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Cardiovascular Disease and Severe Hypoxemia Are Associated With Higher Rates of Noninvasive Respiratory Support Failure in Coronavirus Disease 2019 Pneumonia

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OBJECTIVES: Acute hypoxemic respiratory failure is the major complication of coronavirus disease 2019, yet optimal respiratory support strategies are uncertain. We aimed to describe outcomes with high-flow oxygen delivered through nasal cannula and noninvasive positive pressure ventilation in coronavirus disease 2019 acute hypoxemic respiratory failure and identify individual factors associated with noninvasive respiratory support failure.

DESIGN: Retrospective cohort study to describe rates of high-flow oxygen delivered through nasal cannula and/or noninvasive positive pressure ventilation success (live discharge without endotracheal intubation). Fine-Gray subdistribution hazard models were used to identify patient characteristics associated with high-flow oxygen delivered through nasal cannula and/or noninvasive positive pressure ventilation failure (endotracheal intubation and/or in-hospital mortality).

SETTING: One large academic health system, including five hospitals (one quaternary referral center, a tertiary hospital, and three community hospitals), in New York City.

PATIENTS: All hospitalized adults 18–100 years old with coronavirus disease 2019 admitted between March 1, 2020, and April 28, 2020.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: A total of 331 and 747 patients received high-flow oxygen delivered through nasal cannula and noninvasive positive pressure ventilation as the highest level of noninvasive respiratory support, respectively; 154 (46.5%) in the high-flow oxygen delivered through nasal cannula cohort and 167 (22.4%) in the noninvasive positive pressure ventilation cohort were successfully discharged without requiring endotracheal intubation. In adjusted models, significantly increased risk of high-flow oxygen delivered through nasal cannula and noninvasive positive pressure ventilation failure was seen among patients with cardiovascular disease (subdistribution hazard ratio, 1.82; 95% CI, 1.17–2.83 and subdistribution hazard ratio, 1.40; 95% CI, 1.06–1.84, respectively). Conversely, a higher peripheral blood oxygen saturation to F_{IO_2} ratio at high-flow oxygen delivered through nasal cannula and noninvasive positive pressure ventilation initiation was associated with reduced risk of failure (subdistribution hazard ratio, 0.32; 95% CI, 0.19–0.54, and subdistribution hazard ratio 0.34; 95% CI, 0.21–0.55, respectively).

CONCLUSIONS: A significant proportion of patients receiving noninvasive respiratory modalities for coronavirus disease 2019 acute hypoxemic

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respiratory failure achieved successful hospital discharge without requiring endotracheal intubation, with lower success rates among those with comorbid cardiovascular disease or more severe hypoxemia. The role of high-flow oxygen delivered through nasal cannula and noninvasive positive pressure ventilation in coronavirus disease 2019–related acute hypoxemic respiratory failure warrants further consideration.

KEY WORDS: coronavirus; hypoxia; mechanical ventilators; respiratory insufficiency

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the coronavirus disease 2019 (COVID-19) pandemic, resulting in over 35.6 million cases and more than one million deaths across 235 countries (1). The burden of cases in the United States has exceeded that of any other country, with New York City as the epicenter of the pandemic at the time of this study, accounting for over 248,000 confirmed cases as of October 7, 2020 (2). The hallmark of COVID-19 is the development of an acute respiratory illness, with a significant number of hospitalized adult patients progressing to acute respiratory distress syndrome (ARDS) (3–6) and up to 18% ultimately requiring endotracheal intubation (ETI) and invasive mechanical ventilation (IMV) (5–9). Importantly, mortality rates after ETI may be substantial, ranging from 45% to 96% (3, 4, 7, 9, 10).

Although some experts during the pandemic have advocated for early ETI and IMV (11), the optimal respiratory support strategy for COVID-19 acute hypoxemic respiratory failure (AHRF) remains unclear (12). Compared with low-flow supplemental oxygen, high-flow oxygen delivered through nasal cannula (HFNC) improves oxygenation and work of breathing (13) and reduces ETI rates (14–16), whereas noninvasive positive pressure ventilation (NIPPV) may be associated with a lower risk of both ETI and mortality in certain non–COVID-19 populations with AHRF (14). Despite these benefits, some studies have shown that HFNC and NIPPV failure is associated with worse outcomes, including increased mortality, possibly related to delayed ETI and initiation of IMV (17–19). Reports of outcomes with HFNC and NIPPV in the COVID-19 population, however, remain limited to small case series and cohort studies (20–23), and unclear benefits of HFNC and NIPPV have resulted in some experts advocating for avoidance of these modalities in favor of early ETI during the pandemic (24). Furthermore, individual characteristics associated with HFNC and NIPPV failure in COVID-19 AHRF are unknown.

To address this knowledge gap, we sought to first describe patterns of HFNC and NIPPV use and outcomes for patients admitted with COVID-19 AHRF within a large New York City academic health system. Secondarily, we aimed to identify specific demographic and clinical characteristics at the time of HFNC and NIPPV initiation that were associated with treatment failure.

METHODS

Study Design and Participants

This retrospective cohort study included patients admitted to one of five hospitals within the Mount Sinai Health System, New York City, including a large quaternary referral center, a tertiary care hospital, and three community hospitals, totaling 2,590 beds. The Icahn School of Medicine at Mount Sinai institutional review board approved the study, and the requirement for informed consent was waived due to minimal risk (Study-20-00530).

For the descriptive study aim, we included all hospitalized patients between 18 and 100 years old, admitted between March 1, 2020, and April 28, 2020, with a positive SARS-CoV-2 reverse transcriptase polymerase chain reaction of nasopharyngeal swab samples, and who used HFNC and/or NIPPV prior to achieving an outcome of first ETI, live hospital discharge, or in-hospital mortality (**Fig. 1**). Patients were followed up to May 31, 2020. Patients from the descriptive population without missing covariates were included in the analytic subset (Fig. 1).

Data were extracted from electronic databases. Data collected included hospital disposition, patient demographics, do-not-intubate (DNI) code status, comorbidities (captured using *International Classification of Diseases,* 10th Edition codes), medications (including anticoagulation therapies and corticosteroids), vital signs, laboratory tests, and treatment with respiratory support devices (low-flow supplemental oxygen, HFNC, NIPPV [defined as continuous or bilevel positive pressure devices], and/or ETI with IMV).

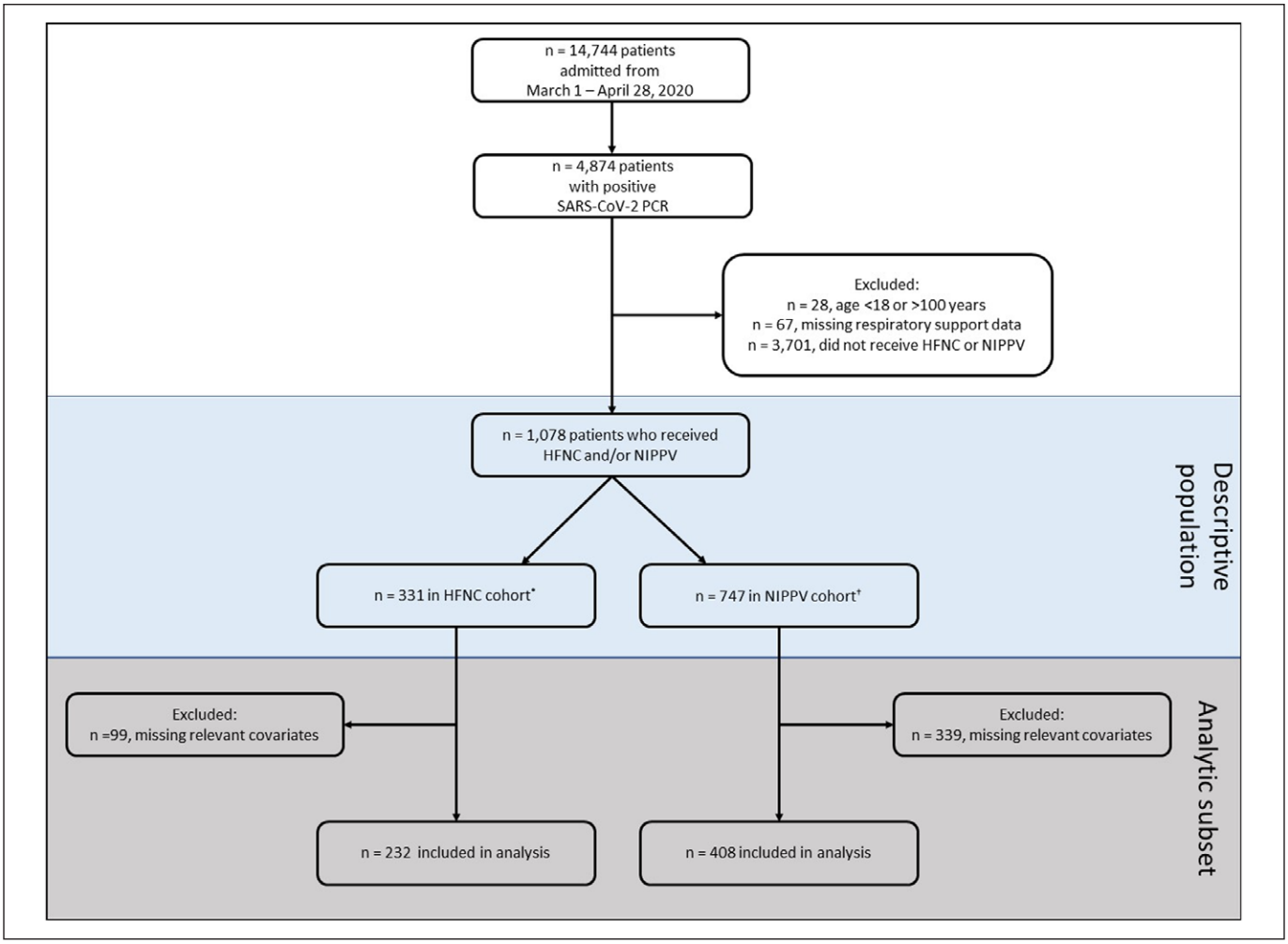

Figure 1. Selection flow diagram for study participant inclusion. The descriptive population includes all patients in the high-flow oxygen delivered through nasal cannula (HFNC) and noninvasive positive pressure ventilation (NIPPV) cohorts, whereas the analytic subset only includes patients without missing relevant covariates. *Includes patients who received HFNC as the highest noninvasive respiratory support prior to outcome of first endotracheal intubation, live hospital discharge, or in-hospital mortality. †Includes patients who received NIPPV as the highest noninvasive respiratory support prior to outcome of first endotracheal intubation, live hospital discharge, or in-hospital mortality. SARS-CoV-2 PCR = severe acute respiratory coronavirus-2 polymerase chain reaction.

Outcomes

The primary outcome was HFNC and/or NIPPV success, defined as live hospital discharge without need for ETI. Treatment failure was defined as ETI and/or in-hospital mortality, whichever occurred first, to account for patients with a DNI code status and those who died during cardiopulmonary resuscitation without ETI documentation. Secondarily, we explored specific demographic and clinical characteristics at the time of HFNC or NIPPV initiation that were associated with treatment failure among the subset of patients with nonmissing covariate data included in the main model. Importantly, we did not aim to compare outcomes between the HFNC and NIPPV cohorts, given differences in baseline patient characteristics and the challenge of accounting for the clinician's decision on which noninvasive respiratory support modality to use, which may have been influenced by device availability, varying institutional policies, and clinician familiarity.

Noninvasive Respiratory Support Cohorts

To simplify multiple transitions between HFNC and NIPPV, each patient was categorized into one of two cohorts based on the highest level of noninvasive respiratory support required prior to outcome or end of study period, whichever occurred first. Accordingly, the HFNC cohort included patients who received HFNC but never NIPPV, whereas the NIPPV cohort included

patients who received NIPPV with or without HFNC at any point between hospital admission and outcome, irrespective of sequence. In addition, timing of initiation and total duration of HFNC and/or NIPPV use from hospital admission to an outcome were calculated.

Covariates

Patient demographics included age, sex, race/ethnicity, and insurance type, as well as hospital site. Clinical factors included comorbidities, smoking status, body mass index (BMI), DNI code status (if documented prior to HFNC or NIPPV initiation), vital signs, ratio of peripheral blood oxygen saturation to Fio_2 (Spo_2/Fio_2) as a validated surrogate for the ratio of Pao_2 to Fio_2 (Pao_2/Fio_2) (25), and laboratory tests at the time of HFNC or NIPPV initiation. Enrollment into investigational drug trials for COVID-19 was not included as a covariate, as only a portion of those enrolled ultimately received the investigational agent, and data regarding specific therapies could not be reported due to embargo.

Statistical Analyses

Baseline demographics and clinical characteristics at the time of device initiation are presented for both HFNC and NIPPV cohorts. Frequencies and proportions are described for categorical variables and median and interquartile range (IQR) used for continuous measures. We determined detailed follow-up time by outcome subgroups. For each cohort, Fine-Gray competing risk regression models were performed at univariable and multivariable levels to estimate the subdistribution hazard ratios (sHRs) with corresponding 95% CIs of treatment failure, treating live hospital discharge as a competing risk. Patients were censored if they did not experience an outcome by study period end. Covariates in the univariable models with p value of less than or equal to 0.15 were entered into multivariable models for each cohort (**Table S2**, Supplemental Digital Content 1, http://links.lww.com/CCX/A516). All continuous variables used in models, except for age and temperature, were natural-log transformed to address observed skew in their underlying distributions (a standard procedure in regression models).

We performed the following sensitivity analyses to test the robustness of the outcomes from the main model: 1) addition of prophylactic- and therapeutic-dose anticoagulation and/or corticosteroids administered prior to device initiation as individual covariates in the multivariable models, as clinical characteristics and risk of failure may have differed by treatment status, 2) exclusion of interleukin-6 and BMI (covariates with the most missing values) from the multivariable models to increase sample size and better represent the initial study population, and 3) evaluation of differences in characteristics between patients with and without any missing covariates (irrespective of whether they were included in adjusted models). Of note, as almost all patients received hydroxychloroquine and azithromycin as part of standard care at the time of this study, these therapies were not included in the sensitivity analysis. p values of less than 0.05 were considered statistically significant. Analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC) and R (Version 3.5.0) using Rstudio (Version 1.1.453; RStudio, Boston, MA).

RESULTS

Population Characteristics

Of the 1,078 total patients receiving noninvasive respiratory support at any point during their hospitalization, 331 (30.7%) and 747 (69.3%) required HFNC and NIPPV, respectively, as their highest level of noninvasive respiratory support with almost half of the NIPPV group receiving both HFNC and NIPPV (316 patients, 42.3%) (**Table S1**, Supplemental Digital Content 1, http://links.lww.com/CCX/A516). There was significant variability in HFNC and NIPPV use across hospital sites, ranging from 3.5% (31/893 patients at community hospital A) to 9.5% (78/820 patients at community hospital C) for HFNC and 11.0% (190/1727 at the quaternary hospital) to 21.6% (177/820 patients at community hospital C) for NIPPV.

Demographic and clinical characteristics of patients in the HFNC and NIPPV cohorts are presented in Table S1 (Supplemental Digital Content 1, http://links.lww.com/CCX/A516). In both cohorts, comorbidities, including chronic lung and cardiovascular diseases, were common (**Table S3**, Supplemental Digital Content 1, http://links.lww.com/CCX/A516), and distributions of age, sex, and race/ethnicity were similar. At time of HFNC and NIPPV initiation, patients had a median (IQR) Spo_2/Fio_2 of 98 (93–125) and 97 (92–121.4), respectively, suggesting severe hypoxemia. Inflammatory markers were elevated in both groups

(Table S1, Supplemental Digital Content 1, http://links.lww.com/CCX/A516).

Considering dynamic respiratory support requirements including room air and low-flow supplemental oxygen over time for a given patient, the highest time-varying probability of receiving HFNC was 36% among those in the HFNC cohort, occurring between days 5 and 6 of admission (**Fig. S1**, Supplemental Digital Content 1, http://links.lww.com/CCX/A516). Among patients in the NIPPV cohort, the highest time-varying probability of being on NIPPV (31%) occurred within the first day of admission, whereas HFNC use in the same group was 12% on day 5 of admission (Fig. S1, Supplemental Digital Content 1, http://links.lww.com/CCX/A516).

Outcomes in the HFNC Cohort

Of 331 patients in the HFNC cohort, 154 (46.5%) were successfully discharged without needing ETI during their hospital stay (**Fig. 2A**). Of the 177 (53.5%) who experienced HFNC failure, 100 (56.5%) required ETI, and 77 (43.5%) died without ETI due to either a DNI code status or unsuccessful cardiopulmonary resuscitation. Among the 100 patients who ultimately required ETI, 35 (35.0%) were eventually discharged, 58 (58.0%) died and 7 (7.0%) were censored (Fig. 2*A*). The median (IQR) follow-up time in the HFNC cohort from time to HFNC initiation to an outcome (failure, success, or end of study) was 5.4 days (1.0–10.7 d), and specifically, was 1.36 day (0.54–3.77 d) and 10.2 days (6.72–15.5 d) among those who experienced treatment failure and successful discharge, respectively.

Factors Associated With HFNC Failure

In multivariable analysis limited to the subset of patients in the HFNC cohort with complete data for all adjusted covariates (n = 232; 70%), a significantly increased frequency of HFNC failure was observed among patients with cardiovascular disease (sHR, 1.82; 95% CI, 1.17–2.83) (**Fig. 3**). Conversely, a higher Spo_2/Fio_2 reduced the risk of HFNC failure (sHR, 0.32; 95% CI, 0.19–0.54), as did a higher platelet count (sHR, 0.61; 95% CI, 0.43–0.87). Admission to community hospital C and the tertiary hospital reduced the risk of failure compared with the quaternary referral hospital (sHR, 0.55; 95% CI, 0.31–0.99, and sHR, 0.29; 95% CI, 0.16–0.55, respectively) (Fig. 3).

Outcomes in the NIPPV Cohort

Of 747 total patients requiring NIPPV, 167 (22.4%) were successfully discharged without requiring ETI. Of the 572 patients (76.6%) who experienced NIPPV failure, 338 (59.1%) required ETI, and 234 (40.9%) died without ETI due to either a DNI code status or unsuccessful cardiopulmonary resuscitation. Of 338 patients who required ETI, 47 (13.9%) were eventually discharged, and 263 (77.8%) died (**Fig. 2*B***). The median (IQR) follow-up time for the NIPPV cohort was 4.1 days (1.2–9.1 d), and specifically, was 2.6 days (0.8–6.7 d) and 11.2 days (6.8–17.6 d) for those with treatment failure and success, respectively.

Factors Associated With NIPPV Failure

In multivariable analysis limited to the subset of patients in the NIPPV cohort with complete data for all adjusted covariates (n = 408), comorbid cardiovascular disease and higher interleukin-6 were associated with increased risk of failure (sHR, 1.40; 95% CI, 1.07–1.84, and sHR, 1.13; 95% CI, 1.02–1.26, respectively) (**Fig. 4**). Conversely, there was a reduced risk of NIPPV failure among patients with a higher Spo_2/Fio_2 (sHR, 0.34; 95% CI, 0.21–0.55), hemoglobin (sHR, 0.41; 95% CI, 0.19–0.88), and peripheral lymphocyte percentage (sHR, 0.74; 95% CI, 0.59–0.94).

Sensitivity Analyses

In sensitivity analyses where receipt of prophylactic or therapeutic anticoagulation and/or corticosteroids prior to device initiation were added as covariates, comorbid cardiovascular disease remained significantly associated with increased risk of failure, whereas higher Spo_2/Fio_2 remained significantly associated with reduced risk of failure in both HFNC (**Table S4**, Supplemental Digital Content 1, http://links.lww.com/CCX/A516) and NIPPV cohorts (**Table S5**, Supplemental Digital Content 1, http://links.lww.com/CCX/A516). Similarly, despite differences in characteristics between patients with complete compared with incomplete covariate data (**Table S6**, Supplemental Digital Content 1, http://links.lww.com/CCX/A516), risk of HFNC and/or NIPPV failure and associations with cardiovascular disease and Spo_2/Fio_2 remained in models where interleukin-6 and BMI were excluded

(Tables S4 and S5, Supplemental Digital Content 1, http://links.lww.com/CCX/A516).

DISCUSSION

This is the largest cohort study in patients with COVID-19 AHRF to date to describe patterns of use and outcomes with noninvasive respiratory support modalities of HFNC and NIPPV. We observed that nearly half of the patients in the HFNC cohort and one fifth of the patients treated with NIPPV were successfully discharged without requiring ETI. Given variable outcomes, we subsequently identified specific clinical features associated with HFNC and NIPPV success and failure. Specifically, comorbid cardiovascular disease was associated with increased risk of failure (need for ETI and/or in-hospital mortality), whereas less severe hypoxemia was associated with treatment success (live hospital discharge without need for ETI). Recognition of these characteristics may help to identify vulnerable patient subgroups at higher risk of failure with noninvasive modalities, thus necessitating closer monitoring. Dedicated studies to evaluate the efficacy of noninvasive modalities in reducing risks of ETI and mortality in COVID-19 AHRF are clearly warranted.

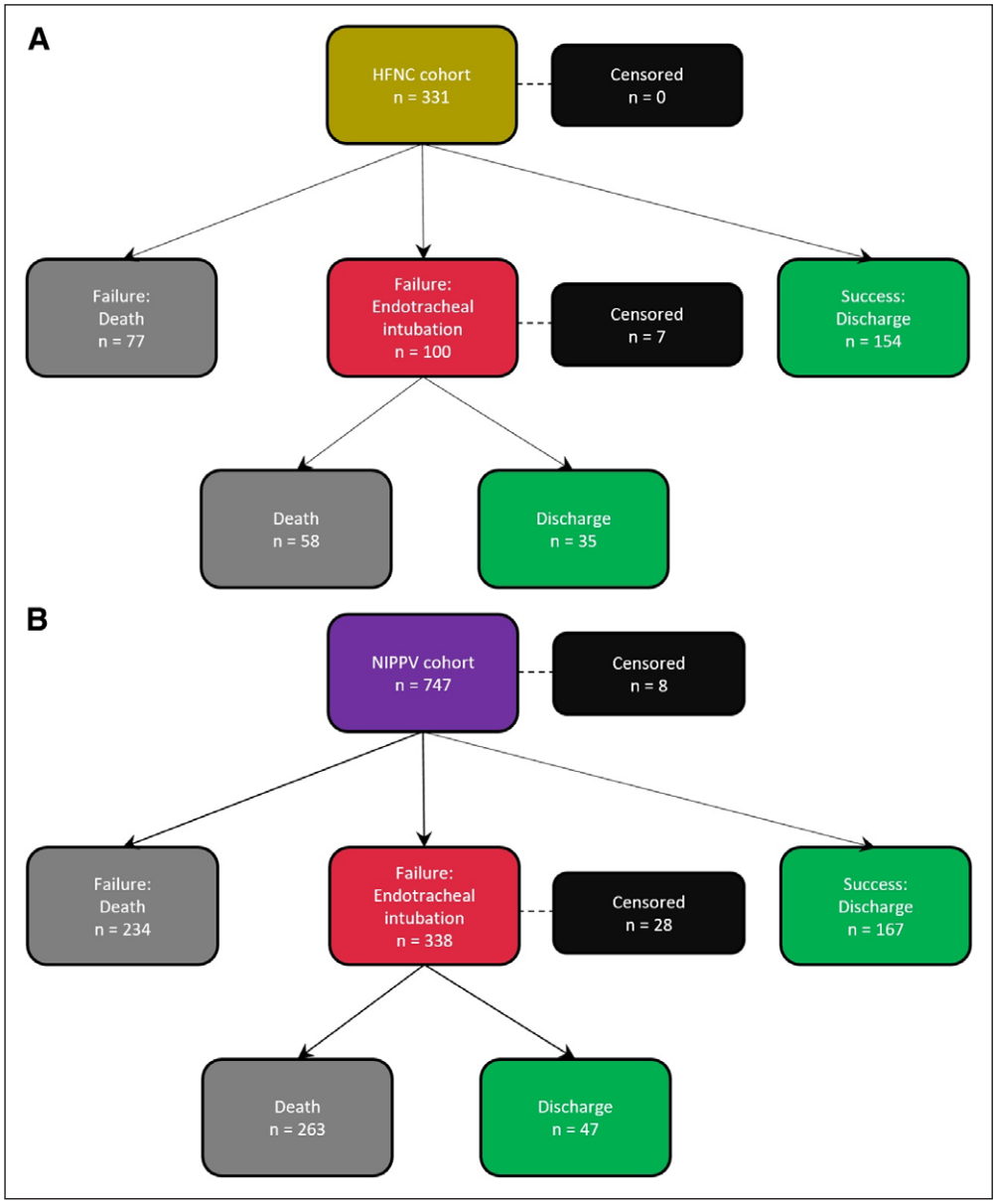

Figure 2. Trajectory of outcomes among patients who were treated with high-flow oxygen delivered through nasal cannula (HFNC) (**A**) and noninvasive positive pressure ventilation (NIPPV) (**B**) as the highest noninvasive respiratory support at any point during hospitalization prior to outcomes of first endotracheal intubation, live hospital discharge, or in-hospital mortality. Treatment success was defined as live hospital discharge without requiring endotracheal intubation. Treatment failure was defined as requiring endotracheal intubation and/or in-hospital mortality. Patients who did not experience an outcome by the end of the study period were censored.

Limited studies of noninvasive respiratory support outcomes in COVID-19 patients report survival rates of 19.5–100% with HFNC (4, 20, 21) and 7.7–37.7% with NIPPV (3, 4). Although our aim was not to directly compare these noninvasive modalities, higher failure rate among the NIPPV cohort may be due to higher illness severity or inherent differences in physiologic mechanisms between HFNC and NIPPV (26). Specifically, NIPPV use in non–COVID-19 severe ARDS patients has been shown to result in higher ICU mortality (19), possibly due to the self-inflicted

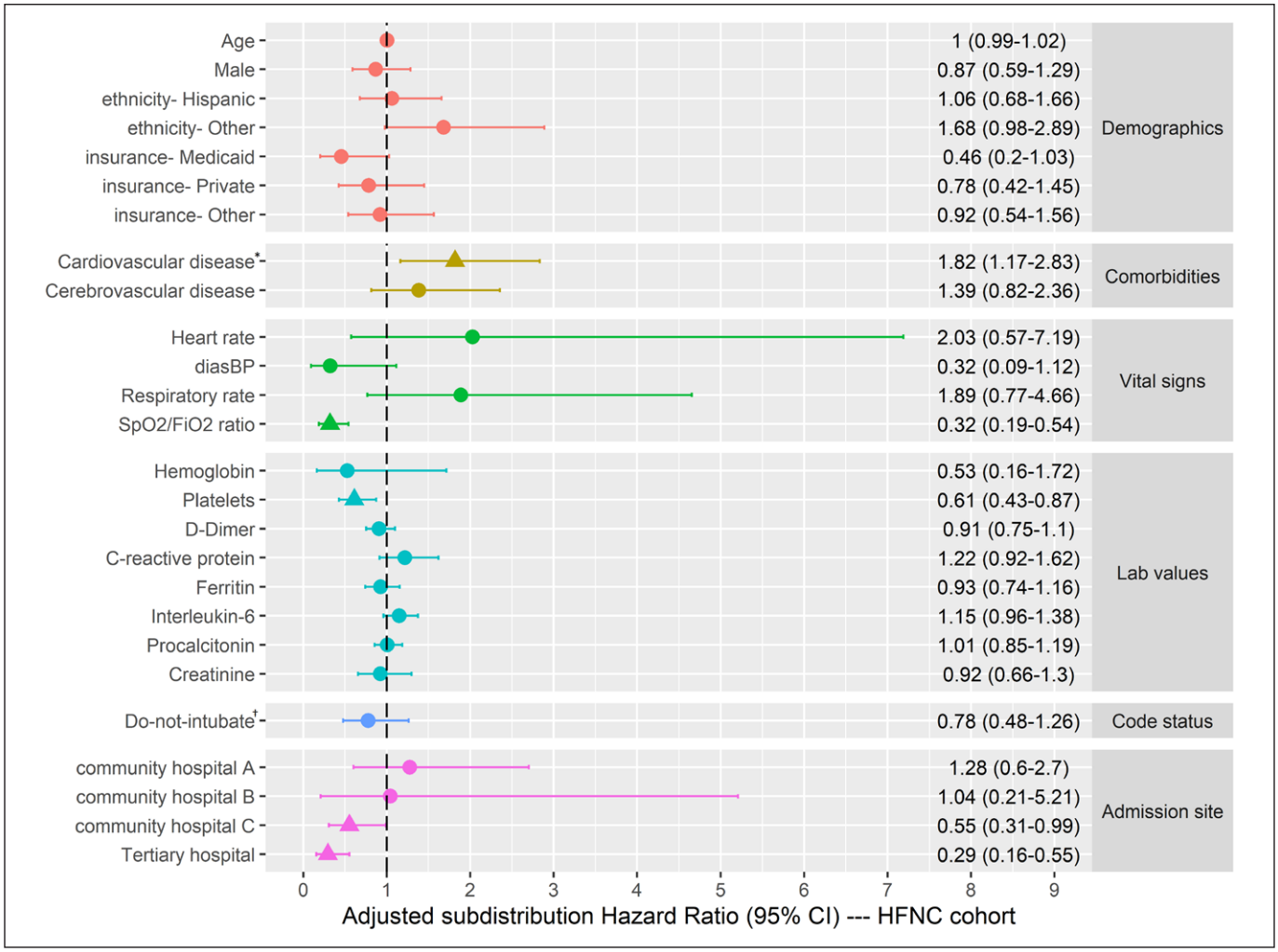

Figure 3. Multivariable analyses with subdistribution hazard ratio estimates for high-flow oxygen through nasal cannula (HFNC) failure among the subset of patients in the HFNC cohort with complete covariates included in the multivariable model ($n = 232$), with live hospital discharge as a competing risk. Statistically significant subdistribution hazard ratios are shown with *triangles*. *Cardiovascular disease includes: atherosclerotic heart disease, ischemic heart disease, congestive heart failure, rheumatic heart disease, pericardial disease, myocarditis, endocarditis, valvular disorders, cardiomyopathy, arrhythmias, history of cardiac arrest, peripheral vascular disease, aortic aneurysm, orthostatic hypotension, pulmonary hypertension, cardiac arrest, postprocedural cardiac complications. †At time of HFNC initiation. All continuous variables, except for age, were natural log-transformed. dias BP = diastolic blood pressure, Spo_2 = peripheral blood oxygen saturation.

lung injury phenomenon (27). Historically, treatment with NIPPV for H1N1 influenza and the Middle East respiratory syndrome coronavirus resulted in high failure rates leading to ETI (28). Although we observed that a small subset of patients experienced good outcomes with NIPPV, further studies comparing NIPPV with other forms of respiratory support are needed. However, our observation that a subset of patients using noninvasive respiratory support was successfully discharged from hospital without requiring ETI suggests that a uniform approach of early ETI for all patients with COVID-19 AHRF deserves reconsideration (29–32). Avoidance of unnecessary ETI and IMV is paramount to reduce IMV-associated complications, limit healthcare worker exposure associated with the ETI process (33), and preserve mechanical ventilators in resource-constrained pandemic settings. Thus, the impact of noninvasive respiratory support modalities on reducing risk for ETI and IMV and mortality merits further investigation.

Closer examination of noninvasive respiratory support use patterns revealed that the highest probabilities of HFNC or NIPPV use occurred relatively early in the hospital course, consistent with other studies reporting deteriorating respiratory status and development of ARDS soon after admission (4, 5, 34). Notably,

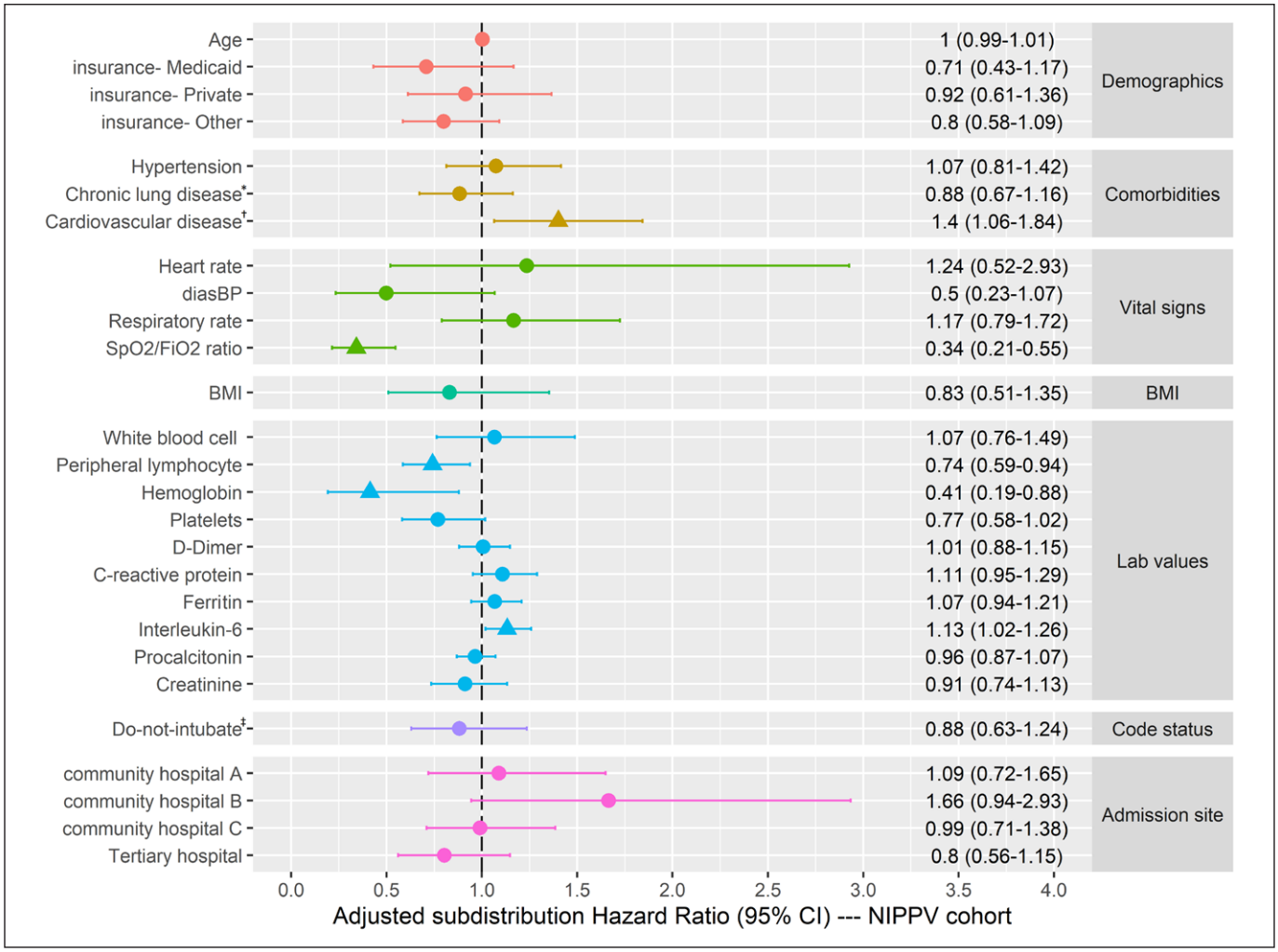

Figure 4. Multivariable analyses with subdistribution hazard ratio estimates for treatment failure among the subset of patients in the noninvasive positive pressure ventilation (NIPPV) cohort with complete covariates included in the multivariable model ($n = 408$), with live hospital discharge as a competing risk. Statistically significant subdistribution hazard ratio are shown in *triangles*. *Chronic lung disease includes: asthma, emphysema, chronic obstructive pulmonary disease, chronic bronchitis, bronchiectasis, atelectasis, diaphragmatic disease, interstitial lung diseases, sarcoidosis, and disorders of mediastinum. †Cardiovascular disease includes: atherosclerotic heart disease, ischemic heart disease, congestive heart failure, rheumatic heart disease, pericardial disease, myocarditis, endocarditis, valvular disorders, cardiomyopathy, arrhythmias, history of cardiac arrest, peripheral vascular disease, aortic aneurysm, orthostatic hypotension, pulmonary hypertension, cardiac arrest, postprocedural cardiac complications. ‡At time of NIPPV initiation. All continuous variables, except for age, were natural log-transformed. BMI = body mass index, dias BP = diastolic blood pressure, Spo_2= peripheral blood oxygen saturation.

we found that the median time to treatment failure was within 2 days after initiation of HFNC or NIPPV, highlighting that the immediate period after initiation of noninvasive respiratory support represents a crucial window for clinical deterioration and progression of disease. This is consistent with non–COVID-19 studies which have demonstrated that, for example, a ROX index (Spo_2/Fio_2 to respiratory rate) (35) of greater than or equal to 4.88 after 12 hours of HFNC treatment for AHRF is associated with a significantly lower likelihood of requiring ETI (35). Furthermore, analysis of a subset of patients with non–COVID-19 ARDS treated with NIPPV from a large, multicenter observational study showed that higher severity of illness, and worse oxygenation and ventilation over the first 2 days of NIPPV use were independently associated with the need for ETI (19, 36). Thus, in keeping with recommendations from the Surviving Sepsis Campaign guidelines for COVID-19 (12), close monitoring and frequent reassessment of patients receiving noninvasive respiratory support, particularly immediately after initiation, is essential.

In addition, we observed important clinical characteristics associated with HFNC and NIPPV outcomes. Importantly, comorbid cardiovascular disease was independently and robustly associated with increased risk of both HFNC and NIPPV failure in our cohort of COVID-19 patients. This relationship may stem from viral-mediated cardiac complications, including myocarditis, vascular inflammation with resultant cardiac injury and dysfunction, and new or worsening cardiac arrhythmias (4, 37–40). Furthermore, patients with higher severity of illness—as represented by more severe hypoxemia at noninvasive respiratory support initiation—were at significantly higher risk of both HFNC and NIPPV failure. Subsequent characterization of the mechanisms and extent to which the distribution of gas exchange and regional ventilation can be corrected by noninvasive therapies are needed to better predict disease trajectory and outcomes specific to COVID-19. Additionally, laboratory markers suggestive of more severe immune dysregulation, specifically elevated interleukin-6 and lymphopenia, were independently associated with failure in the NIPPV cohort. Interleukin-6 is a proinflammatory cytokine frequently up-regulated in patients with severe COVID-19 as part of a dysregulated immune response, and elevated levels have been suggested to portend worse outcomes, including worsening acute respiratory failure and need for IMV (41, 42). Furthermore, viral-mediated disruption of usual immune function may cause lymphocyte exhaustion and lymphopenia (41), which has been associated with more severe disease and increased mortality (3, 5, 43). Last, hospital site influenced outcomes in the HFNC cohort, which may be attributable to differences in patient severity of illness, resources, or capacity strain during pandemic settings, and deserves further exploration. Taken together, specific demographic and early clinical characteristics at the time of noninvasive respiratory support initiation may inform clinicians of susceptible subgroups of patients for whom close monitoring and early consideration of alternative management strategies are warranted.

Our study has notable strengths. First, this is the largest longitudinal cohort study to date to evaluate outcomes in patients treated with HFNC and NIPPV on COVID-19 AHRF. Second, the granularity of our data enabled capture of accurate longitudinal data representing time-varying laboratory results, vital signs, and oxygenation status and allowed us to map outcome trajectories associated with these devices. Third, the diversity of our cohort, drawn from hospital sites representing distinct communities, improves the generalizability of our findings to other COVID-19 populations. Fourth, we explored potential bias with several sensitivity analyses, accounting for patients with missing data and the impact of anticoagulation and corticosteroids on the main analysis. Finally, we had a minimal number of censored patients, improving the reliability of our outcomes.

This study also has several limitations. Our study reports on outcomes during a major surge in cases between March and May 2020 in New York City, the COVID-19 epicenter at that time, at which point COVID-19–specific therapies and institutional practices such as ETI thresholds differed from more recent practices, limiting generalizability of our outcomes with HFNC and NIPPV to the current population. Furthermore, despite severe acute hypoxemia and use of noninvasive respiratory support modalities, many of the patients in our study were not managed in the ICU due to bed availability constraints, potentially contributing to higher than expected mortalities. In addition, as an observational study, we cannot draw conclusions on the utility of HFNC and NIPPV compared with each other or to low-flow supplemental oxygen. However, our study provides a strong basis for further efforts, including case-control studies and randomized controlled trials to investigate the efficacy of noninvasive respiratory support in reducing risks of ETI and mortality in the COVID-19 population. Additionally, we chose to focus on factors at the time of HFNC or NIPPV initiation associated with treatment outcome and did not address the impact of subsequent changes in clinical characteristics or treatments administered. Finally, we did not assess healthcare worker infectious exposure risk, although prior studies of healthcare workers exposed to SARS-CoV-1 patients on HFNC or NIPPV did not report significantly higher transmission risk (44, 45), and in a COVID-19 simulation study, the exhaled air dispersion during well-fitted HFNC and continuous positive airway pressure therapy use was limited (46).

CONCLUSIONS

A subset of patients treated with HFNC and/or NIPPV achieved hospital discharge without requiring ETI and IMV, suggesting that some patients with COVID-19 AHRF can be managed effectively with these respiratory support modalities. Attention to specific

demographic and early clinical factors, such as comorbid cardiovascular disease and severity of hypoxemia, may help inform use of noninvasive respiratory strategies, allowing for a more personalized approach to the management of AHRF in pandemic settings.

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Drs. Wang, Liu, Percha, Pan, and Bose take responsibility for the integrity of the data and accuracy of the analyses. Drs. Wang, Percha, and Bose conceived the original idea and designed the study. Drs. Wang, Gao, Tandon, Tomlinson, Yoo, Howell, Eisenberg, Naymagon, Tremblay, Chokshi, and Bose contributed to the data collection. Drs. Liu, Percha, and Pan performed the statistical analyses. Drs. Wang, Liu, Percha, Pan, Goel, Mathews, Dua, Dunn, Powell, and Bose contributed to data interpretation. Drs. Wang, Liu, and Bose drafted the article. All authors revised the article for intellectual content and approved the final version of the article.

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