases and hospitalizations that stretch resource-limited healthcare settings to capacity [10, 11]. Comparable or improved effectiveness of NIV in certain patients would support its use as an alternative to MV and aid healthcare settings with limited resources and personnel [10, 11]. Moreover, identifying subpopulations who benefit from NIV would help inform clinicians deciding respiratory interventions for hypoxemic patients with COVID-19 and personalize their care. There is currently no consensus on triggers for mechanical ventilation in patients with COVID-19 or criteria for when to opt for less invasive respiratory support instead [12].

The objective of this study was to evaluate and compare the respiratory intervention mortality of hypoxemic patients with COVID-19 who received NIV or MV across 5 hospitals. The incidence of severe COVID-19-related symptoms, time to discharge, and final oxygen saturation (SpO2) at the conclusion of respiratory intervention were also analyzed.

Methods

Study design and participants

We performed a retrospective multi-center cohort study of respiratory interventions in hypoxemic patients with COVID-19. Data were analyzed from the electronic health record and included demographics, disease diagnoses, vital signs, comorbidities, procedures, ICU status, and clinical outcomes (death, symptoms, and hospital discharge). Additional detail on the method for obtaining these data is provided in Additional file 1. The Mount Sinai Institutional Review Board approved this study.

We included patients > 18 years of age with laboratory-confirmed SARS-CoV-2 who were admitted between Mar 1st, 2020 and Apr 30th, 2020 to 5 hospitals in New York City. The positive SARS-CoV-2 laboratory result occurred within 48 h of admission. We included hypoxemic patients with SpO2 ≤ 93% [13–15] at the start of respiratory intervention who were more likely to receive ventilation, particularly MV, and benefit from therapeutic ventilation than those with normal oxygen levels. In addition, patients without any recorded SpO2 measurement or respiratory intervention were excluded. None of the included patients had multiple respiratory interventions or do-not-resuscitate orders.

Respiratory interventions and outcomes

The primary exposure of interest was a respiratory intervention of NIV or MV. Limited mechanical ventilators, ICU capacity, and critical care resources led to the use of NIV in many patients. Respiratory interventions were provided in the ICU (ICU patients) or outside the ICU in the emergency department and surge/overflow areas (non-ICU patients); critical care consults were called for all patients receiving MV. The primary outcome was mortality over the course of respiratory intervention. Temporal data of death and secondary outcomes during the respiratory intervention were recorded and related to the start of the respiratory intervention (time = 0). The secondary outcome of severe COVID-19-related complications was identified from International Classification of Disease 9 and 10 (ICD-9-CM and ICD-10-CM) codes for acute respiratory distress syndrome, shock, arrhythmia, cardiac arrest, acute kidney injury, respiratory failure, and multiple organ dysfunction (Online Additional file 1: Table S1). Other secondary outcomes included time to hospital discharge and final SpO2 at the conclusion of the respiratory intervention. SpO2 measurements on room air were available at the initiation and conclusion of the respiratory

intervention. SpO2 levels at the initiation of respiratory intervention were included as a covariate in multivariable regression and were used in a subgroup analysis. SpO2 levels at the conclusion of respiratory intervention were evaluated as a secondary outcome.

Comorbidities were identified from ICD-9-CM and ICD-10-CM codes for atrial fibrillation, asthma, coronary artery disease, cancer, chronic kidney disease, chronic obstructive pulmonary disease, diabetes, heart failure, hypertension, liver disease, and stroke (Online Additional file 1: Table S2) as previously used and described elsewhere [16, 17]. Data on receipt of COVID-19 medications of azithromycin, hydroxychloroquine, corticosteroids (prednisone, dexamethasone), and antivirals (lopinavir, ritonavir, favipiravir) were also extracted for each participant.

Statistical analysis

Statistical analyses were conducted to compare baseline traits between MV and NIV groups using chi-square tests for binary traits and two-tailed *t* tests for continuous traits. Multivariable regression of respiratory intervention on primary and secondary outcomes was performed, adjusting for age, sex, ethnicity, BMI, hospital, comorbidities, COVID-19 medications, and initial SpO2. Binary outcomes of death and severe COVID-19-related symptoms were assessed with multivariable logistic regression and described with an adjusted odds ratio (OR) and 95% confidence interval (95% CI). Continuous outcomes of time to discharge and final SpO2 were evaluated with multivariable linear regression and described with an adjusted effect size estimate (β) and standard error (SE). Kaplan–Meier curves were used to assess survival after initiation of respiratory intervention. All statistical tests and plots were performed using R version 3.4.2 [18].

Several pre-planned subgroup analyses and sensitivity analyses were completed to further account for confounders beyond multivariable regression. Admission to the ICU and severe hypoxemia are both associated with high mortality in COVID-19 patients [13, 19, 20]. In subgroup analyses, we stratified by ICU status during the respiratory intervention and initial SpO2 at the start of the respiratory intervention (strata of 3% SpO2 descending from 90–93%, as well as binarized SpO2 > 84% or ≤ 84%).

Given the possibility of baseline covariates influencing the probability of receiving NIV or MV, we also performed a sensitivity analysis restricting to propensity score-matched participants. Propensity scores generated with a logistic regression model assessed the probability of receiving NIV versus MV based on the same baseline covariates used in the multivariable regression analyses. Participants were then matched using nearest neighbor matching to produce a 1:1 ratio of propensity-matched NIV to MV participants.

Results

During the study period, 2381 patients were admitted to 5 hospitals in New York City with laboratory-confirmed SARS-CoV-2 infection and 688 hypoxemic patients met the inclusion criteria (Fig. 1). Baseline characteristics of participants are summarized in Table 1. A total of 534 individuals (78%) received NIV and 154 individuals (22%) received MV. Demographics and comorbidities were generally similar between patients with NIV exposure compared to those with MV exposure. The MV group had a higher proportion of males (72 versus 61%) and a greater prevalence of coronary artery disease (15 versus 7%). The mean initial SpO2 for patients in the MV group was 88% (SD = 4.8) and 113 (73%) had an initial SpO2 ≤ 90%; 22 (54%) of those with initial SpO2 > 90% had tachypnea, respiratory distress, and other symptoms of severe pneumonia. COVID-19-related pharmacologic treatments are also described in Table 1. The most common therapies in both groups were azithromycin and hydroxychloroquine.

Mortality

Out of the 688 study participants, 299 (43%) died over the course of respiratory intervention. A total of 128/154 patients (83%) died in the MV group, while 171/534 patients (32%) died in the NV group (unadjusted OR = 10, 95% CI 6.7–17). In the primary analysis, patients on MV had greater adjusted odds of death compared to patients on NIV (OR = 30, 95% CI 16–60; Figs. 2, 3). The mean survival time was 6 days in the MV group and 16 days in the NV group. Characteristics of deceased patients versus patients who survived are described in Table 2. Deceased patients tended to be older and had a higher prevalence of coronary artery disease, diabetes, and hypertension.

Propensity-matched analysis

In the sensitivity analysis, propensity score matches were identified for 100% of the 154 patients in the MV group yielding a total propensity-matched sample of 308 participants. After matching, none of the baseline covariates significantly differed between the MV and NIV groups (Table 1 and Online Additional file 1: Figure S1). Standardized differences in means were less than 0.1 for all variables after propensity matching. In a logistic regression analysis of matched participants with balanced covariates, MV use was associated with elevated odds of death compared to NIV use (OR = 8.0, 95% CI 5.0–15).

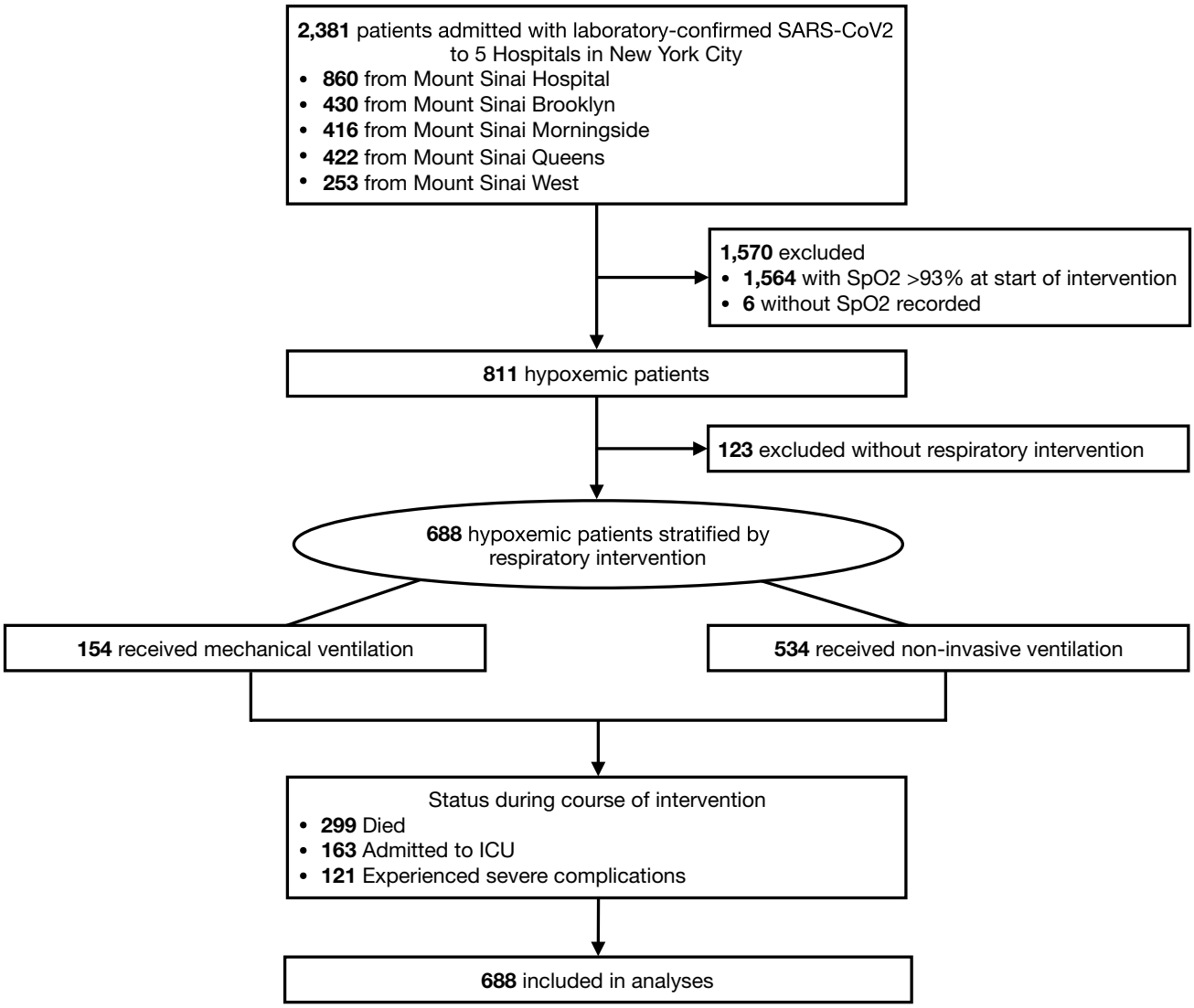

Fig. 1 Patient selection criteria. SpO2, oxygen saturation; severe complications, severe COVID-19-related complications of acute respiratory distress syndrome, shock, arrhythmia, cardiac arrest, acute kidney injury, respiratory failure, or multiple organ dysfunction

Subgroup analyses by ICU and hypoxemia status

Results were similar in all 4 subgroups (Fig. 3). Patients receiving MV had higher mortality than patients receiving NIV under each of the following conditions: patients in the ICU (OR = 15, 95% CI 3.6–85); non-ICU patients (OR = 199, 95% CI 22–3764); moderately hypoxemic patients with initial SpO2 > 84% at the start of the respiratory intervention (OR = 37, 95% CI 18–82); and severely hypoxemic patients with initial SpO2 ≤ 84% at the start of the respiratory intervention (OR = 15, 95% CI 1.9–122). Very high OR and wide CI of death in non-ICU patients receiving MV was due to all 40/40 (100%) non-ICU MV patients having died by 12 days after initiation of respiratory intervention (Online Additional file 1: Figure S2). A summary of the deceased versus survived patients in the ICU and non-ICU groups is provided in Table 2. Non-ICU deceased patients tended to be more female, older, and have a higher prevalence of comorbidities.

Survival trends associated with MV and NIV use differed when stratified by initial SpO2 at the start of the respiratory intervention (Online Additional file 1: Figure S3). For initial SpO2 strata of 90–93% and 87–90%, survival was greater in the NIV group than in the MV group (mean survival 19 versus 7 days and 14 versus 4 days, respectively). For initial SpO2 between 84 and 87%, patients receiving NIV had a non-statistically significant greater survival than patients receiving MV (mean survival 15 versus 8 days). In contrast, there was no difference in survival between NIV and MV groups for the lowest initial

Table 1 Overview of baseline traits in respiratory ventilation groups

Trait	Total study population		Propensity-matched population	
	MV ($n=154$)	NIV ($n=534$)	MV ($n=154$)	NIV ($n=154$)
Male, *n* (%)	111 (72)	326 (61)	111 (72)	110 (71)
Age, mean (SD)	68 (13)	67 (16)	68 (13)	68 (16)
European, *n* (%)	36 (24)	125 (23)	36 (24)	38 (25)
Hispanic, *n* (%)	46 (30)	158 (30)	46 (30)	46 (30)
African, *n* (%)	28 (18)	132 (25)	28 (18)	27 (18)
Asian, *n* (%)	6 (4)	24 (4)	6 (4)	8 (4)
Other, *n* (%)	38 (25)	85 (16)	38 (25)	35 (23)
BMI in kg/m^2, Mean (SD)	31 (8)	29 (7)	31 (8)	31 (8)
Initial SpO2 in %, mean (SD)	88 (5)	90 (4)	88 (4)	88 (5)
Atrial fibrillation, *n* (%)	7 (5)	24 (5)	7 (5)	9 (6)
Asthma, *n* (%)	8 (5)	22 (4)	8 (5)	7 (5)
Coronary artery disease, *n* (%)	23 (15)	38 (7)	23 (15)	21 (14)
Cancer, *n* (%)	4 (3)	21 (4)	4 (3)	5 (3)
Chronic kidney disease, *n* (%)	9 (6)	20 (4)	9 (6)	8 (5)
Chronic obstructive pulmonary disease, *n* (%)	4 (3)	19 (4)	4 (3)	3 (2)
Diabetes, *n* (%)	28 (18)	70 (13)	28 (18)	33 (21)
Heart failure, *n* (%)	14 (9)	24 (5)	14 (9)	16 (10)
Hypertension, *n* (%)	39 (25)	113 (21)	39 (25)	40 (26)
Liver disease, *n* (%)	4 (3)	10 (2)	4 (3)	5 (3)
Stroke, *n* (%)	3 (2)	11 (2)	3 (2)	3 (2)
Azithromycin, *n* (%)	137 (89)	436 (82)	137 (89)	135 (88)
Hydroxychloroquine, *n* (%)	144 (94)	465 (87)	144 (94)	143 (93)
Corticosteroids, *n* (%)	4 (3)	15 (3)	4 (3)	5 (3)
Antivirals, *n* (%)	41 (27)	75 (14)	41 (27)	45 (29)

Other, other ancestry (includes Asian American, Native American, and miscellaneous ancestries); SpO2, oxygen saturation; corticosteroids, includes prednisone and dexamethasone; antivirals, includes lopinavir, ritonavir, and favipiravir

n number, *SD* standard deviation

SpO2 strata of 81–84% and ≤ 81% (mean survival 5 versus 5 days and 3 versus 6 days, respectively).

Secondary outcomes

A higher incidence of severe COVID-19-related symptoms was experienced by patients receiving MV [55/154 (36%)] than patients receiving NIV [66/534 [(12%)] (OR = 4.3, 95% CI 2.7–6.8). In addition, a longer time to discharge occurred in the MV group [mean = 17 days, standard deviation (SD) = 5.0 days] compared to the NIV group (mean = 7.1 days, SD = 4.3 days) ($\beta = 8.7$ days, SE = 0.91 days). Lastly, the final SpO2 level at conclusion of respiratory intervention was lower among those receiving MV (mean = 92%, SD = 6.0%) relative to those receiving NIV (mean = 94%, SD = 3.8%) ($\beta = -1.6\%$, SE = 0.42%).

Discussion

In this retrospective multi-center cohort study, we observed that MV use in hypoxemic patients with SARS-CoV-2 infection was associated with a significantly higher odds of mortality over the course of respiratory intervention compared to NIV use. This outcome was consistent when accounting for differences in demographics, comorbidities, pharmacologic therapies, ICU status, and initial SpO2 level. These preliminary findings form the rationale and conceptual framework for a randomized controlled trial (RCT) to definitively assess the role of NIV in hypoxemic patients with COVID-19.

In clinical practice guidelines from the European Respiratory Society and American Thoracic Society, no recommendations for NIV in acute respiratory failure from pandemic viral illness were issued [21]. This was due to

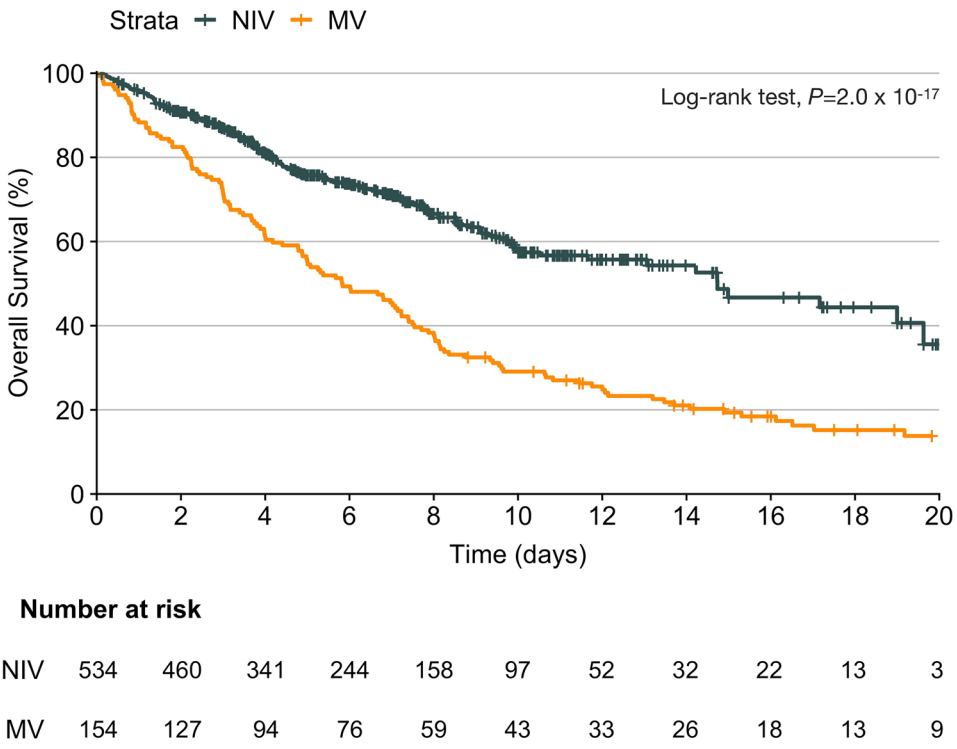

Fig. 2 Survival in mechanically ventilated versus non-invasively ventilated patients. Survival over time in days was assessed up to hospital discharge or death after initiation of respiratory intervention. A total of 128/154 (83%) patients had died in the mechanical ventilation (MV) group and 171/534 (32%) had died in the non-invasive (NIV) group. The mean survival time was 6 days in the MV group and 16 days in the NIV group. Time (days), time in days since the beginning of the respiratory intervention

	n deaths/n patients (%)			
Source	**MV**	**NIV**	**OR (95% CI)**	***P* Value**
Primary analysis	128/154 (83%)	171/534 (32%)	30 (16-60)	1.4×10^{-23}
ICU	88/114 (77%)	24/49 (49%)	15 (3.6-85)	7.0×10^{-4}
Non-ICU	40/40 (100%)	147/485 (30%)	199 (22-3764)	1.4×10^{-11}
SpO2 >84%	94/114 (82%)	132/477 (28%)	37 (18-82)	1.3×10^{-20}
SpO2 ≤84%	34/40 (85%)	39/57 (68%)	15 (1.9-122)	6.3×10^{-3}
Propensity matched	128/154 (83%)	57/154 (37%)	8.0 (5.0-15)	5.9×10^{-15}

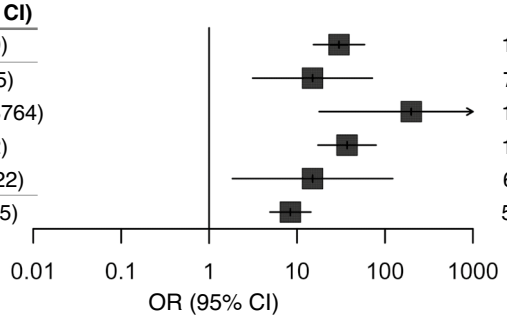

Fig. 3 Association of mechanical ventilation compared to non-invasive ventilation with mortality among hypoxemic patients with COVID-19. Forest plot depicting odds ratio (OR) of death for mechanical ventilation (MV) compared to non-invasive ventilation (NIV). All multivariable regression analyses included covariates of age, sex, ethnicity, BMI, hospital, atrial fibrillation, asthma, coronary artery disease, cancer, chronic kidney disease, chronic obstructive pulmonary disease, diabetes, heart failure, hypertension, liver disease, stroke, azithromycin, hydroxychloroquine, corticosteroids (prednisone, dexamethasone), antivirals (lopinavir, ritonavir, favipiravir), and initial SpO2. Box plots depict the middle 50% estimate (blue box) and corresponding 95% confidence interval (horizontal lines). SpO2, oxygen saturation; n, number; OR (95% CI), adjusted odds ratio with 95% confidence interval; propensity-matched, samples matched with nearest-neighbor matching on probability propensity scores

limited evidence of two retrospective case series studying NIV use in SARS-CoV-1 infection with a small sample size and no controlling of covariates [22, 23]. More recent studies focusing on NIV use in SARS-CoV-2 infection were similarly of limited sample size, did not account for differences in baseline traits, and did not compare effectiveness against conventional MV use [4, 5, 24]. The guidelines ultimately call for further research with carefully selected patients to pave the way for randomized controlled trials to evaluate NIV utility in viral pandemics such as the COVID-19 pandemic. Our study was designed to examine NIV use compared to MV use in reducing mortality associated with COVID-19 and provides preliminary findings that should be tested in an RCT to address this important unmet need in the literature.

The few applications of NIV in COVID-19 reported anecdotally or in the aforementioned studies were made without established criteria for when NIV or MV should be used and

Table 2 Characteristics of patients stratified by survival during respiratory intervention

Trait	Total study population		ICU		Non-ICU	
	Deceased ($n=299$)	Survived ($n=389$)	Deceased ($n=112$)	Survived ($n=51$)	Deceased ($n=187$)	Survived ($n=338$)
Male, *n* (%)	182 (61)	255 (66)	81 (72)	36 (71)	101 (54)	219 (65)
Age, mean (SD)	74 (12)	62 (14)	68 (12)	58 (12)	78 (11)	63 (14)
European, *n* (%)	81 (27)	80 (21)	222 (20)	14 (27)	59 (32)	66 (20)
Hispanic, *n* (%)	77 (26)	127 (33)	32 (29)	16 (31)	45 (24)	111 (33)
African, *n* (%)	70 (23)	90 (23)	25 (22)	11 (22)	45 (24)	79 (23)
Asian, *n* (%)	12 (4)	18 (5)	4 (4)	2 (4)	8 (4)	16 (5)
Other, *n* (%)	59 (20)	74 (19)	29 (26)	8 (16)	30 (16)	66 (20)
BMI in kg/m^2, mean (SD)	29 (8)	30 (7)	31 (8)	31 (7)	28 (7)	29 (7)
Initial SpO2 in %, mean (SD)	88 (5)	90 (3)	88 (4)	89 (5)	88 (5)	90 (3)
Atrial fibrillation, *n* (%)	20 (7)	11 (3)	6 (5)	2 (4)	14 (7)	9 (3)
Asthma, *n* (%)	13 (4)	17 (4)	7 (6)	3 (6)	6 (3)	14 (4)
Coronary artery disease, *n* (%)	39 (13)	22 (6)	15 (13)	4 (8)	24 (13)	18 (5)
Cancer, *n* (%)	12 (4)	13 (3)	5 (4)	0 (0)	7 (3)	13 (4)
Chronic kidney disease, *n* (%)	20 (7)	9 (2)	7 (6)	1 (2)	13 (7)	8 (2)
Chronic obstructive pulmonary disease, *n* (%)	8 (3)	15 (4)	2 (2)	0 (0)	6 (3)	15 (4)
Diabetes, *n* (%)	55 (18)	43 (11)	26 (23)	5 (10)	29 (16)	38 (11)
Heart failure, *n* (%)	20 (7)	18 (5)	8 (7)	3 (6)	12 (6)	15 (4)
Hypertension, *n* (%)	82 (27)	70 (18)	31 (28)	13 (25)	51 (27)	57 (17)
Liver disease, *n* (%)	5 (2)	9 (2)	4 (4)	1 (2)	1 (1)	8 (2)
Stroke, *n* (%)	10 (3)	4 (1)	1 (2)	0 (0)	10 (5)	3 (1)
Azithromycin, *n* (%)	242 (81)	331 (85)	101 (90)	47 (92)	141 (75)	284 (84)
Hydroxychloroquine, *n* (%)	252 (84)	357 (92)	107 (96)	49 (96)	145 (78)	308 (91)
Corticosteroids, *n* (%)	8 (3)	11 (3)	3 (3)	2 (4)	5 (3)	9 (3)
Antivirals, *n* (%)	52 (17)	64 (16)	36 (32)	19 (37)	16 (9)	45 (13)

Other, other ancestry (includes Asian American, Native American, and miscellaneous ancestries); SpO2, oxygen saturation; corticosteroids, includes prednisone and dexamethasone; antivirals, includes lopinavir, ritonavir, tocilizumab, and favipiravir

n number, *SD* standard deviation

which patients may benefit from one modality over the other [12]. In the present study, there was a wide distribution of initial SpO2 at the initiation of MV and NIV ranging from 77–93%, indicating that factors such as availability of ventilators and clinical gestalt were used to decide initiation of a respiratory intervention rather than an empirical framework. This included 135 of the 154 (88%) patients receiving MV who had hypoxemia with initial SpO2 ≤ 90% and/or severe pneumonia as indications for intubation. We investigated whether use of NIV instead of MV was optimal for patients in certain initial SpO2 ranges in a stratified analysis. Survival after initiation of respiratory intervention was higher for NIV than MV when initial SpO2 strata were > 84%, while no difference in survival was observed at initial SpO2 strata ≤ 84% (Online Additional file 1: Figure S2). This is in line with previous studies of non-COVID-19-related acute hypoxemia respiratory failure that have demonstrated improved survival on NIV except in cases of very severe hypoxemia [25, 26]. Among patients with SpO2 ≤ 84%, a greater proportion of patients were deceased in the MV group than in the NIV group (OR = 15; 95% CI 1.9–122) while there was no difference in time to death between the MV and NIV groups (e.g., mean of 5 days in both groups for those with SpO2 between 81–84%).

There were several limitations to the study, the foremost one being its retrospective nature with non-random allotment

of respiratory intervention. We attempted to address this by adjusting for covariates in the primary analysis, performing stratified analyses of ICU status and hypoxemia severity, and conducting a sensitivity analysis of propensity score-matched participants. The propensity-matched analysis revealed an increased OR of mortality associated with MV use compared to NIV use (OR = 8.0, 95% CI 5.0–15), yet the magnitude was less than that of the primary analysis (adjusted OR = 30, 95% CI 16–60) suggesting control of potential confounders. However, this cannot preclude all possible confounding and selection bias that may have occurred. Different times to intervention in the NIV and MV groups [mean (SD) time from admission to intervention, 0.40 (1.4) and 1.6 (3.3) days, respectively] may have introduced further bias. A future study that examines the primary and secondary outcomes of patients on MV versus NIV in an RCT is needed to truly minimize confounding and selection bias.

In addition, the assessment of oxygen saturation was estimated by pulse oximetry. The SpO2 recorded by this method may differ from measured arterial oxygen saturation by ± 4% [27]. Thus, validation of this study's results using measured arterial oxygen saturation would be an important next step. Despite this technical consideration, we affirm that pulse oximetry is readily available at the bedside and could enhance the rapid and appropriate triage of patients with COVID-19 when determining whether to initiate NIV or MV.

We were also unable to examine the temporality of ICD-9- and ICD-10-coded comorbidities and diagnoses of severe COVID-19 symptoms. Time to these events from admission was occasionally inconsistent as providers may have recorded them in the electronic health record after the patient encounter or discharge. Regardless, this limitation was present in both MV and NIV groups, and any measured differences in comorbidities were addressed by multivariable regression and propensity-matching.

Lastly, high mortality occurred in the study population. This may be explained in part by the initial surge of COVID-19 cases during the study period in which critical care resources (e.g., mechanical ventilators, ICU capacity and staff) were in short supply, and knowledge of the disease and its management were limited. However, this presented a unique opportunity for comparing hypoxemic patients who were administered MV versus NIV short of conducting an RCT.

Conclusions

In the present study, we observed that, compared to MV, use of NIV was associated with reduced mortality, decreased severe COVID-19-related symptoms, shorter time to discharge, and less deterioration of SpO2 in patients with COVID-19 who are in the ICU, outside the ICU, and with different severity of hypoxemia. Survival trends associated with MV and NIV use differed based on the severity of hypoxemia, with improved survival for NIV use in patients with milder hypoxemia (initial SpO2 > 84%) and no difference in survival between MV and NIV use in patients with severe hypoxemia (initial SpO2 ≤ 84%). The study's retrospective nature and limitations preclude its application to clinical practice until a prospective follow-up investigation can be made. Further study of NIV use in hypoxemic patients with COVID-19 is warranted, especially in resource-limited clinical settings and during surges of COVID-19 in the community. These data form the conceptual basis for a large RCT to definitively address this timely and critical research question.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s15010-021-01633-6.

Acknowledgements The authors thank all of the nurses, physicians, and healthcare providers who contributed to the care of these patients, as well as the patients and their family members who were affected by the pandemic.

Author contributions ISF conceived the project idea, analyzed the data, conducted the statistical analyses, wrote the initial drafts of the manuscript, created tables, and figures, and finalized the manuscript. SKJ performed the data extraction, assisted with data analysis, and edited the manuscript. IP conceived the project idea, assisted with data analysis, and edited the manuscript. BSG conceived the project idea, assisted with data analysis, and edited the manuscript. GNN conceived the project idea, assisted with data analysis, and edited the manuscript. RD conceived the project idea, assisted with data analysis, and edited the manuscript. All authors critically reviewed the manuscript and approved the final version prior to submission.

Funding IF was supported by T32GM007280 the Medical Scientist Training Program Training Grant from the National Institute of General Medical Sciences of the National Institutes of Health (NIH). RD is supported by R35GM124836 from the National Institute of General Medical Sciences of the NIH, and R01HL155915 and R01HL139865 from the National Heart, Lung, and Blood Institute of the NIH. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Data availability Datasets used and analyzed in the current study can be made available from the corresponding author on reasonable request.

Declarations

Conflict of interest RD reported receiving grants from AstraZeneca, grants, and nonfinancial support from Goldfinch Bio, being a scientific co-founder and equity holder for Pensieve Health and a consultant for Variant Bio. GN reported being a scientific co-founder, consultant, advisory board member, and equity owner of Renalytix AI, a scientific co-founder and equity holder for Pensieve Health, a consultant for Variant Bio, and receiving grants from Goldfinch Bio and personal fees from Renalytix AI, BioVie, Reata, AstraZeneca, and GLG Consulting.

All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Ethical approval The Institutional Review Board of Mount Sinai approved the study.

Consent for publication Not applicable. No individual participant data is reported.

References

1. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA. 2020;323:2052. https://doi.org/10.1001/jama.2020.6775.
2. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in critically ill patients in the Seattle region—case series. N Engl J Med. 2020;382:2012–22. https://doi.org/10.1056/nejmoa2004500.
3. Lim ZJ, Subramaniam A, Reddy MP, Blecher G, Kadam U, Afroz A, et al. Case fatality rates for COVID-19 patients requiring invasive mechanical ventilation: a meta-analysis. Am J Respir Crit Care Med. 2020. https://doi.org/10.1164/rccm.202006-2405oc.
4. Carter C, Aedy H, Notter J. COVID-19 disease: non-invasive ventilation and high frequency nasal oxygenation. Clin Integr Care. 2020;1:100006. https://doi.org/10.1016/j.intcar.2020.100006.
5. Guy T, Créac'hcadec A, Ricordel C, Salé A, Arnouat B, Bizec JL, , et al. High-flow nasal oxygen: a safe, efficient treatment for COVID-19 patients not in an ICU. Eur Respir J. 2020;56:2001154. https://doi.org/10.1183/13993003.01154-2020.
6. Franco C, Facciolongo N, Tonelli R, Dongilli R, Vianello A, Pisani L, et al. Feasibility and clinical impact of out-of-ICU non-invasive respiratory support in patients with COVID-19-related pneumonia. Eur Respir J. 2020;56:2002130. https://doi.org/10.1183/13993003.02130-2020.
7. Ãamendys-Silva SA. Respiratory support for patients with COVID-19 infection. Lancet Respir. 2020;8:e18. https://doi.org/10.1016/S2213-2600(20)30110-7.
8. Tobin MJ, Laghi F, Jubran A. Why COVID-19 silent hypoxemia is baffling to physicians. Am J Respir Crit Care Med. 2020;202:356–60. https://doi.org/10.1164/rccm.202006-2157CP.
9. Lari A, Alherz M, Nouri A, Botras L, Taqi S. Caution against precaution: a case report on silent hypoxia in COVID-19. Ann Med Surg. 2020;60:301–3. https://doi.org/10.1016/j.amsu.2020.11.007.
10. Dar M, Swamy L, Gavin D, Theodore A. Mechanical ventilation supply and options for the COVID-19 pandemic: leveraging all available resources for a limited resource in a crisis. Ann Am Thorac Soc. 2020. https://doi.org/10.1513/annalsats.202004-317cme.
11. Chillag KL, Lee LM. Synergistic disparities and public health mitigation of COVID-19 in the rural United States. J Bioeth Inq. 2020;17:649–56. https://doi.org/10.1007/s11673-020-10049-0.
12. Wunsch H. Mechanical ventilation in COVID-19: interpreting the current epidemiology. Am J Respir Crit Care Med. 2020;202:1–4. https://doi.org/10.1164/rccm.202004-1385ED.
13. Xie J, Covassin N, Fan Z, Singh P, Gao W, Li G, et al. Association between hypoxemia and mortality in patients with COVID-19. Mayo Clin Proc. 2020;95:1138–47. https://doi.org/10.1016/j.mayocp.2020.04.006.
14. Voshaar T, Stais P, Köhler D, Dellweg D. Conservative management of COVID-19 associated hypoxaemia. ERJ Open Res. 2021;7:00026–2021. https://doi.org/10.1183/23120541.00026-2021.
15. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: Interim guidance. World Health Organization. 2020;16:9–26. https://doi.org/10.15557/PiMR.2020.0003.
16. Nadkarni GN, Lala A, Bagiella E, Chang HL, Moreno PR, Pujadas E, et al. Anticoagulation, bleeding, mortality, and pathology in hospitalized patients with COVID-19. J Am Coll Cardiol. 2020;76:1815–26. https://doi.org/10.1016/j.jacc.2020.08.041.
17. Somani SS, Richter F, Fuster V, De Freitas JK, Naik N, Sigel K, et al. Characterization of patients who return to hospital following discharge from hospitalization for COVID-19. J Gen Intern Med. 2020;35:2838–44. https://doi.org/10.1007/s11606-020-06120-6.
18. R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2018. https://www.R-project.org.
19. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy. Italy JAMA Intern Med. 2020;180:1345–55. https://doi.org/10.1001/jamainternmed.2020.3539.
20. Armstrong RA, Kane AD, Cook TM. Outcomes from intensive care in patients with COVID-19: a systematic review and meta-analysis of observational studies. Anaesthesia. 2020;75:1340–9. https://doi.org/10.1111/anae.15201.
21. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure task force report ERS/ATS Guidelines. Eur Respir J. 2017;50:1602426. https://doi.org/10.1183/13993003.02426-2016.
22. Cheung TMT, Yam LYC, So LKY, Lau ACW, Poon E, Kong BMH, et al. Effectiveness of noninvasive positive pressure ventilation in the treatment of acute respiratory failure in severe acute respiratory syndrome. Chest. 2004;126:845–50. https://doi.org/10.1378/chest.126.3.845.
23. Han F, Jiang YY, Zheng JH, Gao ZC, He QY. Noninvasive positive pressure ventilation treatment for acute respiratory failure in SARS. Sleep Breath. 2004;8:97–106. https://doi.org/10.1055/s-2004-829634.
24. Sivaloganathan AA, Nasim-Mohi M, Brown MM, Abdul N, Jackson A, Fletcher SV, et al. Noninvasive ventilation for COVID-19-associated acute hypoxaemic respiratory failure: experience from a single centre. Br J Anaesth. 2020;125:e368–71. https://doi.org/10.1016/j.bja.2020.07.008.
25. Ferreyro BL, Angriman F, Munshi L, Del Sorbo L, Ferguson ND, Rochwerg B, et al. Association of noninvasive oxygenation strategies with all-cause mortality in adults with acute hypoxemic respiratory failure: a systematic review and meta-analysis. JAMA. 2020;324:57–67. https://doi.org/10.1001/jama.2020.9524.
26. Patel BK, Kress JP, Hall JB. Alternatives to invasive ventilation in the COVID-19 pandemic. JAMA. 2020;324:43–4. https://doi.org/10.1001/jama.2020.9611.
27. Tobin MJ. Basing respiratory management of COVID-19 on physiological principles. Am J Respir Crit Care Med. 2020;201:1319–20. https://doi.org/10.1164/rccm.202004-1076ED.