Noninvasive Ventilation at Home Reduces Mortality in COPD With CRF

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Chronic obstructive pulmonary disease (COPD) affects approximately 7% of the US population.[1] COPD is the third-leading cause of death, at 120,000 deaths per year,[2] and accounts for 1.5 million emergency department (ED) visits and 700,000 hospitalizations annually. COPD produces approximately $50 billion in annual direct and indirect costs to society.[3-5]

As COPD progresses from mild to severe disease associated with chronic respiratory failure (CRF), it becomes deadlier and consumes more health care resources. In an international cohort of patients with CRF due to COPD (COPD-CRF), the 3-year mortality rate was almost 20%.[6] CRF is debilitating to older patients, who have a higher mortality rate than their younger counterparts.[6] CRF negatively affects quality of life (QOL) and limits a patient's ability to engage in the activities of daily living.[7]

Because COPD has no cure, treatment is palliative; goals include reducing mortality and hospitalizations and improving QOL. Many treatment strategies, including noninvasive ventilation at home (NIVH), have been employed to mitigate adverse outcomes, with mean adherence having been reported at 6 hours of use per day.[8] Despite conflicting evidence of efficacy, NIVH use among patients with COPD-CRF is increasing. The number of patients prescribed NIVH in the United States grew from 120 in 2009 to 27,921 in 2015.[9,10] However, NIVH still remains a rarely used intervention, with less than 5% of US patients with COPD-CRF receiving this therapy.[9]

Early studies, summarized in a 2013 Cochrane review, found no benefit for NIVH use in patients with COPD-CRF.[10] However, recent studies have reported significant improvements in QOL and reductions in hospitalization rates.[11-16] Additionally, a European randomized controlled trial showed a significant mortality reduction in hypercapnic patients with COPD when treated with high-intensity NIVH.[13] The findings of this trial have been replicated in other notable trials across Europe, Australia, and China, lending more evidence to support the efficacy of NIVH in reducing mortality and hospital readmissions.[17] These studies were included in a recent meta-analysis reporting improvements in clinical outcomes associated with NIVH use.[18]

ABSTRACT

OBJECTIVES: Patients with chronic respiratory failure resulting from chronic obstructive pulmonary disease (COPD-CRF) have limited treatment options and poor health outcomes. We examined the effect of noninvasive ventilation at home (NIVH) treatment on all-cause mortality, hospitalizations, and emergency department (ED) visits.

STUDY DESIGN: Retrospective cohort study.

METHODS: Using Medicare claims data between 2012 and 2017, we divided patients with COPD-CRF into a treatment group, defined by NIVH receipt within 2 months of CRF diagnosis, and a control group without NIVH receipt in the entire follow-up period. We modeled time to death, first hospitalization, and first ED visit. Cox regressions were performed, mitigating selection bias using stabilized inverse probability of treatment weights with regression controls. Sensitivity analyses with time-varying exposure to NIVH were conducted on the full sample irrespective of treatment timing.

RESULTS: We identified 410 patients treated with NIVH and 36,247 controls. We observed a reduced risk of hospitalizations (HR, 0.790; 95% CI, 0.592-0.988), ED visits (HR, 0.571; 95% CI, 0.457-0.686), and mortality (HR, 0.617; 95% CI, 0.462-0.772). The benefit of NIVH diminished over time for mortality and ED visits but remained constant for hospitalizations. However, no survival benefit was observed in the sensitivity analyses that accounted for immortal-time bias; further exploration suggests that earlier NIVH treatment following CRF diagnosis may be an important factor in improving survival outcomes.

CONCLUSIONS: Patients with COPD-CRF who received NIVH had statistically significant reductions in hospitalizations and ED visits compared with patients not treated with NIVH. Further research is needed to examine the effect of NIVH on mortality.

Despite these reports, evidence for the effectiveness of NIVH for patients with COPD-CRF in the United States is limited. To address this gap, we conducted a retrospective study on the effectiveness of NIVH in the Medicare COPD-CRF population.

TAKEAWAY POINTS

This study explores the association between receiving noninvasive ventilation at home (NIVH) and mortality, hospitalizations, and emergency department (ED) visits in patients with chronic obstructive pulmonary disease (COPD) with chronic respiratory failure (CRF).

▸ Patients with COPD and CRF who were prescribed NIVH had statistically significant reductions in risk of death (38.3%), hospitalizations (21.0%), and ED visits (42.9%) compared with similar patients not treated with NIVH.

▸ NIVH is associated with a 1-year risk difference of 13.0% for mortality, 8.4% for first hospitalization, and 17.6% for first ED visit, yielding relative risk reductions of 30.7%, 12.9%, and 20.1%, respectively. The numbers needed to treat are 7.7 to prevent a death, 12.0 to prevent a first hospitalization, and 5.7 to prevent a first ED visit.

METHODS

Data Source

A patient-level analytic file was created using the Medicare Limited Data Set (LDS) between 2012 and 2017. The LDS contains information on claims through Part A and Part B for a randomly selected 5% sample of the complete Medicare fee-for-service population.[19]

Study Cohort

We restricted our sample to patients with a CRF diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] codes 518.53, 518.83, 518.84; *International Classification of Diseases, Tenth Revision, Clinical Modification* [*ICD-10-CM*] codes J95.822, J96.10, J96.11, J96.12, J96.20, J96.21, J96.22) and a concurrent COPD diagnosis (*ICD-9-CM* codes 490, 491.0, 491.1, 491.8, 492.0, 492.8, 491.20, 491.21, 491.22, 496; *ICD-10-CM* codes J40, J41.1, J41.8, J42, J43.0, J43.1, J43.2, J43.8, J43.9, J44.0, J44.1, J44.9). All patients had at least 18 months of continuous enrollment in Medicare, except those who died in that period. Additionally, patients were excluded if they resided outside the United States at any point during the enrollment period, were ever enrolled in Medicare Advantage, had dementia in the 6-month preindex period (*ICD-9-CM* codes 290.x, 294.1, 331.2; *ICD-10-CM* codes F00.x-F03.x, F05.1, G30.x, G31.1), or ever had obstructive sleep apnea (OSA) (*ICD-9-CM* code 327.23; *ICD-10-CM* code G47.33). Patients with dementia were excluded because of the difficulty of such patients tolerating NIVH.[20] Because NIVH is an effective treatment for OSA, we excluded patients with OSA to ensure that any benefit observed due to NIVH treatment was due to its effect on COPD-CRF.[21] **Figure 1** shows the attrition table.

We divided the final sample into 2 groups: (1) a treatment group consisting of patients who received NIVH (pre-2016 Healthcare Common Procedure Coding System [HCPCS] codes E0460, E0461, E0464; 2016 and 2017 HCPCS code E0466) within 2 months of CRF diagnosis, and (2) a control group consisting of patients who did not receive NIVH at any point in the follow-up period. The index date was the date of CRF diagnosis.

Outcomes

The primary study outcome was all-cause mortality (time to death). The secondary outcomes were time to first hospital admission and time to first ED visit after index date. All patients were followed until event occurrence or were censored if patients did not experience the event by the end of the study period (December 31, 2017).

Statistical Analysis

Time-to-event analysis. The associations between NIVH and outcomes were estimated using time-to-event analyses (Cox regressions). The semiparametric Cox model assumes that the ratio of the treatment group hazard to the control group hazard is constant over time. Violation of this assumption may yield biased estimates.[22] We found that the proportional hazard assumption was violated by regressing Schoenfeld residuals on a time index.[23] As such, we included a time-by-treatment interaction (treatment*log[time]) in the regressions.[24] This approach results in the simultaneous estimation of 2 parameters related to the treatment effect: an HR describing the difference in event rates at the start of the analysis period and a second parameter describing the rate of change in the HR over time.

Due to the observational nature of this study, 2 methods were employed to control for confounding and selection bias: inverse probability of treatment weighting (IPTW; described later) and inclusion of covariates as regression controls. Using both methods is a conservative approach, as either can provide consistent estimates of treatment effects if properly specified.[25]

The demographics controlled for and used for matching included race/ethnicity, gender, age, and region of the country. We also used the Charlson Comorbidity Index (to control for the presence of chronic diseases), total health care spending 6 months pre–index date, county-level smoking prevalence, and comorbid hypercapnia.

Propensity score weighting. We estimated the probability of receiving NIVH (the propensity score) as a function of observable demographic and clinical covariates. We then reweighted the sample using stabilized IPTW weights as described by Austin.[26] This approach reweights the treatment and control groups such that differences in observable characteristics between the 2 groups are minimized. Additionally, it permits the estimation of an average treatment effect across the entire population of eligible patients. The IPTW and propensity score weighting approach has been used in a number of recent cardiovascular retrospective studies and has been shown effective at reducing bias compared with other methods.[27-29]

Bootstrapping to calculate statistical significance. Because both the propensity score estimation procedure and the regression models were computed with error, we used bootstrapping to

FIGURE 1. Study Cohort Attrition Flowchart
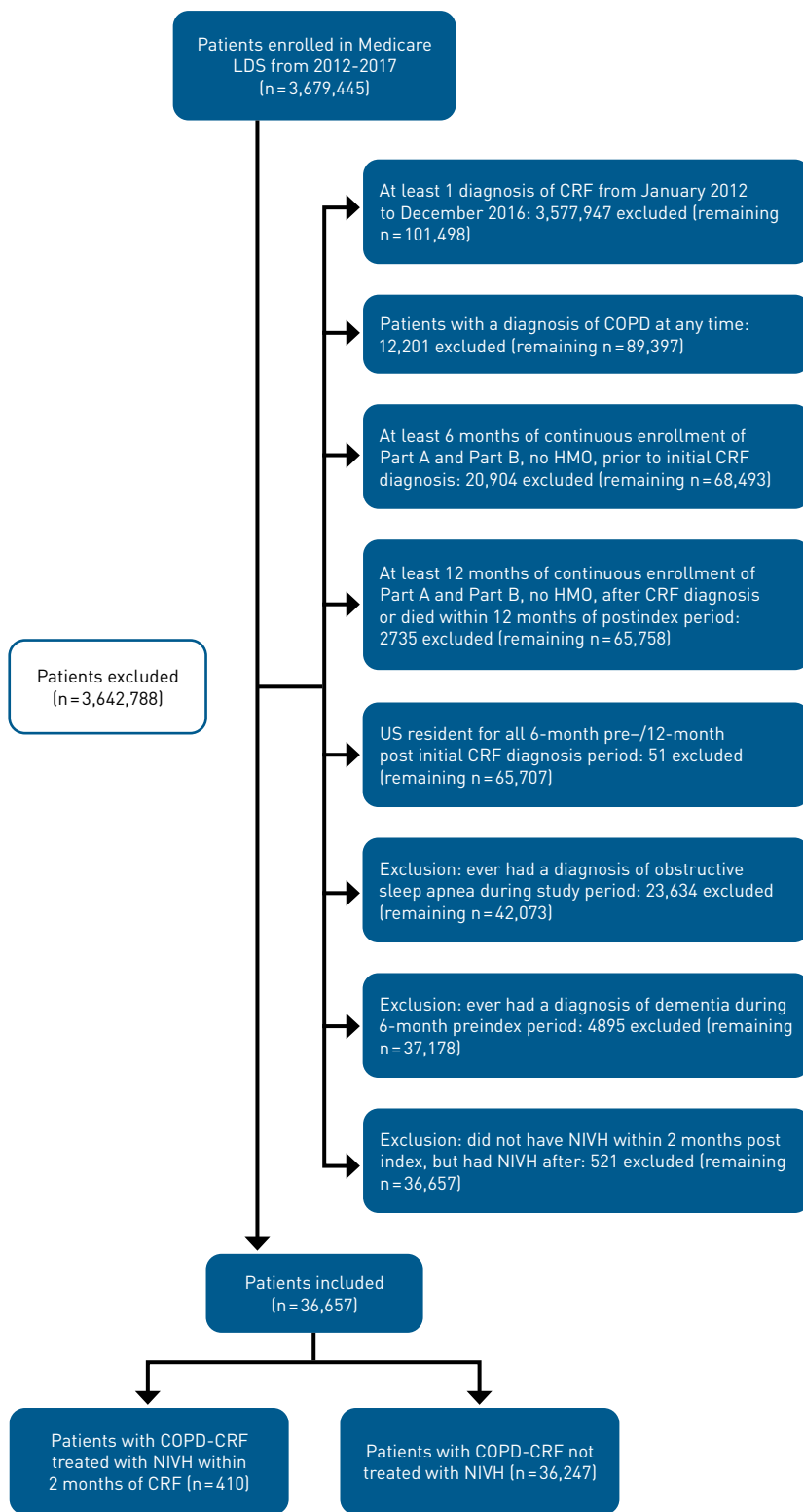
COPD, chronic obstructive pulmonary disease; CRF, chronic respiratory failure; HMO, health maintenance organization; LDS, Limited Data Set; NIVH, noninvasive ventilation at home.

calculate standard errors (SEs) that incorporate both sources of uncertainty. Austin and Small have previously demonstrated that this approach correctly estimates SEs in 2-part models.[30] We generated 500 bootstrap samples.

Models. We estimated HRs for all-cause mortality, first hospitalization, and first ED visit using 4 different models: (1) a naive comparison of the unweighted treatment and control groups, (2) model 1 adding demographic and clinical covariates, (3) comparison of the IPTW sample including demographic and clinical covariates, and (4) model 3 with bootstrapped SEs.[31] Model 4 is the preferred model because it incorporates both techniques to address confounding and uses SEs that address joint uncertainty.

Risk difference, relative risk reduction, and numbers needed to treat. In addition to reporting the HRs for each end point, we implemented the methodology of Austin to estimate the percentage of patients who experience an event in the treatment group (P_T) and control group (P_C), the risk difference (RD), relative risk reduction (RRR), and numbers needed to treat (NNT) at 1 year after index date using our preferred model (Cox model with demographic and clinical covariates, and bootstrapped SEs on the IPTW sample).[32] The RD, RRR, and NNT were calculated as:

$$RD = P_C - P_T$$

$$RRR = 1 - \frac{P_T}{P_C}$$

$$NNT = \frac{100}{ARR}$$

with ARR indicating absolute risk reduction.

Sensitivity analysis. We incorporated the shortest possible window of receiving treatment after index that provided a treatment group large enough for our main analysis to have sufficient study power to reduce the possibility of immortal-time bias.[33] However, this study design does not completely eliminate the concern of immortal-time bias. As such, we implemented a Cox model with time-varying exposure to NIVH for each end point as sensitivity analyses. We estimate 3 models: (1) a naive Cox model, (2) a Cox model with demographic and clinical covariates, and

TABLE 1. Balance Diagnostics

	Treatment group (unweighted)	Control group (unweighted)	Difference in means *P*	Treatment group (weighted)	Control group (weighted)	Difference in means *P*
Patient count	410	36,247		391	36,088	
Age in years at index date, mean (SD)	70.3 (10.8)	75.0 (10.9)	<.01	74.8 (10.3)	75.0 (10.9)	.75
Male	43.4%	44.2%	.76	37.4%	44.0%	.04
Race						
White	86.6%	87.9%	.43	89.9%	88.0%	.29
Black	7.6%	8.0%	.73	6.0%	7.9%	.14
Asian	2.0%	1.1%	.08	0.7%	1.1%	.13
Hispanic	2.0%	1.3%	.23	1.0%	1.3%	.52
Native American	0.5%	0.6%	.71	0.8%	0.6%	.78
Other/unknown	1.5%	1.1%	.52	1.8%	1.1%	.47
Region at index date						
Northeast	12.4%	16.1%	.04	19.8%	16.1%	.33
Midwest	18.0%	25.5%	<.01	24.5%	25.5%	.74
South	47.8%	41.9%	.02	38.1%	42.0%	.23
West	21.7%	16.5%	<.01	17.7%	16.5%	.62
Medical spending 6 months pre–index date, mean (SD)	$18,351 ($24,418)	$33,027 ($50,901)	<.01	$26,916 ($35,883)	$32,742 ($50,579)	.08
County-level smoking prevalence at index date, mean (SD)	0.2 (0.04)	0.2 (0.04)	<.01	0.2 (0.04)	0.2 (0.04)	.40
Hypercapnia	8.0%	1.7%	<.01	3.6%	1.8%	.27
Comorbidities						
Cerebrovascular disease	14.1%	21.9%	<.01	19.4%	21.8%	.42
Congestive heart failure	32.0%	43.8%	<.01	44.2%	43.7%	.89
Chronic pulmonary disease[a]	89.8%	82.2%	<.01	83.5%	82.3%	.73
Diabetes	21.2%	20.9%	.86	23.0%	20.9%	.56
Hemiplegia, paraplegia	4.1%	3.8%	.68	4.4%	3.7%	.67
Any malignancy, except neoplasm of the skin	11.0%	15.3%	.02	16.2%	15.2%	.74
Metastatic solid tumor	2.9%	6.4%	<.01	4.8%	6.4%	.35
Mild liver disease	3.9%	6.8%	.02	7.3%	6.7%	.82
Moderate/severe liver disease	0.5%	1.2%	.18	0.8%	1.2%	.47
Myocardial infarction	8.0%	15.7%	<.01	13.9%	15.6%	.53
Peptic ulcer disease	1.0%	3.2%	.01	4.3%	3.2%	.65
Peripheral vascular disease	19.3%	30.9%	<.01	31.0%	30.8%	.95
Renal disease	12.7%	28.2%	<.001	24.6%	28.0%	.36
Rheumatologic disease	4.1%	6.2%	.09	9.3%	6.1%	.33
AIDS/HIV	0.0%	0.4%	.22	0	0	N/A

N/A, not applicable.

[a]Chronic pulmonary disease was measured within 6 months prior to index date. Forty-two patients in the treatment sample received a chronic obstructive pulmonary disease diagnosis at index date (ie, the same date as the chronic respiratory failure diagnosis).

(3) model 2 with bootstrapped standard errors. In this time-varying covariate approach, individuals switch between the treatment and control groups depending on whether they are on or off treatment, and thus propensity score matching would not be appropriate. We reconstructed the analytic file to the patient–treatment period level and included all patients with COPD-CRF into the study sample irrespective of timing of NIVH receipt. The results are reported in the **eAppendix** (available at **ajmc.com**).

RESULTS

Descriptive Statistics

Our sample consisted of 36,657 total patients: 410 patients with COPD-CRF treated with NIVH within 2 months of CRF diagnosis (treatment group) and 36,247 controls. **Table 1** summarizes the demographic and clinical characteristics of both groups before and after IPTW implementation. Before reweighting, statistically

TABLE 2. Primary and Secondary Results, HRs

Outcome	(1) Naive model HR (95% CI)	(2) Model with covariates HR (95% CI)	(3) Reweighted model with covariates HR (95% CI)	(4) Reweighted model with covariates and bootstrapped errors HR (95% CI)
Time to death	0.469*** (0.388-0.567)	0.573*** (0.473-0.693)	0.617*** (0.487-0.782)	0.617*** (0.462-0.772)
Change in HR over time for mortality	1.001*** (1.001-1.001)	1.001*** (1.001-1.001)	1.001*** (1.001-1.001)	1.001*** (1.001-1.001)
Time to first hospitalization	0.720*** (0.618-0.838)	0.808*** (0.693-0.940)	0.790** (0.658-0.949)	0.790** (0.592-0.988)
Change in HR over time for time to first hospitalization	1.000 (1.000-1.001)	1.000 (1.000-1.000)	1.000 (1.000-1.001)	1.000 (0.999-1.001)
Time to first ED visit	0.529*** (0.467-0.599)	0.542*** (0.478-0.614)	0.571*** (0.496-0.658)	0.571*** (0.457-0.686)
Change in HR over time for time to first ED visit	1.001*** (1.000-1.001)	1.001** (1.000-1.001)	1.001* (1.000-1.001)	1.001* (1.000-1.001)

ED, emergency department.

*$P < .1$; **$P < .05$; ***$P < .01$.

significant differences in baseline demographic characteristics and clinical factors existed between the treatment and control group. Notably, the treatment group was younger than the control group and had substantially lower 6-month pre–index date total health care spending. IPTW achieved good balance between the treatment and control groups: No statistically significant differences remained, except for gender ($P < .05$).

Primary End Point Results

Table 2 describes results for the time-to-event analysis for each end point and the 4 analysis specifications. Model 1 is the naive comparison, model 2 is regression with controls using the original sample, model 3 is regression with controls using the reweighted population using IPTW, and model 4, the preferred model, is model 3 with bootstrapped SEs. For all-cause mortality and ED visits, regression of Schoenfeld residuals indicated a violation of the proportional hazard assumption (results not shown). As such, a time-by-treatment interaction (treatment*log[time]) was included for all outcomes in all model specifications.

NIVH was associated with improved survival in patients with COPD-CRF. Each model specification revealed a statistically significant reduction in risk of death associated with NIVH at the start of the analysis period. In model 4, patients receiving NIVH had a 38.3% reduction in risk of death compared with those not receiving NIVH (HR, 0.617; 95% CI, 0.462-0.772) at index date. The associated decay parameter (1.001) describes the extent to which this benefit is time varying; in other words, the decreased risk of death for those receiving NIVH diminishes by 0.1% per day (HR, 1.001; 95% CI, 1.001-1.001). The 2 parameters can be combined to estimate the HR for NIVH at time *t*. For example, a year after diagnosis, the HR is estimated to be $0.617 \times (1.001)^{365} = 0.889$. As such, the survival benefit of NIVH disappeared after 69 weeks. The time-varying nature of the survival benefit of NIVH is evident in **Figure 2**, which plots the survival rate across a 1-year time frame estimated using the preferred model (model 4). The survival benefit is largest in the period immediately following diagnosis and then diminishes over time.

Table 3 presents results for the year after COPD-CRF diagnosis. One year from index date, 29.4% of patients receiving NIVH had died and 42.4% of controls had died. This translates to an RD of 13.0% and an RRR of 30.7% for all-cause mortality. The NNT to prevent a death at 1 year was 7.7.

Secondary End Point Results

NIVH was associated with improvement in time to first hospitalization and to first ED visit (Table 2). In our preferred model (model 4), receiving NIVH resulted in a 21.0% reduction in risk of hospitalization (HR, 0.790; 95% CI, 0.592-0.988) at index date and a 42.9% reduction in risk of ED visit (HR, 0.571; 95% CI, 0.457-0.686) at index date. The benefit conferred by NIVH in reducing the risk of time to first ED visit declined by 0.1% per day (HR, 1.001; 95% CI, 1.000-1.001), whereas the reduced risk of first hospitalization remained constant (Table 2). The HR of NIVH for ED visits was $0.571 \times (1.001)^{365} = 0.822$ after a year. There was no decreased risk of an ED visit for patients receiving NIVH after 81 weeks.

Table 3 shows that after 1 year, 56.3% of patients prescribed NIVH had been hospitalized compared with 64.6% of controls. This translates to an RD of 8.4% and an RRR of 12.9% for first hospitalization. The NNT to prevent a first hospitalization at 1 year was 12.0. Additionally, after 1 year, 70.0% of patients prescribed NIVH had been to the ED compared with 87.7% of controls. This translates to an RD of 17.6% and an RRR of 20.1% for ED visits. The NNT to prevent a first ED visit at 1 year was 5.7.

DISCUSSION

We estimated the comparative effectiveness of NIVH in patients with COPD-CRF in the US Medicare population. Analyzing 2012 to 2017 data, we found that NIVH use following a COPD-CRF diagnosis was associated with significant reductions in hospitalizations and ED visits. Further analysis is needed to explore the association between NIVH and all-cause mortality.

Our main analysis results suggest that patients with COPD-CRF receiving NIVH treatment have a 38.3% reduction in risk of death,

21.0% reduction in risk of hospitalizations, and 42.9% reduction in risk of ED visits compared with untreated controls. The reduction in risk of hospitalizations is constant over the study period, whereas the reductions in risk of all-cause mortality and ED visits diminish over time. After 69 weeks, NIVH no longer showed a survival benefit, and after 81 weeks, it no longer showed a reduced risk of ED visits.

The sensitivity analyses included patients receiving NIVH 2 months or more after CRF diagnosis, and no survival benefit was observed. This observation combined with the diminishing survival benefit of NIVH observed in the main analysis suggests that the earlier individuals receive NIVH treatment following CRF diagnosis, the greater the impact on reducing risk of death. Further support of this hypothesis is the observation that patients live longer if NIVH is started earlier following CRF diagnosis. For those receiving NIVH within the first 60 days following diagnosis, median survival is 184 days and mean survival is 268 days. For those starting NIVH more than 60 days following diagnosis, median survival is 132 days and mean survival is 192 days. Further research is needed to explore the association between timing of NIVH treatment and all-cause mortality.

One year after index date, results show an RD for mortality of 13.0% and an RRR for mortality of 30.7% in patients with COPD-CRF receiving NIVH compared with those not receiving NIVH. These findings suggest that NIVH provides a mortality reduction larger than any COPD-CRF treatment outside of smoking cessation.[34] The NNT to prevent a death for 1 year was 7.7. This compares favorably with findings from another recently reported COPD treatment. The IMPACT trial reported that treatment with a long-acting muscarinic antagonist/long-acting β antagonist/inhaled corticosteroid inhaler (closed triple therapy) provided a mortality benefit compared with dual-therapy inhalers in a COPD population. In that study, the NNT to prevent a death with triple therapy was greater than 100.[35]

The 1-year RD and RRR for first hospitalization and first ED visit were clinically meaningful and statistically significant and resulted in an NNT to prevent a hospitalization of 12.0 and an NNT to prevent an ED visit of 5.7. Extrapolation of these results to the full Medicare fee-for-service population suggests that providing NIVH to all patients with COPD-CRF could save as many as 96,000 lives annually while eliminating 62,000 hospitalizations and 130,000 ED visits.

Because 60% of the patients in our study initially received a diagnosis of COPD-CRF while hospitalized, the high mortality rates observed in our sample (7% at 1 week post diagnosis and 47% at 1 year post diagnosis) were expected. These findings are similar to previously reported results in patients receiving NIV while hospitalized for a COPD exacerbation.[36] Our findings of a rapid, robust, and persistent reduction in mortality rates following the institution of NIVH in patients with COPD-CRF are also observed in a randomized controlled trial by Köhnlein et al.[13]

Although our results show significant results in reduced mortality risk, risk of hospitalizations, and risk of ED events, they do not speak to the health-related QOL (HRQOL) of patients receiving NIVH treatment. The literature shows mixed results regarding

FIGURE 2. Stratified Kaplan-Meier Failure Curves for (A) Survival Rate, (B) Time to First Hospitalization, and (C) Time to First ED Visit (IPTW-balanced population)
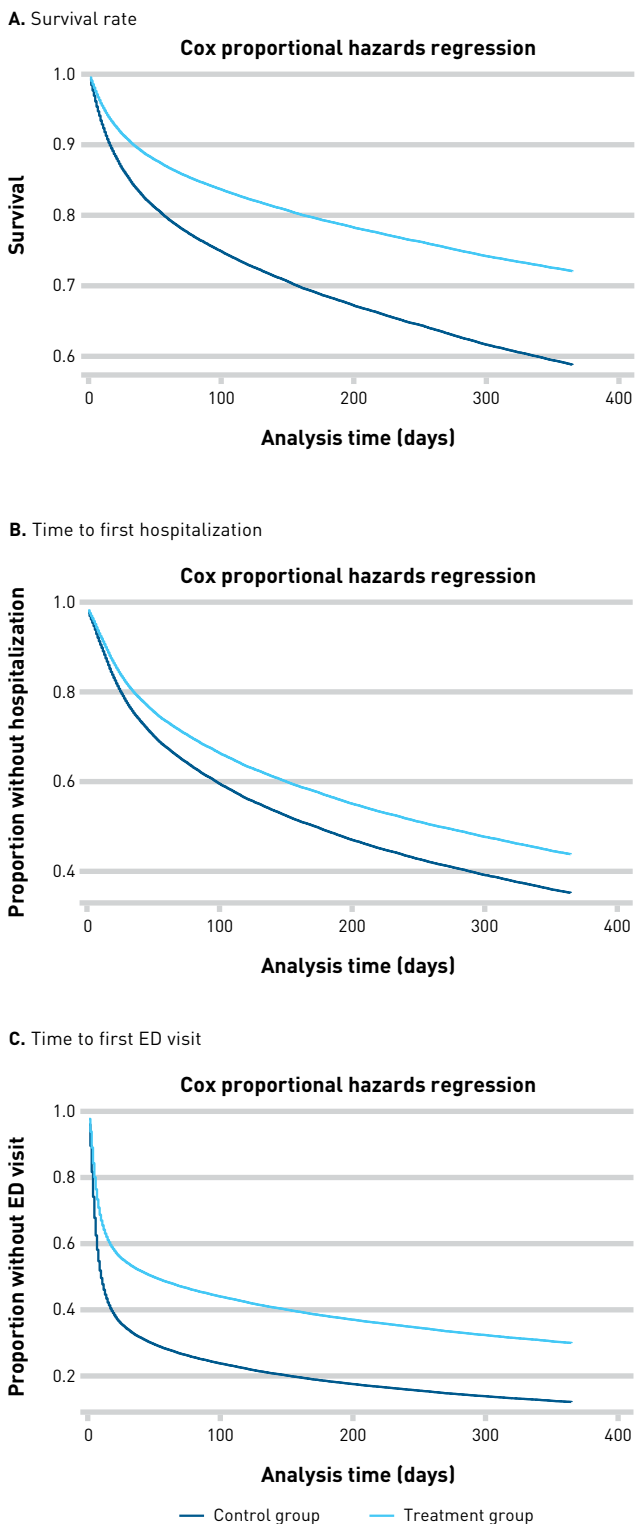
ED, emergency department; IPTW, inverse probability of treatment weighting.

TABLE 3. Risk Difference, Relative Risk Reduction, and Number Needed to Treat by Outcome (IPTW-balanced population; 1-year time frame)

Outcome	Treatment group % with event (95% CI)	Control group % with event (95% CI)	Risk difference (95% CI)	Relative risk reduction (95% CI)	Number needed to treat (95% CI)
Mortality	29.4%*** (22.6%-36.2%)	42.4%*** (42.1%-42.7%)	13.0%*** (6.3%-19.8%)	30.7%*** (14.7%-46.7%)	7.7** (2.3-13.1)
Hospitalizations	56.3%*** (52.7%-59.9%)	64.6%*** (64.2%-65.1%)	8.4%*** (4.6%-12.1%)	12.9%*** (7.1%-18.7%)	12.0*** (8.4-15.5)
ED visits	70.0%*** (65.0%-75.0%)	87.7%*** (86.8%-88.5%)	17.6%*** (12.7%-22.6%)	20.1%*** (14.4%-25.8%)	5.7*** (4.4-7.0)

ED, emergency department; IPTW, inverse probability of treatment weighting.

*$P < .1$; **$P < .05$; ***$P < .01$.

the effect of NIVH on QOL. Duiverman et al reported that NIVH and NIV improved HRQOL among patients with COPD.[37] However, Tissot et al found that HRQOL did not improve among older patients receiving NIVH.[38]

Limitations

This study has important limitations. Foremost is the concern about making causal inferences from retrospective data. Because randomization was impossible with our design, we employed statistical techniques to control for confounders. Additionally, immortal-time bias is an important concern,[33] which we addressed by choosing the shortest possible window of receiving treatment after the index date that provided a treatment group large enough for our analysis to have sufficient power and by performing sensitivity analyses that incorporated time-varying exposure to NIVH.

We used *ICD-9-CM* and *ICD-10-CM* codes to identify CRF diagnosis in the Medicare LDS. We were unable to determine whether patients were hypercapnic, hypoxic, or had another form of CRF prior to October 2015 because *ICD-9-CM* codes do not provide that level of detail. Other studies of this topic have limited NIVH use to hypercapnic patients based on the theory that this group is most likely to benefit. Although this seems rational, no study of NIVH has compared outcomes among different forms of CRF. Our data suggest that clinical benefits are associated with NIVH use in patients with COPD-CRF, but we cannot infer whether one clinical phenotype benefits more than another.

In addition, the Medicare LDS does not include Medicaid dual eligibility status prior to 2017. Medicaid dual eligibility is used as a proxy to adjust for low socioeconomic status in prior studies. As such, this study was unable to control for differences in socioeconomic status between the treatment and control groups.

Furthermore, the findings of this study cannot be extrapolated to the Medicare non–fee-for-service population, such as those in managed care programs or health maintenance organizations, because claims data for these patients are not reported in the Medicare LDS.[39]

Finally, our study cannot speculate about the level of compliance with NIVH or the optimal settings necessary to achieve improved clinical outcomes. All treated patients in our analysis had NIVH available within 2 months of index diagnosis, but neither the ventilator settings nor the frequency and duration of NIVH use are reported in the Medicare LDS.

CONCLUSIONS

NIVH was associated with lower risks of hospitalizations and ED visits in patients with COPD-CRF. Further research is needed to examine the effect of NIVH on all-cause mortality. ◼

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eAppendix

In this eAppendix, we present the results of sensitivity analyses examining the effect of non-invasive ventilation at home (NIVH) on time to death, time to first hospitalization, and time to first ER visit. We performed Cox regressions using time-varying exposure to NIVH on individuals with chronic obstructive pulmonary disease with chronic respiratory failure (COPD-CRF). Our sensitivity analyses samples retained all qualifying COPD-CRF patients who received NIVH regardless of when this therapy was started, whereas our primary analysis restricted the sample to those who received NIVH within the first two months following CRF diagnosis. This change added 521 patients, and resulted in a total sample size of 37,178 patients.

We estimated three models: (1) a naïve Cox model that only includes time-varying exposure to NIVH, (2) model 1 plus controls for demographic and clinical characteristics, and (3) model 2 with bootstrapped standard errors. We also calculated the risk difference (RD), relative risk reduction (RRR), and numbers needed to treat (NNT) at one year after CRF diagnosis.

Results

Table 1 shows the results of the Cox models for all endpoints. Not controlling for demographic and clinical characteristics, we observed a reduction in risk of death of 7.4% (HR: 0.926, 95%CI: 0.826–1.039) for individuals receiving NIVH compared to individuals not receiving NIVH. This result was not significant. When controlling for demographic and clinical characteristics and adding bootstrapped standard errors, we observed that NIVH increased the risk of death by 14.4% (HR: 1.144, 95%CI: 1.027-1.262). In the main analysis, we observed the survival benefit of NIVH to be the largest right after CRF diagnosis and diminishing over time. We no longer observed a survival benefit at 69 weeks. The diminishing survival benefit of NIVH observed in the main analysis and the change in direction of the effect of NIVH on survival using the full COPD-CRF sample in the sensitivity analysis suggests that the timing of NIVH treatment is an important factor in reducing the risk of death in COPD-CRF patients. To explore this possibility, we compared the number of days from the start of the treatment period in which patients died until death between those who died in the main analysis and those who died in the sensitivity analysis. In the main analysis, 17% of patients who died while on treatment did so within 30 days of treatment initiation, while in the sensitivity analysis, 20% of those who died did so

within 30 days of treatment initiation. Similarly, the difference in death rates following NIVH initiation at 90 days and 180 days is 33% vs 37% and 50% vs 56% respectively between the main and sensitivity analyses. We also compared the mean and median number of days a patient lived after starting NIVH during the treatment period in which they died based on whether this treatment period began before or after the first 60 days following CRF diagnosis. We found that patients lived on average 268 days (median of 184 days) after treatment initiation if it occurred within two months of CRF diagnosis, compared to 192 days (median of 132 days) if treatment imitation occurred later than two months after CRF diagnosis (median are significantly different at p=0.038 using Wilcox rank sum test). These simple assessments support a hypothesis that patients receiving delayed treatment die more quickly once starting therapy than patients who start NIVH sooner following the diagnosis of COPD-CRF.

For healthcare utilization, we observe a significant reduction in risk of hospitalization and ER visit of 26.3% (HR: 0.737, 95%CI: 0.818-0.838) and 44.2% (HR: 0.558, 95%CI: 0.490-0.634), respectively, in patients treated with NIVH compared to patients not treated with NIVH in the naïve Cox model. When adding demographic and clinical covariates and bootstrapped standard errors, these results remained largely the same. Patients receiving NIVH experienced a significant reduction in risk of hospitalization of 19.2% (HR: 0.808, 95%CI: 0.658-0.949) and a significant reduction in risk in ER visit of 42.8% (HR: 0.572, 95%CI: 0.494-0.650). These results are similar to the results in the main analysis.

Table 1 Primary and secondary results, hazard ratios

Outcome	(1) Naive model HR (95% CI)	(2) Model with covariates HR (95% CI)	(3) Model with covariates and bootstrapped standard errors HR (95% CI)
Time to death	0.962 (0.826, 1.039)	1.144** (1.020, 1.284)	1.144*** (1.027, 1.262)
Time to first hospitalization	0.737*** (0.646, 0.840)	0.808*** (0.709, 0.921)	0.808*** (0.686, 0.930)

Time to first ER visit	0.558*** (0.490, 0.634)	0.572*** (0.503, 0.651)	0.572*** (0.494, 0.650)

*** p<0.01, ** p<0.05, *p<0.1

Abbreviations: CI = Confidence Interval, HR = Hazard Ratio, NIVH = Non-invasive ventilation at home

Table 2 shows the RD, RRR, and NNT at one year after CRF diagnosis for each outcome. For mortality, we estimated that more patients on NIVH experienced death than patients who did not receive NIVH (50.1% versus 45.9%). As a result, the RD, RRR, and NNT for mortality are negative. This is consistent with the result of the Cox regression shown in Table 1.

For hospitalizations, NIVH is associated with an RD and RRR of 7.5% (95%CI: 1.4%-13.5%) and 11.0% (95%CI: 2.1%-19.8%), respectively. To prevent a patient having a hospitalization within a year of CRF diagnosis, we need to treat 13.4 patients. For ER visits, NIVH is association with an RD of 17.3% (95%CI: 11.6%-23.1%) and an RRR of 19.6% (95%CI: 13.2%, 26.1%). NNT is 5.8 patients to prevent an ER visit within a year of CRF diagnosis.

Table 2 Risk difference, relative risk reduction, and number needed to treat, by outcome

Outcome	% with event (treatment group)	% with event (control group)	Risk difference (95% CI)	Relative risk reduction (95% CI)	Number needed to treat (95% CI)
Mortality	50.1%*** (45.2%, 46.5%)	45.9%*** (45.8%, 54.5%)	-4.3%* (-8.7%, 0.2%)	-9.3%* (-18.9%, 0.3%)	-23.5 (-124.2, 77.1)
Hospitalizations	60.8%*** (54.8%, 66.9%)	68.3%*** (67.6%, 69.0%)	7.5%** (1.4%, 13.5%)	11.0%** (2.1%, 19.8%)	13.4*** (7.6, 19.1)

| ER visits | 70.9%*** | 88.3%*** | 17.3%*** | 19.6%*** | 5.8*** |
| | (65.2%, 76.6%) | (87.8%, 88.7%) | (11.6%, 23.1%) | (13.2%, 26.1%) | (4.6, 6.9) |

*** p<0.01, ** p<0.05, *p<0.1

Conclusion

The primary analysis presented in the paper indicates receiving NIVH treatment provides benefits for survival, hospitalizations, and ER visits. The finding that NIVH is associated with decreased survival in the sensitivity analysis suggests interesting differences between patients included in the main analysis – those who receive NIVH within two months of CRF diagnosis – and patients in the sensitivity analysis – those who receive NIVH at any time during the study period. Importantly, the time-varying covariate approach allows us to observe death at any time at the start of a new treatment window. Including patients treated with NIVH later in the course of their disease, likely means these patients were sicker at the time they received treatment and which minimized the potential benefits of therapy. In fact, given how infrequently NIVH is used in current day practice, this analysis may be pointing out that withholding NIVH until late in the disease course of COPD-CRF markedly limits the chances of reducing mortality. Upon further examination, we found that during treatment periods occurring after the two-month window used in the main analysis, median death occurred significantly earlier compared to treatment periods starting during the first two months after CRF diagnosis. This supports our hypothesis and increases our confidence in the findings of the main analysis.