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Acute Respiratory Failure From Early Pandemic COVID-19:

Noninvasive Respiratory Support vs Mechanical Ventilation

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Abstract

BACKGROUND: The optimal strategy for initial respiratory support in patients with respiratory failure associated with COVID-19 is unclear, and the initial strategy may affect outcomes.

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RESEARCH QUESTION: Which initial respiratory support strategy is associated with improved outcomes in patients with COVID-19 with acute respiratory failure?

STUDY DESIGN AND METHODS: All patients with COVID-19 requiring respiratory support and admitted to a large health care network were eligible for inclusion. We compared patients treated initially with noninvasive respiratory support (NIRS; noninvasive positive pressure ventilation by facemask or high-flow nasal oxygen) with patients treated initially with invasive mechanical ventilation (IMV). The primary outcome was time to in-hospital death analyzed using an inverse probability of treatment weighted Cox model adjusted for potential confounders. Secondary outcomes included unweighted and weighted assessments of mortality, lengths of stay (ICU and hospital), and time to intubation.

RESULTS: Nearly one-half of the 2,354 patients (47%) who met inclusion criteria received IMV first, and 53% received initial NIRS. Overall, in-hospital mortality was 38% (37% for IMV and 39% for NIRS). Initial NIRS was associated with an increased hazard of death compared with initial IMV (hazard ratio, 1.42; 95% CI, 1.03-1.94), but also an increased hazard of leaving the hospital sooner that waned with time (noninvasive support by time interaction: hazard ratio, 0.97; 95% CI, 0.95-0.98).

INTERPRETATION: Patients with COVID-19 with acute hypoxemic respiratory failure initially treated with NIRS showed an increased hazard of in-hospital death.

Keywords

COVID-19; high-flow nasal oxygen; mechanical ventilation; noninvasive respiratory support; respiratory failure

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The optimal management strategy for patients with respiratory failure resulting from SARS-CoV-2 infection has undergone particular scrutiny. Intense discussion occurred in the published literature and on social media, particularly early in the pandemic. High failure rates with noninvasive positive pressure ventilation (NIPPV) during the severe acute respiratory syndrome coronavirus outbreak in 2003,[1] concerns over aerosol transmission with noninvasive support strategies,[2-8] proposed physiologic novelty of COVID-19,[9-18] impending ventilator shortages,[19-21] and the high mortality initially reported with invasive mechanical ventilation (IMV)[22,23] all influenced early discussions over timing of intubation and the usefulness of noninvasive strategies.

Publications evaluating noninvasive respiratory support (NIRS)—NIPPV or high-flow nasal oxygen (HFNO)—for patients with COVID-19 report disparate outcomes. Importantly, studies compared noninvasive strategies with each other or with conventional oxygen therapy, but ignored the comparison with IMV, which could minimize or eliminate patient self-inflicted lung injury.[24] We sought to evaluate any differences early in the pandemic between invasive and noninvasive strategies in patients with COVID-19 with acute hypoxemic respiratory failure.

Study Design and Methods

Study Design, Setting, and Participants

This was a retrospective cohort study using de-identified structured clinical data generated from the electronic health record (Cerner Corporation) of 26 hospitals across a large health care network. Data were extracted for all adult patients (≥ 18 years of age) admitted for acute respiratory failure with suspected (before availability of confirmatory tests) or confirmed COVID-19 between January 1, 2020, and September 30, 2020. We used a phenotyping algorithm[25] to classify patients based on the sequence of respiratory support: (1) IMV only, (2) NIPPV only, (3) HFNO only, (4) NIPPV requiring subsequent IMV, (5) HFNO requiring subsequent IMV, (6) IMV extubated to NIPPV, (7) IMV extubated to HFNO, and (8) evidence of all three treatments but unclear ordering. The NIRS cohort included patients initially treated with any NIRS method (phenotypes 2, 3, 4, and 5) and was compared with the initial IMV cohort (phenotypes 1, 6, and 7). Subsequent analyses separated NIPPV and HFNO groups and included pairwise comparisons of initial IMV, NIPPV, and HFNO groups. We considered both CPAP and bilevel positive airway pressure as NIPPV, because both are provided using a noninvasive ventilator and not a Boussignac device. Patients receiving conventional oxygen therapy only were excluded. Transfers were identified as visits < 24 h apart and were combined into a single record. Admissions with nonsensical time courses (eg, treatment assignment after hospital discharge) were excluded from relevant analyses. This work adheres to the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines and was approved by the university (Identifier: 1907780973) and health network (Identifier: 483-20-0018) institutional review boards.

Treatment Assignment

All patients in the eight phenotypes were included in the analyses given that criteria for NIRS, NIRS method, and intubation timing were determined clinically, which is highly heuristic, and that objective criteria for intubation are unreliable as a result.[26] We included the cohort with unclear treatment ordering because they were part of the target population and excluding them potentially results in biased estimates. For the 326 patients of phenotype 8 (three treatments but unclear ordering), the first treatment was imputed using multiple imputation by chained equations (MICE).[27,28] We estimated the propensity for each method using generalized boosted models and used inverse probability of treatment weighting to account for nonrandom treatment assignment.[29] The variables for propensity score estimation included age; BMI; sex; ethnicity (non-Hispanic, Hispanic); race (White, all others); respiratory rate and oxygen saturation to F_{IO_2} ratio immediately before first treatment; the comorbidities heart failure, COPD, neoplasm or immunosuppression, and chronic liver disease; vasopressor infusion before first treatment; first treatment location (ED, ICU, stepdown, medical or surgical unit); hospital; season of hospital admission (spring [before April 1, 2020], summer [April 1-July 1, 2020], autumn [on or after July 1, 2020]); and either hours from hospital admission to first treatment (for all models except the time to ICU discharge alive models) or hours from ICU admission to first treatment (for time to ICU discharge alive models only), transformed via the Box-Cox method with negatives.[30] Hospitals with fewer than 10 observations were grouped together. The same

variables additionally were included in Cox models to improve balance between groups further. Sample propensity score and covariate balance information are given in e-Tables 1 and 2 and e-Figures 1 and 2.

Outcomes and Data Analysis

The primary outcome was time to in-hospital death. We fit a cause-specific Cox model from first treatment initiation to death with hospital discharge considered a competing event. We conducted a sensitivity analysis excluding the patients with unclear treatment ordering. Because multiple potential outcomes exist—(1) death, (2) discharge alive (from hospital or ICU), (3) remain hospitalized, and (4) intubation (if receiving NIRS)—we modeled discharge alive and intubation with three additional models. First, we fit a cause-specific hazard model for time to hospital discharge alive with death as a competing event where time zero (t_0) was time of first treatment initiation, and a planned sensitivity analysis with t_0 as time of hospital entrance. Second, we fit a cause-specific hazard model for time-to-ICU discharge alive (from ICU admission) with in-ICU death as a competing event. Only visits with an ICU stay were included in the time to ICU discharge model, thus by nature excluding ICU-level patients outside of the ICU. The key predictor in the above models was initial treatment (IMV vs NIRS), and a series of secondary models separated NIRS into NIPPV and HFNO. For all Cox cause-specific hazard models, we estimated cumulative incidence curves to understand event probability accumulation, because hazard ratios (HRs) and relative probability estimates do not always pair in the presence of competing events.[31] We estimated cumulative incidence curves (one per imputed data set) for a variety of combinations of factors. Third, we conducted a competing risks analysis for time-to-intubation with death as a competing event and censoring occurring at hospital discharge. Only patients receiving NIRS with known time to event (96.3% of records) were included. The competing risks analysis used a modification of Gray's test that incorporates inverse probability of treatment weighting.[32] Statistical significance was judged via the median *P* value approach.[33] Planned competing risks sensitivity analyses were performed to assess preprocessing and analysis decisions (e-Table 3). Example cumulative incidence curves across sensitivity analyses are shown in e-Figure 3.

We assessed if the proportional hazard assumption was violated in the Cox models by including an interaction of time by first treatment. If the interaction (or either interaction in the models that split NIRS into NIPPV and HFNO) was statistically significant at $\alpha = 0.05$, we report the interaction model; otherwise, we report the proportional hazards model. We analyzed NIRS vs IMV differences in unweighted outcomes of mortality, intubation rate, duration of mechanical ventilation in patients for whom initial NIRS failed, length of hospital stay, and ICU-free days using the Fisher exact and Kruskal-Wallis rank sum tests where appropriate.

Data preprocessing is described in detail in e-Appendix 1. As a retrospective study based on routinely collected electonic health record data, we expected the extent of observed data to vary among variables.[34-36] Missing data were handled by using MICE. For each noncompeting risks analysis with missing data, we created 50 imputed data sets using all variables in the propensity score, the Nelson-Aalen estimate of the available time to

event data, the time to event itself, and event information (eg, in-hospital death, hospital discharge alive, ICU discharge alive). Age, BMI, oxygen saturation to F_{IO_2} ratio, the transformed time from hospital admission (or ICU admission) to first treatment, respiratory rate, time to event, and the Nelson-Aalen estimate of the time to event were imputed via predictive mean matching. Sex, ethnicity, race, the outcome event, season, first treatment location, and first treatment were imputed with logistic regression (two-category variables) or multinomial log-linear models via neural networks (more than two category variables) as appropriate. Raw time to event was imputed, but was not used to predict other variables in the MICE algorithm. Instead, for the Cox models and some competing risk models, temporal information was used in the prediction of other missing values via the Nelson-Aalen estimate. For the competing risk models using the median *P* value inference approach, no outcome information was allowed to predict other variables in the MICE algorithm. We estimated propensity scores for each imputed data set separately. For the Cox models, the propensity scores from a specific imputed data set were used for inverse probability of treatment weighting for that data set,[37] and results were combined using Rubin's rules. For the competing risks analyses, the propensity scores from each imputed data set were handled differently depending on the inference approach. See e-Appendix 1 for further details. All data preprocessing and statistical analyses were carried out using R version 4.0.4 software (R Foundation for Statistical Computing)[38] and were included the following packages: twang,[34] survival,[39,40] survminer,[41] MICE,[27] xtable,[42] and tidyverse.[43]

Results

Two thousand three hundred fifty-four patients with COVID-19 met the inclusion criteria. Demographics for phenotype 8 are reported separately because treatment assignments may have varied between imputed data sets (e-Table 4). Of the 2,028 patients reliably classified, IMV was used as the first therapy in 947 patients (47%) and NIRS was used as the first therapy in 1,081 patients (53%) (Fig 1, Table 1). Of those receiving NIRS, 811 patients (75%) received NIPPV first and 270 patients (25%) received HFNO first (e-Table 5). Larger hospitals disproportionately used initial NIPPV (large hospitals, 81% [433/536]; medium hospitals, 70% [346/495]; and small hospitals, 64% [32/50]) (Table 1), with differences both between hospitals (e-Fig 4) and over time (e-Fig 5).

All-cause in-hospital mortality was 38%. For those receiving IMV first, mortality was 37%. For those treated with NIRS first and who never required intubation, mortality was 29%, but rose to 60% for those who required intubation. Also an imbalance in mortality rates was identified between NIPPV and HFNO (e-Table 6). Intubation rates for those treated with HFNO and NIPPV were 32% (87/270) and 33% (268/811), respectively.

NIRS vs IMV

All cause-specific Cox modeling results are presented in Table 2.[44] Initial NIRS was associated with an increased hazard of in-hospital death (HR, 1.42; 95% CI, 1.03-1.94), with no significant interaction of treatment and time (e-Table 7, e-Fig 6). The sensitivity analysis on only patients with clear treatment ordering was consistent, but not statistically significant (HR, 1.33; 95% CI, 0.92-1.94) (e-Table 8, e-Fig 7). Initial NIRS also was

associated with an early increased hazard of leaving the hospital alive that waned with time, eventually reversed, and later was associated with a decreased hazard of leaving the hospital alive (interaction HR, 0.97; 95% CI, 0.95-0.98), (Fig 2, e-Table 9, e-Fig 8). The sensitivity analysis with t_0 as hospital admission was similar (e-Table 10, e-Fig 9). A similar pattern was found between initial NIRS and initial IMV in the time to ICU discharge alive (e-Table 11, e-Fig 10). Initial NIRS was associated with an increased hazard of discharge alive from the ICU very briefly early on, but this HR decreased over time because of a statistically significant interaction between treatment and time (interaction HR, 0.989; 95% CI, 0.97-1.00), resulting in no significant differences between noninvasive and invasive initial support, then eventually reversing direction.

HFNO vs NIPPV vs IMV

HFNO (HR, 2.19; 95% CI, 1.57-3.04), but not NIPPV (HR, 1.32; 95% CI, 0.96-1.83), was associated with an increased hazard of in-hospital mortality compared with IMV, and HFNO showed an increased hazard of in-hospital death compared with NIPPV (HR, 1.66; 95% CI, 1.31-2.10) (Table 2, e-Table 12, e-Fig 11). The interactions of time and both NIPPV and HFNO were not statistically significant. The sensitivity analysis for patients with clear treatment ordering did show a statistically significant interaction between time and HFNO (HR, 1.05; 95% CI, 1.02-1.08), but not between time and NIPPV (HR, 1.01; 95% CI, 0.98-1.03) (e-Table 13, e-Fig 12). Consistent with the all-patient model, an increased hazard of death was found for HFNO after a brief initial lack of difference between HFNO and both IMV and NIPPV, and the hazard for NIPPV did not differ from that of IMV.

For time to hospital discharge alive, a significant interaction was found between treatment and time for both HFNO (HR, 0.96; 95% CI, 0.94-0.99) and NIPPV (HR, 0.99; 95% CI, 0.97-1.00) (e-Table 14, e-Fig 13). Increased hazards of discharge alive for both HFNO and NIPPV compared with IMV were found that decreased over time, but at different rates (HFNO faster, NIPPV slower) (Fig 3). This resulted in no significant differences between NIPPV and IMV at later time points, but a decreased hazard of discharge alive for HFNO compared with IMV. The sensitivity analysis with t_0 as hospital admission was consistent, showing the interaction between time and HFNO as statistically significant (HR, 0.98; 95% CI, 0.96-1.00), the interaction between time and NIPPV is not statistically significant (HR, 0.99; 95% CI, 0.98-1.00), and the overall pattern of effects over time quite similar, except for no significant difference between HFNO and IMV in the hazard of discharge alive at later time points (e-Table 15, e-Fig 14).

Initial NIPPV was associated with a higher hazard of ICU discharge alive than initial HFNO (HR, 1.85; 95% CI, 1.20-2.86), but neither was significantly different than IMV (NIPPV: HR, 1.27; 95% CI, 1.00-1.62; HFNO: HR, 0.69; 95% CI, 0.45-1.06) (e-Table 16, e-Fig 15). No significant interaction was found between time and treatment for time to ICU discharge alive. Patients who started on HFNO first and were intubated were more likely to be intubated sooner than those who started on NIPPV ($P < .001$). All competing risk sensitivity analyses showed the same pattern and also were statistically significant ($P < .001$ for all) (e-Table 3, e-Fig 3).

Discussion

Our results show that early in the pandemic, initial NIRS showed both positive and negative consequences. Patients supported first by NIRS were more likely to experience in-hospital death compared with those intubated first. However, those same patients also experienced a greater probability of being discharged alive early on, with the probability decreasing and eventually reversing direction over time. In essence, patients initially treated noninvasively showed a higher probability of both discharge alive and death in the first month or so with little difference later. We found more intricate trends when exploring potential differences between the NIRS methods. The probability of hospital discharge alive was higher for HFNO than for IMV, but the association was temporal (waned and then reversed), whereas the probability of in-hospital death was consistently higher for HFNO than for IMV. Yet, patients treated first with NIPPV consistently were more likely to be discharged alive and were more likely to die only in the first few weeks. The opposing effects of HFNO and NIPPV on the hazard of death and the greater number of patients receiving initial NIPPV versus initial HFNO potentially explain the overall lack of difference when they are compared with patients receiving initial IMV and patients with unclear treatment ordering are left out of the analysis. These results are hypothesis generating and require further exploration.

These results offer several important contributions. Some studies of NIRS in patients with COVID-19 report improved outcomes with HFNO compared with conventional oxygen therapy[45-47] or to NIPPV,[48] whereas others report improved outcomes with NIPPV compared with conventional oxygen therapy[49] or to HFNO.[50] Yet, other studies report no difference in outcomes with NIRS compared with conventional oxygen therapy[47,49,51-53] or with each other.[50,51,54-56] None of these studies use IMV as a comparison, and instead use intubation as the primary outcome either alone or in composite with mortality.[45-51,54,57,58] We found that IMV as a comparator intervention may have been the optimal choice in the early pandemic, although it was not without its limitations.

Most studies are limited to patients admitted to the ICU, which carries inherent selection bias and confounding potentially reflected as higher intubation rates of around 50%. We included all patients in the primary outcome, regardless of location, because many patients were cared for outside of the physical ICU location or the ICU service because of pandemic-strained resources. Additionally, studies that censor death at 28 days likely miss important comparisons that occur after 28 days, given the prolonged hospital course of many patients with COVID-19.

We found that the benefit of leaving the hospital alive has a relationship with time. Several potential explanations for this are possible. First, NIRS cohorts were classified by a phenotyping algorithm based on the first therapy, but could have crossed over between NIRS methods at any point with or without intubation. Crossover in those patients requires NIRS failing twice before intubation. Second, intubation could have been delayed for various reasons at the cost of worsening acute lung injury that may have benefitted from lung protective ventilation. Gershengorn et al[58] found similar results in that the overall 46% failure rate on HFNO evolved from a decreased odds of failure for those receiving HFNO

for a short time to an increased odds of failure for those receiving HFNO for longer periods. Similar findings were reported with NIPPV, which reduced mortality only in patients with short hospital stays, but was associated with higher mortality in those hospitalized longer than 7 days.[59]

Several issues should be considered when generalizing and interpreting data on NIRS and IMV in patients with COVID-19. Early in the pandemic, early intubation often was preferred to avoid aerosol exposure to staff and based on the high failure rates of NIPPV during the severe acute respiratory syndrome epidemic in 2003. This was followed by a high mortality reported in patients receiving mechanical ventilation,[22] and debate over the physiologic features seen in COVID-19 contributed to variability in mechanical ventilation (eg, high tidal volumes or alternative ventilator modes) or an avoidance of intubation altogether.[60-65] Simultaneously, pharmacologic treatments evolved over time, especially during the duration of this study,[66] including convalescent plasma,[67-69] corticosteroids,[70-74] interleukin[75-82] and janus kinase[83-85] inhibitors, antivirals,[86-89] hydroxychloroquine,[86,90,91] and anticoagulation strategies.[92-94] Finally, patient surges[95] and surge capacity almost certainly contributed to outcomes as more patients were managed outside of traditional ICUs and facilities were faced with impending ventilator shortages, staffing ratio changes, and increases in traveling staff. However, these results are hypothesis generating for patients with non-COVID-19 ARDS, for whom NIPPV has been shown in some studies to be associated with higher mortality than IMV.[96]

Our study also has important limitations. Because our data are limited to patients in 2020, the evolution of COVID-19 management may limit generalizability and potentially may confound treatment assignment not accounted for in our propensity models. Clinical care was not protocolized, and important confounding differences were likely among treatment assignments, settings, and failure determination among HFNO (eg, flow rates), NIPPV (eg, pressures), and IMV (eg, modes and settings). As our e-value calculations showed, it is possible that unmeasured confounders associated with both initial treatment and outcomes at small to moderate minimum risk ratio levels of between 1.1 and 3.4 could nullify the results, indicating that additional research is needed in this area. Further, results are based on the first assigned therapy, and symptom onset time is not available in our data set. Thus, crossover (and imbalanced crossover) and symptom duration may confound the findings. Also some necessary assumptions and simplifications were made based on the nature of observational data sets from electronic health records, such as considering only the first hospital visit requiring respiratory support. If two visits for the same patient were fewer than 24 h apart, we assumed that a hospital transfer occurred and combined these records, yet we had no way to identify patients transferred from outside the health system. We attempted to control for confounding by inverse probability for treatment assignment weighting, further adjusting for potential confounders in the Cox models, and by a competing risks analysis in which death and intubation were competing events. Additionally, some patients showed evidence of all three treatments, but no clear treatment ordering, for which we performed sensitivity analyses to assess how dependent our results are on our specific inclusion, exclusion, or imputation decisions. Finally, end-of-life issues during this time were complex and may confound these results. Despite these limitations, our results still

provide a high-level overview of outcomes among respiratory support methods that were applied pragmatically in the early pandemic across a large health care network.

Interpretation

We found that in the early pandemic, patients intubated without a trial of NIRS showed a lower probability of both in-hospital death and hospital discharge alive up to 1 to 2 months. Studies are needed identifying optimal patients for each NIRS method and accurate early prediction of failure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS:

HFNO	high-flow nasal oxygen
HR	hazard ratio
IMV	invasive mechanical ventilation
MICE	multiple imputation by chained equations
NIPPV	noninvasive positive pressure ventilation
NIRS	noninvasive respiratory support
SpO_2	oxygen saturation

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Take-home Points

Study Question:

What are the outcomes in patients with COVID-19 associated acute respiratory failure early in the pandemic when supported initially by noninvasive respiratory support (NIRS) compared to invasive mechanical ventilation?

Results:

NIRS was associated with both an increased hazard of death and also an increased probability of early hospital discharge alive.

Interpretation:

NIRS presented both positive and negative consequences early in the COVID-19 pandemic, both increasing the risk of death and the probability of early discharge alive.

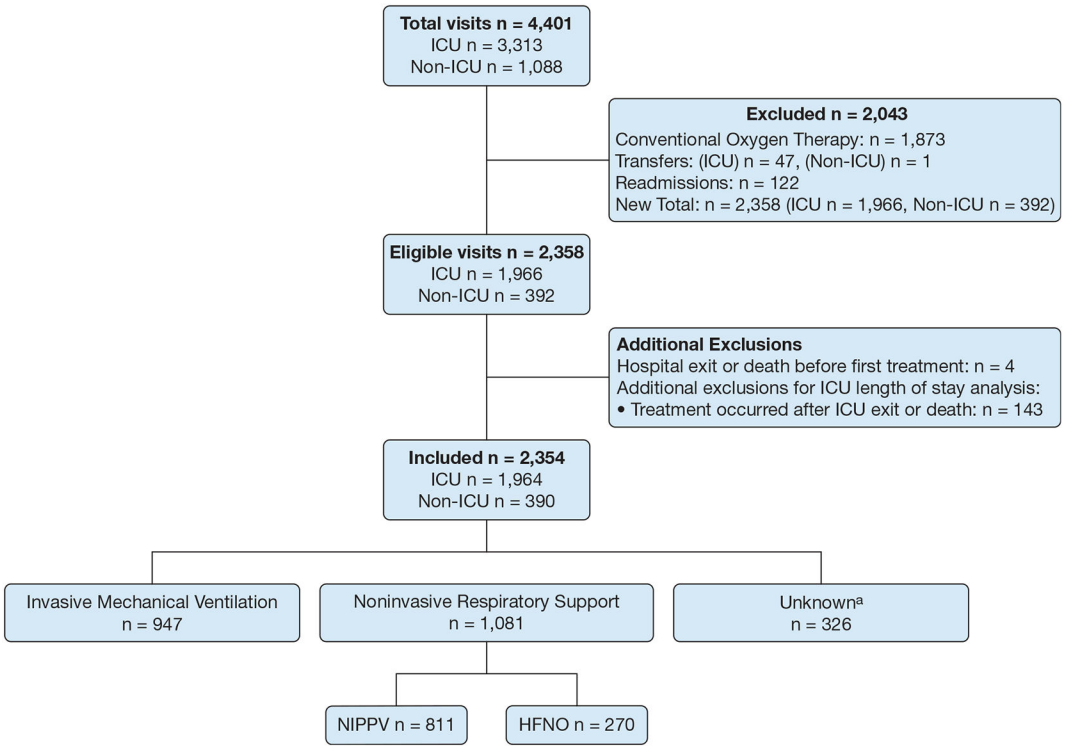

Figure 1 –.

Strengthening the Reporting of Observational Studies in Epidemiology Statement flow diagram. Eligible visits are associated with patients ≥ 18 years of age who were admitted for acute respiratory failure and had either suspected or confirmed COVID-19 identified between January 1, 2020, and September 30, 2020, received invasive mechanical ventilation or noninvasive respiratory support, and for whom this was the first visit of this type in that period. Three hundred twenty-six participants had evidence of high-flow nasal oxygen, noninvasive positive pressure ventilation, and invasive mechanical ventilation, but were unable to be classified reliably by the phenotyping algorithm because of nonsensical time stamps for timing of therapies. See text and e-Appendix 1 for further description and demographics of this group. “Additional exclusions” includes four participants who were excluded because of nonsensical hospital discharge time stamps and an additional group of patients excluded only from the model assessing time to ICU exit. HFNO = high-flow nasal oxygen; NIPPV = noninvasive positive pressure ventilation.

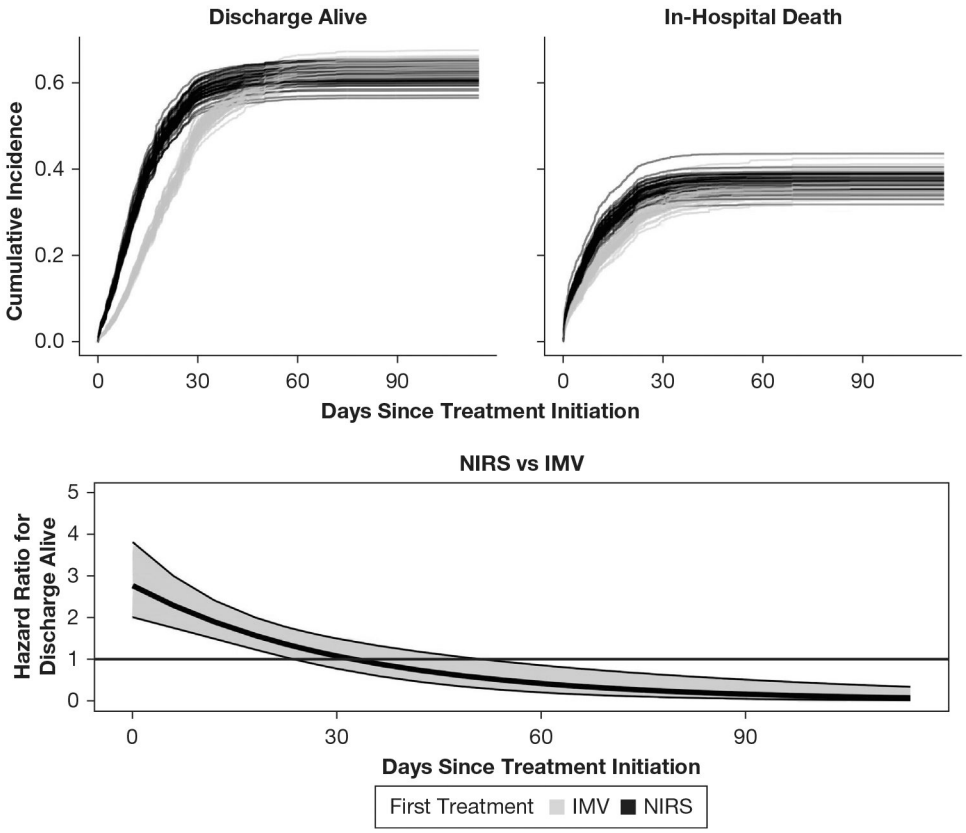

Figure 2 –.

A, B, Graphs showing model-estimated cumulative incidence curves for NIRS vs IMV for hospital discharge alive (A) and in-hospital death (B) for the following covariate values: female sex, not Hispanic or Latino, White race, hospital A, summer hospital admission, and continuous covariates set at their median or most frequent values (age, 63 years; SpO_2 to FIO_2 ratio, 100; respiratory rate, 22 breaths/min; BMI, 31.69 kg/m^2; transformed hours from hospital admission to first treatment, 6.02; vasopressor before treatment, no; heart failure, no; COPD, no; neoplasm or immunosuppression, no; chronic liver disease, no; first treatment location type, ICU). Each imputed data set generates a pair of curves (one for IMV, one for NIRS). C, Estimated time-varying hospital discharge alive hazard ratios for NIRS vs IMV with pointwise 95% CIs. Estimates show the probabilities of being discharged alive for NIRS and IMV trending together around 45 to 60 days and the corresponding probabilities for in-hospital death trending together around 30 to 60 days, depending on the specific covariate combination. IMV = invasive mechanical ventilation; NIRS = noninvasive respiratory support; Spo_2= oxygen saturation.

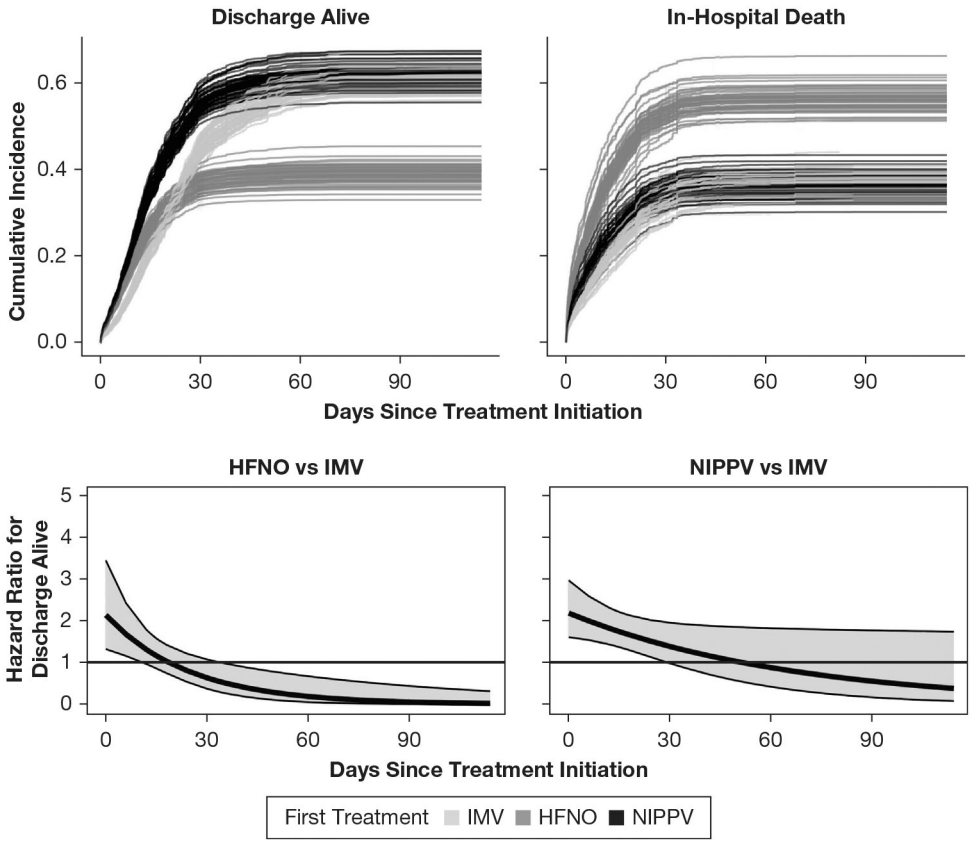

Figure 3 –.

A, B, Graphs showing model-estimated cumulative incidence curves for NIPPV, HFNO, and IMV for hospital discharge alive (A) and in-hospital death (B)for the following covariate values: female sex, not Hispanic or Latino, White race, hospital A, summer hospital admission, and continuous covariates set at their median or most frequent values (age, 63 years; SpO_2 to FIO_2, 100; respiratory rate, 22 breaths/min; BMI, 31.69 kg/m^2; transformed hours from hospital admission to first treatment, 6.02; vasopressor before treatment, no; heart failure, no; COPD, no; neoplasm or immunosuppression, no; chronic liver disease, no; first treatment location type, ICU). Each imputed data set generates a triple of curves (one for IMV, HFNO, and NIPPV). C, D, Estimated time-varying hospital discharge alive hazard ratios for HFNO vs IMV (C) and NIPPV vs IMV (D) with pointwise 95% CIs. Patients initially treated with either noninvasive method showed a higher probability of in-hospital death and a higher probability of discharge alive early on. However, the hospital discharge alive hazard ratio of HFNO to IMV decreased to 1 around 18 days and reversed direction starting at around 35 days; the hazard ratio of NIPPV to IMV decreased more slowly, reaching 1 at around 50 days, with no statistically significant difference afterward. The probability of discharge alive for NIPPV remained greater than that for IMV for about 2 months, at which point they leveled out. However, for HFNO, the probability of discharge alive crossed to become less likely than for IMV around day 23, depending on the specific covariate combination. The cumulative incidence curves for in-hospital death showed consistently higher probabilities of death for HFNO compared with IMV. The probability of in-hospital death for NIPPV was only a bit higher than or about the same as

that for IMV until around day 30, at which point the probability of death for IMV became about level with NIPPV. HFNO = high-flow nasal oxygen; IMV = invasive mechanical ventilation; NIPPV = noninvasive positive pressure ventilation; SpO_2 = oxygen saturation.

TABLE 1]

Demographics

Measure	Invasive Mechanical Ventilation	Noninvasive Respiratory Support	Total
No. of patients (%)	947 (47)	1,081 (53)	2,028
Sex			
Male	555 (59)	624 (58)	1,179 (58)
Female	392 (41)	457 (42)	849 (42)
Age, y	60 (49-69)	65 (53-76)	63 (51-73)
BMI, kg/m^2	31.43 (26.57-37.74)	31.97 (26.63-38.31)	31.64 (26.58-37.97)
Ethnicity[a]			
Not Hispanic or Latino	537 (59)	643 (60)	1,180 (60)
Hispanic or Latino	380 (41)	423 (40)	803 (40)
Race[a]			
White	652 (71)	851 (80)	1,503 (76)
Black or African American	43 (5)	55 (5)	98 (5)
Asian/Native Hawaiian/other Pacific Islander	11 (1)	24 (2)	35 (2)
American Indian or Alaska Native	136 (15)	77 (7)	213 (11)
Other	72 (8)	59 (6)	131 (7)
Hospital size[b]			
Small	21 (2)	50 (5)	71 (4)
Medium	329 (35)	495 (46)	824 (41)
Large	597 (63)	536 (50)	1,133 (56)
APACHE IVa score on admission	67 (51-90)	57 (45-74)	63 (48-83)
Vital signs on treatment assignment			
Heart rate, beats/min	96 (78-112)	84 (70-98)	89 (74-105)
BP, mm Hg			
Systolic	120 (103-142)	125 (111-141)	123 (108-141)
Diastolic	68 (59-80)	72 (64-80)	71 (61-80)
SpO_2, %	96 (93-99)	93 (90-96)	95 (91-98)
Oxygen flow rate, L	15 (15-50)	15 (12.25-40)	15 (15-40)

Measure	Invasive Mechanical Ventilation	Noninvasive Respiratory Support	Total
FIO_2, %[c]	100 (60-100)	80 (50-100)	90 (60-100)
Spo_2 to FIO_2 ratio	100 (95-152.08)	121.25 (93-188)	104.44 (94-166.67)
Temperature, ° C	37 (36.6-37)	37 (36.9-37)	37 (36.8-37)
Respiratory rate, breaths/min	22 (0-26)	23 (19-30)	22 (18-28)
Comorbidities[d]			
Diabetes	513 (54)	617 (57)	1,130 (56)
Chronic kidney disease	226 (24)	223 (21)	449 (22)
Heart failure	203 (21)	224 (21)	427 (21)
Hypertension	663 (70)	767 (71)	1,430 (71)
Chronic liver disease	182 (19)	132 (12)	314 (15)
Neoplasm or immunosuppression	70 (7)	63 (6)	133 (7)
COPD	216 (23)	307 (28)	523 (26)
Laboratory values on admission			
PaO_2, worst value, mm Hg	70 (58-90)	65 (56-81.4)	68 (57-86)
PaO_2 to FIO_2 ratio, worst value	82.5 (62.9-133.5)	83.33 (61-131.83)	83 (62-132)
WBC count, K/μL	9.6 (6.6-13.65)	8 (5.8-11.2)	8.7 (6.2-12.3)
Lactate, mM	1.75 (1.2-2.8)	1.6 (1.2-2.2)	1.6 (1.2-2.4)
pH	7.37 (7.28-7.43)	7.42 (7.37-7.46)	7.4 (7.32-7.45)
$PaCO_2$, mm Hg	38 (33-47)	35 (30-41)	37 (31.4-44)
HCO_3, mM	21 (18-24)	22 (20-24)	22 (19-24)
BNP, pg/mL	619 (177-3034)	510 (184-2119)	562.5 (180-2413.5)
Creatinine, mg/dL	1.05 (0.76-1.56)	0.98 (0.74-1.39)	1 (0.75-1.45)
Therapies			
Therapeutic anticoagulation[e]	726 (77)	876 (81)	1,602 (79)
Hydroxychloroquine	146 (15)	36 (3)	182 (9)
Remdesivir	229 (24)	677 (63)	906 (45)
corticosteroids[f]	779 (82)	999 (92)	1,778 (88)
Tocilizumab	1 (0)	0 (0)	1 (0)
continuous paralysis	297 (31)	NA	297 (15)
Vasopressors			

Measure	Invasive Mechanical Ventilation	Noninvasive Respiratory Support	Total
Before treatment	263 (28)	99 (9)	362 (18)
At or after treatment	745 (79)	355 (33)	1,100 (54)
Treatment assignment location[a]			
ED	218 (23)	86 (8)	304 (15)
ICU	640 (68)	405 (38)	1045 (52)
Non-ICU ward	34 (4)	163 (15)	197 (10)
Stepdown	48 (5)	425 (39)	473 (23)

Data are presented as No. (%) or median (interquartile range). APACHE = Acute Physiology and Chronic Health Evaluation; BNP = brain natriuretic peptide; HCO_3 = bicarbonate; IMV = invasive mechanical ventilation; NA = not applicable; NIRS = noninvasive respiratory support; SpO_2 = oxygen saturation.

[a]Data are presented as percent of available. The number of available patients are as follows: ethnicity: IMV, 917/947; NIRS, 1,066/1,081; race: IMV, 914/947; NIRS, 1,066/1,081; treatment assignment location: IMV, 940/947; NIRS, 1,079/1,081.

[b]Categorized by American Hospital Association category: small, < 100 beds; medium, 100-499 beds; large, > 500 beds.

[c]Determined by documented FIO_2, if documented, or by FIO_2 = 100(0.21 + oxygen flow [L/min] × 0.03, if a flow rate was documented.

[d]Determined by documented International Classification of Diseases codes.

[e]Included continuous infusions of an anticoagulant (eg, heparin, bivalirudin) or therapeutic weight-based dosing of subcutaneous injections, oral direct anticoagulants, therapeutic dosing antiplatelet agents, and oral warfarin.

[f]Included systemic oral or IV hydrocortisone, prednisone, dexamethasone, and methylprednisolone.

Table 2]

Cox Cause-Specific Hazard Model Results

Outcome	Parameter	HR	95% CI	*P* Value	E Value	CL E Value
Time to in-hospital death	First treatment: NIRS	1.42	1.03-1.94	.03	1.86	1.18
	First treatment: HFNO	2.19	1.57-3.04	< .0001	2.82	2.07
	First treatment: NIPPV	1.32	0.96-1.83	.0924	1.72	1
	HFNO compared to NIPPV	1.66	1.31-2.1	< .0001	2.19	1.7
Time to in-hospital death (sensitivity analysis)	First treatment: NIRS	1.33	0.92-1.94	.1318	1.74	1
	First treatment: HFNO	1.38	0.82-2.33	.2303	1.81	1
	First treatment: NIPPV	1.15	0.7-1.9	.5832	1.44	1
	Time × HFNO	1.05	1.02-1.08	.0023	1.22	1.12
	Time × NIPPV	1.01	0.98-1.03	.559	1.08	1
Time to hospital discharge alive	First treatment: NIRS	2.77	2.01-3.82	< .0001	3.44	2.62
	Time × NIRS	0.97	0.95-0.98	< .0001	1.17	1.12
	First treatment: HFNO	2.14	1.33-3.45	.0018	2.77	1.73
	First treatment: NIPPV	2.19	1.62-2.98	< .0001	2.83	2.14
	Time × HFNO	0.96	0.94-0.99	.003	1.2	1.11
	Time × NIPPV	0.99	0.97-1	.0432	1.11	1.02
Time to hospital discharge alive (sensitivity analysis)	First treatment: NIRS	2.34	1.65-3.3	< .0001	2.98	2.18
	Time × NIRS	0.99	0.97-1	.0091	1.11	1.05
	First treatment: HFNO	1.81	1.15-2.85	.0105	2.38	1.43
	First treatment: NIPPV	2.06	1.51-2.82	< .0001	2.68	1.99
	Time × HFNO	0.98	0.96-1	.0321	1.13	1.04
	Time × NIPPV	0.99	0.98-1	.207	1.08	1
Time to ICU discharge alive	First treatment: NIRS	1.32	1-1.72	.0468	1.71	1.05
	Time × NIRS	0.98	0.97-1	.0128	1.13	1.06
	First treatment: HFNO	0.69	0.45-1.06	.0869	1.91	1
	First treatment: NIPPV	1.27	1-1.62	.0507	1.65	1
	HFNO—NIPPV	0.54	0.35-0.83	.0052	2.43	1.53

Results from final Cox cause-specific hazard models. Only treatment-related results are presented. For each outcome, NIRS model results are presented first, followed by results from models that split NIRS into NIPPV and HFNO. E values[44] for the HRs and for the HR CL closest to 1 (column CL E-Value) are presented to gauge the level of residual confounding that would be needed to nullify a given result.

The association between a potential confounder and both the outcome and the given predictor variable would need to be at least as large as the presented E-value (or CL E-value) to drop the corresponding HR (or CL) to 1. CL = confidence limit; HFNO = high-flow nasal oxygen; HR = hazard ratio; NIPPV = noninvasive positive pressure ventilation; NIRS = noninvasive respiratory support.