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Original Research

Early Initiation of non-invasive ventilation at home improves survival and reduces healthcare costs in COPD patients with chronic hypercapnic respiratory failure: A retrospective cohort study

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ABSTRACT

Background: While non-invasive ventilation at home (NIVH) is gaining wider acceptance as a treatment option for chronic obstructive pulmonary disease with chronic respiratory failure (COPD-CRF), uncertainty remains about the optimal time to begin NIVH, whether a specific phenotype of COPD-CRF predicts improved outcomes, and how NIVH affects healthcare costs.

Materials and methods: Using 100% research identifiable fee-for-service Medicare claims from 2016 through 2020, we designed an observational, retrospective, cohort study to determine how NIVH use in COPD-CRF patients stratified by CRF phenotype and by timing of initiation affected mortality, healthcare utilization, and total healthcare costs compared to a matched control group.

Results: In hypercapnic COPD-CRF patients starting NIVH within the first week following diagnosis, risk of death was reduced by 43% (HR, 0.57; 95% CI 0.51–0.63, $p < .0001$), those starting 8–15 days following diagnosis had mortality reduction of 31% (HR, 0.69; 95% CI 0.62–0.77, $p < .0001$), and those starting 16–30 days following diagnosis showed mortality reduction of 16% (HR 0.84, CI 0.073-0.096, $p < .01$) compared to controls. Medicare spending was also associated with timing of NIVH initiation in hypercapnic COPD-CRF. Those beginning treatment 0–7 days and 0–15 days following diagnosis had a $5484 and a $3412 reduction in Medicare expenditures respectively the next year. NIVH was not associated with improved clinical outcomes or decreased Medicare spending in COPD-CRF patients who were not hypercapnic.

Conclusion: In this study, early initiation of NIVH for hypercapnic COPD-CRF patients was associated with reductions in the risk of death and in total Medicare spending.

1. Introduction

Chronic obstructive pulmonary disease (COPD) affects more than 20 million Americans and is the fourth leading cause of death in the United States (U.S.), responsible for an estimated 120,000 deaths per year [1]. Caring for COPD patients in the U.S. is resource intensive, accounting for 700,000 hospitalizations, 1.5 million emergency department (ED) visits, and 50 billion dollars in annual cost to society [2].

COPD has no cure, is often progressive, and may lead to the development of chronic respiratory failure (CRF), which is defined by a combination of symptoms, frequent exacerbations, chronic hypoxia, and/or chronic hypercapnia [3,4]. Patients with COPD-CRF have a poor quality of life, high morbidity and mortality, and consume a disproportionate share of healthcare resources. Therapies for COPD-CRF are limited and primarily supportive with goals of improving symptoms, decreasing mortality, and reducing healthcare utilization [5,6].

As evidenced by a recent clinical practice guideline, non-invasive ventilation at home (NIVH) is gaining wider acceptance as a treatment option for COPD-CRF [7]. Despite emerging evidence of benefit and an increase in NIVH utilization, it remains an infrequently used treatment with less than 5% of COPD-CRF patients receiving this therapy [8].

A meta-analysis published in 2020 concluded NIVH use in COPD-CRF reduced hospitalizations but that it did not reduce mortality [9]. In comparison, two retrospective cohort studies published in 2021

Abbreviations: chronic obstructive pulmonry disease, COPD; chronic respiratory failure, CRF; non-invasive ventilation at home, NIVH.

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demonstrated NIVH use in COPD-CRF patients was associated with significant reductions in mortality, hospitalizations, and emergency department visits [8,10]. These latter findings are in line with results from small, randomized trials of NIVH in COPD-CRF performed in Europe [11,12].

To date, no U.S. based studies have been published exploring the effects of NIVH on total healthcare costs for COPD-CRF patients. Additionally, uncertainty remains regarding the optimal time to begin NIVH during the clinical course of COPD-CRF, as well as whether the presence of a specific phenotype of CRF better predicts improved clinical outcomes with NIVH therapy [7,13].

To help answer these questions, we designed an observational, retrospective cohort study using research identifiable Medicare claims from 2016 through 2020. Our primary objectives were defining how NIVH use stratified by COPD-CRF phenotype and by timing of initiation affected mortality, healthcare utilization, and total healthcare costs.

2. Research questions

We sought to answer the following three research questions:

- What is the optimal time to begin NIVH treatment during the clinical course of COPD-CRF?
- Is a specific phenotype of COPD-CRF associated with improved outcomes with NIVH use?
- What is the impact of NIVH treatment on Medicare expenditures?

3. Materials and methods

3.1. Data source

The data used in this study were from the Medicare 100% research identifiable files (RIF) fee-for-service (FFS) and Medicare Beneficiary Summary File (MBSF) administrative claims under Data Use Agreement (DUA) 54757. Data from January 2016 through June 2020 were extracted. The RIF claims files include inpatient and outpatient hospital, skilled nursing facility, hospice, home health agency, physician, and durable medical equipment claims. The MBSF includes beneficiaries' entitlement and eligibility information, enrollment, and socio-demographic data (date of birth, age, gender, race, date of death if applicable, and state of residence).

3.1.1. Study cohort

The study cohort comprised Medicare beneficiaries who were concurrently diagnosed with COPD and CRF during the period of January 2016 through December 2019. Beneficiaries were identified using International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM] codes J96.10, J96.20, J96.11, J96.21, J96.12, J96.22 for CRF, and 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 for COPD. The index date was the date of the claim when both COPD and CRF first appeared.

We excluded patients with dementia (ICD-10-CM codes F00.x-F03.x, F05.1, G30.x, G31.1) since such patients often have difficulty tolerating NIVH [14]. We also excluded patients with obstructive sleep apnea (OSA) (ICD-10-CM G47.33) since NIVH is an effective treatment for this disorder and we wanted to ensure that any observed benefits were due to treatment of COPD-CRF and not OSA [15].

To allow the full scope of healthcare services utilization, costs, and comorbidities to be captured in our analysis, beneficiaries were excluded if they were not enrolled in Medicare FFS Parts A and B during the 12-months before and after the index date, or if they were enrolled in a Medicare Part C plan at any time during this same 2-year period. Beneficiaries who had no Medicare expenditures during the 12 months before or after the index date were also excluded from our analysis. Fig. 1A in the Appendix presents the different steps and exclusions of the sample selection.

The sample was divided into a treatment group who received NIVH (Healthcare Common Procedure Coding System [HCPCS] E0466) within two months of the combined COPD-CRF diagnosis, and a control group who did not receive NIVH at any point in the follow-up period. The treatment and control groups were then assigned to one of three COPD-CRF phenotypes based on ICD-10-CM coding. The 3 phenotypes were COPD-CRF unspecified (J96.10, J96.20), COPD-CRF with hypoxia (J96.11, J96.21), and COPD-CRF with hypercapnia (J96.12, J96.22). These phenotypes were mutually exclusive so that each subject was only assigned to one group. Each treatment group member was then assigned to one of four treatment initiation windows defined as the time elapsed between the diagnosis of COPD-CRF and the start of NIVH. These time windows were 0–7 days, 8–15 days, 16–30 days, and 31–60 days.

3.1.2. Outcome variables

The primary study outcome was all-cause mortality (time-to-death). The secondary outcomes were time to first hospital admission, and time to first emergency department (ED) visit after the index date. We also estimated total Medicare expenditures during the 12 months following the index date. Patients were followed until death or for one year if they remained alive.

3.1.3. Statistical analysis

We conducted regression analyses using Cox proportional hazard models for time-to-event outcomes (i.e., time-to-death, time to first hospital admission, and time to first ED visit after the index date). We estimated a generalized linear model for the impact on Medicare expenditures in the next year for the treatment group (NIVH use) versus the control group (non-NIVIH use).

Throughout the modeling, different techniques were used to appropriately answer each research question, while also addressing different forms of bias such as: 1) confounding factors, 2) selection bias, and 3) immortal time bias.

Addressing Potential Biases: Potential confounding factors were addressed by adjusting the different models using numerous socio-demographic and clinical factors. The sociodemographic characteristics included race/ethnicity, gender, age, Medicare/Medicaid dual eligibility, and region of the country where subjects lived. The clinical and health-related factors were the conditions comprising the Charlson Comorbidity Index (to control for the presence of chronic diseases) and total Medicare expenditures in the 12 months before the index date.

Because of the observational nature of the study, we used an inverse probability of treatment weighting (IPTW) propensity score model to address selection bias. Propensity score methods are statistical techniques widely used in observational studies to mitigate self-selection bias [16]. This approach synthetically creates randomness in the incidence of treatment to address the problem of self-selection between treatment and control individuals without losing any observations from the dataset. Previously published literature suggested that applying these techniques to observational studies sufficiently addresses selection bias such that the results approximate those of randomized clinical trials [17].

Although there are several methods of matching patient cohorts, all rely on the propensity score to estimate the probability of treatment assignment conditional on observed baseline covariates using logistic

regression. IPTW requires the construction of weights using propensity scores, and then estimating a weighted regression using the constructed weights. Along with the Cox proportional hazards model, IPTW was applied to estimate the three time-to-event outcomes. IPTW was also applied to a generalized linear regression model with a gamma distribution and a log link function to estimate the Medicare expenditures outcome.

For all time-to-event models, we addressed immortal time bias by modeling each beneficiary in the treatment group as a control group member for the time elapsed between the diagnosis date and the treatment initiation date, and as a treatment group member thereafter. We also considered alternative specifications of the Cox models that accounted for the time dependency of the treatment. We used a generalized linear model with gamma distribution and a log link function to estimate total Medicare expenditures. Generally, we use GLM with Log-link function and Gamma Distribution because of non-negative and positively skewed distribution of spending data.

Determining the optimal time to begin NIVH treatment: To determine whether early initiation of NIVH affected survival, we estimated a Cox proportional hazard model with four service receipt categories (0–7 days, 8–15 days, 16–30 days, and 31–60 days). Each service receipt category represented the elapsed time between the index date (i.e., first instance of a combined COPD-CRF diagnosis) and the NIVH treatment initiation date. Based on these results, we constructed additional models with binary treatment indicators that covered three treatment initiation windows (0–7 days, 0–15 days, and 0–30 days).

We also investigated whether the different time-to-treatment windows affected all cause ED visits, all cause hospitalizations, and Medicare expenditures by running the appropriate models for the secondary outcome variables using the different treatment windows. In the case of binary treatment, given that the estimating effect represents an average over two or three time periods, we expected that if late treatment was less effective, the estimated effect would decrease with longer treatment initiation windows.

That is, if the benefit in the second week was less than the benefit in the first week, and if both weeks were combined (expanded treatment initiation window), the average of the two weeks combined would be less than the average in the first week. Ideally, we would use categorized treatment windows for all models; however, we opted for cumulative windows that allowed us to use binary, yes or no, treatment indicators to implement the IPTW to address selection bias, while also accounting for immortal time bias.

Determining whether a specific phenotype of COPD-CRF was associated with improved outcomes- Subsample analyses: In addition to estimating our different models using the full samples, we conducted subsample analyses to assess whether different COPD-CRF phenotypes responded differently to NIVH. Specifically, we divided the patients into 3 groups using the ICD-10-CM coding information contained in the RIF and ran the time -to-event models on the phenotype subsamples described above. We then ran the model for total Medicare expenditures on these same COPD-CRF phenotype subsamples.

For each of these models, we assessed how well the reweighting improved the balancing of the baseline characteristics by reporting the absolute values of the standardized mean differences. A common rule in the literature is that the standardized mean differences should be within the interval of [0, 1] for a well-balanced baseline [18]. We examined these values using "love plots" for the full sample and for the full sample at treatment window 0–30 days.

4. Results

The statistical results are organized as follows. We first show the distribution of the study population, followed by the summary statistics of the covariates used in this analysis. The different characteristics (demographics, geographic location and patient health) of treatment and control groups are well balanced after the IPTW propensity score match; the groups are thus similar in terms of all of the characteristics. Finally, we present the regression results.

4.1. Baseline characteristics of the study sample

Fig. 1 (in the Appendix) reports the selection process of the study sample, showing all exclusions.

Table 1 shows the distribution of patients according to NIVH use, COPD-CRF phenotype, and by time elapsed between the index date and treatment initiation. The final sample consisted of 499,717 patients with COPD-CRF of which 6707 (1.3%) were prescribed NIVH (treatment group) and 493,010 (98.7%) were not (control group). The sample was further divided into 3 subsamples based on the ICD-10-CM coding for COPD-CRF phenotype.

The first subsample was the 80,000 patients with hypercapnic COPD-CRF (J96.12 and J96.22), of which 3629 (4.5%) received NIVH. These patients comprised 16% of the total sample, 15% of the control group and 54% of the NIVH treatment group. The second subsample was the 316,564 patients who had hypoxic COPD-CRF (J96.11 and J96.21) of which 1941 (0.6%) received NIVH. These patients comprised 63% of the total sample, 64% of the control group, and 29% of the NIVH treatment group.

The third subsample was the 103,153 patients with COPD-CRF unspecified (J96.10 and J96.20) of which 1137 (1.1%) received NIVH.

Table 1
Distribution of study population.

	Total Study Sample		Hypercapnic Subsample		Hypoxic Subsample		Unspecified	
	Count	Percentage	Count	Percentage	Count	Percentage	Count	Percentage
Never Used NIVH	493,010	98.70%	76,371	95.50%	314,623	99.40%	102,016	98.90%
NIVH within 60 Days	6707	1.30%	3629	4.50%	1941	0.60%	1137	1.10%
Time To Treatment								
00–07 Days	1962	0.40%	1143	1.40%	459	0.14%	360	0.35%
08–15 Days	1648	0.30%	955	1.20%	401	0.13%	292	0.28%
16–30 Days	1364	0.30%	666	0.80%	459	0.14%	239	0.23%
31–60 Days	1733	0.30%	865	1.10%	622	0.19%	246	0.24%
Total	**499,717**	**100%**	**80,000**	**100.00%**	**316,564**	**100.00%**	**103,153**	**100.00%**

Table 2
Characteristics of the study population.

Characteristics	NIVH Use		All	*P*-values
	No	Yes		
Patient count	**493,010**	**6707**	**499,717**	
Age	75.83 ± 10.53	72.13 ± 9.74	75.78 ± 10.53	0.0001
Female	56.50%	57.20%	56.50%	0.2640
Race-White	88.70%	89.40%	88.70%	0.0590
Race-Black	7.10%	6.50%	7.10%	0.0290
Race-Asian	1.00%	1.10%	1.00%	0.5060
Race-Hispanic	1.10%	0.90%	1.10%	0.0570
Race- American Indian/ Pacific Islander	0.70%	0.70%	0.70%	0.8160
Race -Other	1.40%	1.40%	1.40%	0.6940
Dual Medicare/Medicaid	25.90%	27.60%	25.90%	0.0020
ESRD	4.90%	1.70%	4.90%	0.0001
Inpatient Index [1]	37.20%	34.60%	37.10%	0.0001
Region 1: CT, ME, MA, NH, RI, VT	5.00%	2.90%	4.90%	0.0001
Region 2: NY, NJ, PR	7.00%	7.30%	7.20%	0.7270
Region 3: DE, MD, DC, WV, VA, PA	11.00%	9.20%	10.50%	0.0001
Region 4: NC, SC TN, FL, GA, AL, KY, MS	23.00%	25.00%	23.40%	0.0020
Region 5: MI, MN, OH, IL, IN, WI	18.00%	14.50%	17.90%	0.0001
Region 6: TX, LA, AR, OK, NM	12.00%	17.80%	12.50%	0.0001
Region 7: MO, KS, IA, NE	6.00%	5.80%	5.80%	0.8780
Region 8: ND, UT, SD, WY, CO, MT	4.00%	4.40%	4.00%	0.1130
Region 9: NV, AS, AZ, CA, GU, HI, MIS	10.00%	9.70%	10.30%	0.1180
Region10: AK, ID, OR, WA	3.00%	3.50%	3.50%	0.8610
Myocardial infarction	19.10%	12.50%	19.00%	0.0001
Malignancy, except neoplasm of skin	24.90%	17.00%	24.80%	0.0001
Cerebrovascular disease	25.40%	16.80%	25.30%	0.0001
Congestive heart failure	46.80%	35.90%	46.60%	0.0001
Chronic pulmonary disease	85.20%	90.50%	85.30%	0.0001
Diabetes	35.20%	29.50%	35.10%	0.0001
Diabetes with complications	22.30%	14.70%	22.20%	0.0001
Hemiplegia, paraplegia	4.00%	2.50%	3.90%	0.0001
Metastatic solid tumor	8.30%	4.00%	8.20%	0.0001
Mild liver disease	10.50%	6.70%	10.50%	0.0001
Moderate/severe liver disease	1.70%	0.70%	1.70%	0.0001
Peptic ulcer disease	4.10%	2.40%	4.00%	0.0001
Peripheral vascular disease	41.60%	30.80%	41.50%	0.0001
Renal disease	33.60%	19.40%	33.50%	0.0001
Rheumatologic disease	7.60%	5.90%	7.60%	0.0001
AIDS/HIV	0.40%	0.20%	0.40%	0.0001
Chronic Hypercapnia with or without chronic hypoxia	15.50%	54.10%	16.00%	0.0001
Chronic Hypoxia without chronic hypercapnia	63.80%	28.90%	63.30%	0.0001
Log (Prior 12 months Total Spending)	9.82 ± 1.44	9.34 ± 1.37	9.82 ± 1.44	0.0001

(1)Inpatient index is a flag that is coded 1 if the index COPD-CRF diagnosis was made during an inpatient stay.
(2)Chronic conditions comprise the Charlson Comorbidity Index.

These patients comprised 21% of the total sample, 21% of the control group and 17% of the NIVH treatment group. We analyzed how each of these subsamples responded to NIVH treatment as compared to untreated control groups with the same COPD-CRF phenotype.

Table 2 contains the sociodemographic and clinical characteristics of the overall study sample. The unweighted summary statistics show significant differences between the NIVH treatment group and the control group. For example, the NIVH treatment group was younger, had lower prior 12-month healthcare spending, and were more likely to have COPD-CRF with hypercapnia than those in the control group. The Charlson Comorbidity conditions all occurred more commonly in the control group than in the treatment group, except for a chronic pulmonary disease diagnosis occurring after a CRF diagnosis, which occurred in 91% of the treatment group and 85% of the control group.

An analysis of the characteristics of the study population by CRF phenotype found that hypercapnic patients tended to be more likely black, dually eligible for Medicare and Medicaid, diabetic, and to have received the COPD-CRF diagnosis during an inpatient stay. All differences were highly significant ($p < .0001$). These unadjusted results can be found in Table 1A in the Appendix.

4.2. Outcome results

4.2.1. Primary end point: time-to-death

Table 3 contains the hazard ratios for mortality associated with the different treatment initiation windows and different COPD-CRF phenotypes corrected for immortal time bias. Risk reduction for death associated with NIVH treatment in the full sample and the hypercapnic subsample significantly decreases as the time between diagnosis and treatment initiation increases. This suggests that the earlier a hypercapnic patient starts NIVH treatment, the greater the reduction in mortality. Of note, no mortality reduction was found in the hypoxic or unspecified COPD-CRF patients treated with NIVH in any treatment initiation window. In fact, hypoxic COPD-CRF patients had a significantly increased mortality risk in the 16–30 days and 31–60 days treatment initiation windows. Given that the hypercapnic subsample, comprising 54% of the full sample, is the only one associated with NIVH benefit, it is this subsample that is responsible for the benefit seen in the full sample analysis.

Table 4 contains results of the regression analysis for the full sample and the different COPD-CRF phenotypes and three treatment windows, and accounts for immortal time bias. Regardless of the specifications, NIVH was associated with improved survival in the full sample and in patients with hypercapnia. The immortal time bias analysis for the three treatment initiation windows and COPD-CRF phenotypes showed that NIVH became less effective in reducing risk of death in both the full sample and in hypercapnic COPD-CRF the longer the delay in treatment initiation (see the above comments regarding the effects of the hypercapnic sample on the full sample). As in Table 3, the hypoxic COPD-CRF group had an increased mortality risk if NIVH was started 0–30 days following diagnosis.

Table 3
Time-to-death models by ordinal treatment window results.

Treatment Window	Full Sample				Hypercapnic Subsample				Hypoxic Subsample				Unspecified			
	HR	Confidence Limits		p-values	HR	Confidence Limits		*P*-values	HR	Confidence Limits		*P*-values	HR	Confidence Limits		*P*-values
0-7days	0.70	0.64	0.76	0.0001	0.57	0.51	0.64	0.0001	1.01	0.84	1.35	0.6064	0.88	1.08	1.46	0.2280
8–15days	0.76	0.69	0.83	0.0001	0.69	0.62	0.77	0.0001	1.02	0.90	1.28	0.4391	0.85	1.07	1.87	0.1720
16–30days	0.92	0.84	1.02	0.0988	0.84	0.73	0.96	0.0110	1.23	1.01	1.34	0.0404	1.03	0.67	1.07	0.8280
31–60 days	1.10	1.01	1.19	0.0288	1.01	0.89	1.13	0.9152	1.54	1.34	1.76	<.0001	1.18	0.92	1.50	0.1866

Note: Estimates are corrected for immortal time bias.

Table 4
Death risk difference from cox proportional hazard models.

	Full Sample				Hypercapnic Subsample				Hypoxic Subsample				Unspecified			
Treatment Window	HR	Confidence Limits		p-values	HR	Confidence Limits		*P*-values	HR	Confidence Limits		*P*-values	HR	Confidence Limits		*P*-values
0–7 days	0.69	0.62	0.76	0.0001	0.57	0.50	0.66	0.0001	1.06	0.84	1.35	0.0606	0.97	0.73	1.28	0.8080
0–15 days	0.74	0.68	0.81	0.0001	0.64	0.57	0.71	0.0001	1.07	0.90	1.28	0.7965	0.92	0.75	1.14	0.4664
0–30 days	0.82	0.76	0.88	0.0001	0.70	0.64	0.77	0.0110	1.16	1.16	1.34	0.0404	0.98	0.8	1.11	0.7069

Note: Estimates are corrected for immortal time bias.

Table 5
Time-to-first inpatient admission after index date.

	Full Sample				Hypercapnic Subsample				Hypoxic Subsample				Unspecified			
Treatment Window	HR	Confidence Limits		p-values	HR	Confidence Limits		*P*-values	HR	Confidence Limits		*P*-values	HR	Confidence Limits		*P*-values
0–7 days	0.92	0.84	1.01	0.0670	0.85	0.75	0.96	0.0088	1.05	0.87	1.28	0.6013	1.08	0.87	1.34	0.5049
0–15 days	0.91	0.85	0.98	0.0110	0.85	0.78	0.93	0.0007	1.09	0.94	1.25	0.2519	0.96	0.82	1.13	0.6389
0–30 days	0.89	0.84	0.95	0.0002	0.85	0.78	0.92	0.0001	0.98	0.88	1.10	0.7573	0.97	0.85	1.12	0.7102

Note: Estimates are corrected for immortal time bias.

4.3. Outcome results

Secondary End Points:

Time-to-First Inpatient Admission and Time-to-First ED Visit after Index Date.

Table 5 presents the results of the Cox proportional hazard analysis for time-to-first hospitalization following the index date. Among patients with hypercapnia, NIVH reduced the risk of hospitalization. This model corrected for immortal time bias, was adjusted and IPTW reweighted, and showed all time to treatment initiation windows had comparable, statistically significant reductions in hospitalizations. Initiating NIVH between 0 and 7, 0–15, or 0–30 days, led to decreases in the risk of hospitalizations of approximately 23%. There was no effect of NIVH on the risk of hospitalizations in patients with hypoxic or unspecified COPD-CRF, regardless of the treatment initiation window.

Table 6 contains the results for time-to-first ED Visit following the index date. NIVH reduced the risk of ED visits for patients with hypercapnic COPD-CRF who begin treatment between 0 and 30 days, but not in the 0–7 day or 0- 15-day windows. No reduction in ED visits was seen in any treatment initiation window in unspecified or hypoxic COPD-CRF.

4.4. Outcome results

4.4.1. Secondary end point: Medicare expenditures

Table 7 presents the Medicare healthcare expenditures for the year following the diagnosis of COPD-CRF. Results are shown for both the NIVH treated group and the control group as a function of time to initiation of NIVH, if it was started, and for the phenotype of CRF.

In the hypercapnic COPD-CRF group, starting NIVH in the 0–7 day or 0-15-day windows resulted in significant reductions in Medicare spending of $5484 ($p < .0001$) and $3412 ($p < .0001$) respectively in the year following diagnosis. Beginning treatment in the 0–30-day window resulted in no significant change in spending compared to the untreated patients. These results suggest that, as with mortality reduction, the sooner NIVH is begun following a diagnosis of hypercapnic COPD-CRF, the greater are the healthcare cost savings.

Irrespective of treatment initiation window, NIVH use in hypoxic COPD-CRF patients resulted in a significant ($p < .0001$) increase in Medicare expenditures. For unspecified patients, if NIVH was initiated in the 8–15 day window, there was a reduction in Medicare expenditures of $1184 ($p < .0001$), but if NIVH was initiated in either of the other two windows, increases in Medicare expenditures were observed.

Table 6
Time-to-first ED visit after index date.

	Full Sample				Hypercapnic Subsample				Hypoxic Subsample				Unspecified			
Treatment Window	HR	Confidence Limits		p-values	HR	Confidence Limits		*P*-values	HR	Confidence Limits		*P*-values	HR	Confidence Limits		*P*-values
0–7 days	0.96	0.89	1.05	0.3777	0.92	0.83	1.03	0.1448	1.05	0.89	1.25	0.5645	1.10	0.91	1.33	0.3116
0–15 days	0.96	0.90	1.02	0.1498	0.92	0.85	1.00	0.0582	1.06	0.93	1.20	0.3771	1.00	0.87	1.16	0.9974
0–30 days	0.94	0.89	0.99	0.0153	0.92	0.86	0.99	0.0209	0.99	0.90	1.10	0.8969	0.98	0.86	1.11	0.7090

Note: Estimates are corrected for immortal time bias.

Table 7
Effect of NIVH on medicare expenditures.

		Full Sample			Hypercapnic Subsample			Hypoxic Subsample			Unspecified		
Treatment Window	Treatment	Healthcare Costs for following year	Standard Error	Pr > ChiSq	Healthcare Costs for following year	Standard Error	Pr > ChiSq	Healthcare Costs for following year	Standard Error	Pr > ChiSq	Healthcare Costs for following year	Standard Error	Pr > ChiSq
0–7days	**NIVH**	$41,143	101.49	0.0001	$41,598	234.23	0.0001	$39,565	6194.20	0.0001	$38,546	330.63	0.0001
0–7days	**Comparison**	$43,209.	106.88	0.0001	$47,082	259.28	0.0001	$38,050	6194.18	0.0001	$38,522	334.58	0.0001
0–7days	**Difference**	<$2066>	100.06	0.0001	-<$5484>	279.29	0.0001	$1515	138.24	0.0001	$24	273.41	0.9812
0–15days	**NIVH**	$42,983	102.69	0.0001	$43,944	241.87	0.0001	$44,069	141.75	0.0001	$36,987	291.21	0.0001
0–15days	**Comparison**	$43,598	104.55	0.0001	$47,356	255.63	0.0001	$38,291	118.95	0.0001	$38,171	302.59	0.0001
0–15days	**Difference**	-<$615>	101.47	0.0001	<$3412>	282.12	0.0001	$5778	139.68	0.0001	<$1184>	261.37	0.0001
0–30days	**NIVH**	$46,357	108.53	0.0001	$48,090	263.66	0.0001	$46,398	144.7	0.0001	$39,589	296.92	0.0001
0–30days	**Comparison**	$43,699	102.61	0.0001	$47,737	258.12	0.0001	$38,346	115.98	0.0001	$38,222	283.85	0.0001
0–30days	**Difference**	$2658	106.15	0.0001	$352.18	296.35	0.0001	$8052	144.79	0.0001	$1366	263.79	0.0001

5. Discussion

This is the third Medicare claims data study showing significant clinical benefits using NIVH in COPD-CRF patients [8,10], and the first to demonstrate cost savings associated with NIVH use. Additionally, this is the first study to report outcomes as a function of COPD-CRF phenotype and timing of NIVH initiation.

Since one important physiological effect of mechanical ventilation is to lower pCO2, many experts suggest limiting NIVH in COPD-CRF to hypercapnic patients theorizing that only these patients will benefit [7, 11–13].While this recommendation makes sense, we are unaware of any published data empirically investigating this idea. Additionally, the optimal time to prescribe NIVH for COPD-CRF is controversial with some experts suggesting waiting several weeks after an exacerbation before beginning NIVH while others favor immediate treatment. This uncertainty is underscored by a recent practice guideline for NIVH use in COPD-CRF [7] and a technical expert panel on the same topic [13] coming to different conclusions. We therefore designed our study to investigate how the timing of initiation of NIVH affected the outcomes of death, hospitalization risk, ED utilization, and Medicare expenditures in different phenotypes of COPD-CRF.

5.1. Mortality

In both the phenotype and time to treatment initiation analysis, only the hypercapnic COPD-CRF group had a reduction in mortality associated with NIVH. Specifically, hypercapnic COPD-CRF patients begun on NIVH within 0–7 days, 8–15 days and 16–30 days of diagnosis had significant reductions in the risk of death with HR of 0.57 (CI 0.51–0.64, $p < .0001$), 0.69 (CI 0.62–0.77, $p < .0001$), and 0.84 (CI 0.73–0.96, $p = .01$) respectively, suggesting that the earlier this group started NIVH, the more they benefitted. Conversely, neither the hypercapnic patients started on NIVH between days 31–60 nor the unspecified or hypoxic patients started on NIVH during any treatment window had a reduction in mortality.

5.2. Hospitalizations and ED visits

In hypercapnic COPD-CRF patients, NIVH started at 0–7 days, 0–15 days, and 0–30 days following diagnosis, was associated with a significant, similar reduction in the risk of hospitalization of approximately 23%. As with the mortality reduction, if NIVH was begun more than 30 days following diagnosis, no reduction in hospitalizations was seen in the hypercapnic subsample and no reduction in hospitalizations in the unspecified and hypoxic COPD-CRF subsample occurred regardless of when treatment began.

Furthermore, only hypercapnic COPD-CRF patients begun on NIVH between 0 and 30 days had a reduction in ED visits with a HR of 0.94 (CI 0.89–0.99, $p = .020$). Those started between 0-7 days and 0–15 days had no significant reduction in ED visits with HR of 0.96 (CI 0.90–1.02) and 0.94 (CI 0.89–1.00) respectively. These results suggest that hypercapnic COPD-CRF patients begun on NIVH shortly after diagnosis may have a reduction in mortality at the expense of higher ED use. However, these ED visits do not result in increased hospitalizations since hospitalizations are significantly reduced in hypercapnic COPD-CRF treated with NIVH within 30 days of diagnosis. One possible explanation for this observation may be that NIVH improves patients' clinical condition so that an ED visit, instead of a hospitalization, provides a sufficient level of care in the event of an exacerbation.

5.3. Economic outcomes

The economic impact on the Medicare program of NIVH use in COPD-CRF has never been reported. To address this, we controlled for immortal time bias and analyzed total Medicare expenditures of Part A (covering inpatient hospital, skilled nursing facility, hospice, lab tests,

and home health care) and Part B (covering health care providers' services, outpatient care, and durable medical equipment) in the NIVH group compared to the control group.

As with the clinical benefits, the economic benefit of reduced total cost of care was greatest in hypercapnic COPD-CRF patients and was most pronounced the earlier treatment was begun. For hypercapnic COPD-CRF patients, Medicare expenditures for the year following NIVH initiation was decreased by $5484 (11.6%) compared to controls if treatment was begun within 7 days of diagnosis ($p < .001$). The cost reduction was $3412 (7.2%) if NIVH was begun 0–15 days after diagnosis ($p < .001$), and the cost of care benefit disappeared if NIVH was begun more than 15 days after diagnosis. Importantly, even in the hypercapnic group started more than 15 days following diagnosis, NIVH use was not associated with an increase in Medicare expenditures.

The unspecified COPD-CRF phenotype had no change in costs for those started at 0–7 days, a $1184 decrease if started between 8 and 15 days ($p < .0001$), and a $1366 increase in Medicare expenditures for those begun on NIVH between 16 and 30 days after diagnosis ($p < .0001$) resulting in cost neutrality for this group. In hypoxic COPD-CRF, NIVH use was associated with higher Medicare expenditures compared to controls in all treatment initiation windows ($p < .001$).

5.4. Device choice to deliver NIVH

Another area of controversy involves the particular devices best suited to deliver NIVH. Some experts recommend a step approach where less powerful and sophisticated, but cheaper, machines such as time-cycled bi-level devices termed respiratory assist devices by CMS (RADS, HCPCS EO471) or bi-level positive airway pressure devices (BPAP, HCPCS EO470) are used initially, with the more expensive home ventilators (HCPCS EO466) reserved for those who fail initial therapy [7,9,13]. To our knowledge, no clinical trial has been published testing this proposed "tried and failed" strategy.

Attempting to answer this question, we analyzed the data based on the type of device used to treat COPD-CRF. During the 4-year period from 2016 to 2020, total prescriptions for devices prior to exclusions showed 96 patients (1.2% of the NIVH cohort) received RADS, 512 (6.6%) received BPAP, and 7329 (92%) received home ventilators. The small sample sizes of RADS and BPAP patients did not allow for a statistically meaningful analysis of their effect on COPD-CRF outcomes. Therefore, our results are limited to patients treated with ventilators and our opinion is that given the overwhelming use of ventilators by US providers, these devices are the current standard of care to treat hypercapnic COPD-CRF. Use of RADS or BPAP in this population should be confined to clinical trials until they have been shown safe and effective in treating hypercapnic COPD-CRF.

5.5. Limitations

The major limitation of this study is its retrospective, non-randomized design. To address this, we minimized confounding factors by adjusting the models using numerous socio-demographic and clinical factors. We limited selection bias by employing IPTW propensity scoring techniques and accounted for immortal time bias by modeling each beneficiary in the treatment group as a control group member for the period between the diagnosis date and the treatment initiation date, and as a treatment group member thereafter.

Since the Medicare 100% RIF claims data does not include information from non-fee-for-service populations such as health maintaince organizations, Part C comprehensive Medicare Advantage plans, or for people not covered by Medicare, these results should not be generalized to those populations.

Currently, 3.4 million COPD patients are enrolled in traditional fee-for-service (FFS) Medicare. This represents 60% of all Medicare COPD patients and 23% of all U.S. COPD patients [19]. Since COPD-CRF, the most severe form of COPD, is more common with advancing age, and since older Medicare patients are more likely to enroll in fee-for-service Medicare, it is likely that the COPD-CRF patients which are the subject of this study represent a significantly larger proportion of the overall Medicare and general U.S. COPD population then these percentages imply [20,21].

Finally, since the Medicare RIF does not contain data regarding compliance with NIVH or the specific pCO2 level above normal used to establish hypercapnia, we cannot comment as to any correlation between hours of NIVH use or degree of pCO2 elevation and the outcomes presented in this paper.

6. Conclusions

This retrospective cohort study suggests that treating hypercapnic COPD-CRF with NIVH is associated with significant reductions in mortality, hospitalizations, and total Medicare costs. Additionally, the sooner NIVH is begun following the diagnosis of hypercapnic COPD-CRF, the greater are these benefits. Patients with hypoxic COPD-CRF or unspecified COPD-CRF do not appear to benefit from NIVH.

Author confirmation

As submitting author, I attest that I have written consent from all authors to submit the manuscript, and that all authors accept complete responsibility for the contents of the manuscript entitled "Early Initiation of Non-Invasive Ventilation at Home Improves Survival and Reduces Healthcare Costs in COPD Patients with Chronic Hypercapnic Respiratory Failure."

This manuscript has not been previously published. It is not currently under consideration elsewhere. The work reported here will not be submitted for publication elsewhere until a final decision has been made as to its acceptability by *Respiratory Medicine*.

Finally, I attest that the manuscript is independent and original work, and all conclusions are from the authors. At the time of its writing, Dr. Frazier was employed by VieMed which funded the study, and the other four authors were employed by Dobson DaVanzo & Associates, LLC. The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript:

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CRediT authorship contribution statement

William D. Frazier: Writing – review & editing, Writing – original draft, Study concept and design, clinical research, review of clinical findings, draft manuscript. **Joan E. DaVanzo:** Writing – review & editing, Writing – original draft, Heath: Study concept and design, research, review, draft manuscript. **Allen Dobson:** Writing – review & editing, Writing – original draft, Heath: Study concept and design, research, review, draft manuscript. **Komi Mati:** Writing – review & editing, Writing – original draft, Econometric methodology and programmed all analyses using 100% claims, draft and reviewed manuscript.

Appendix

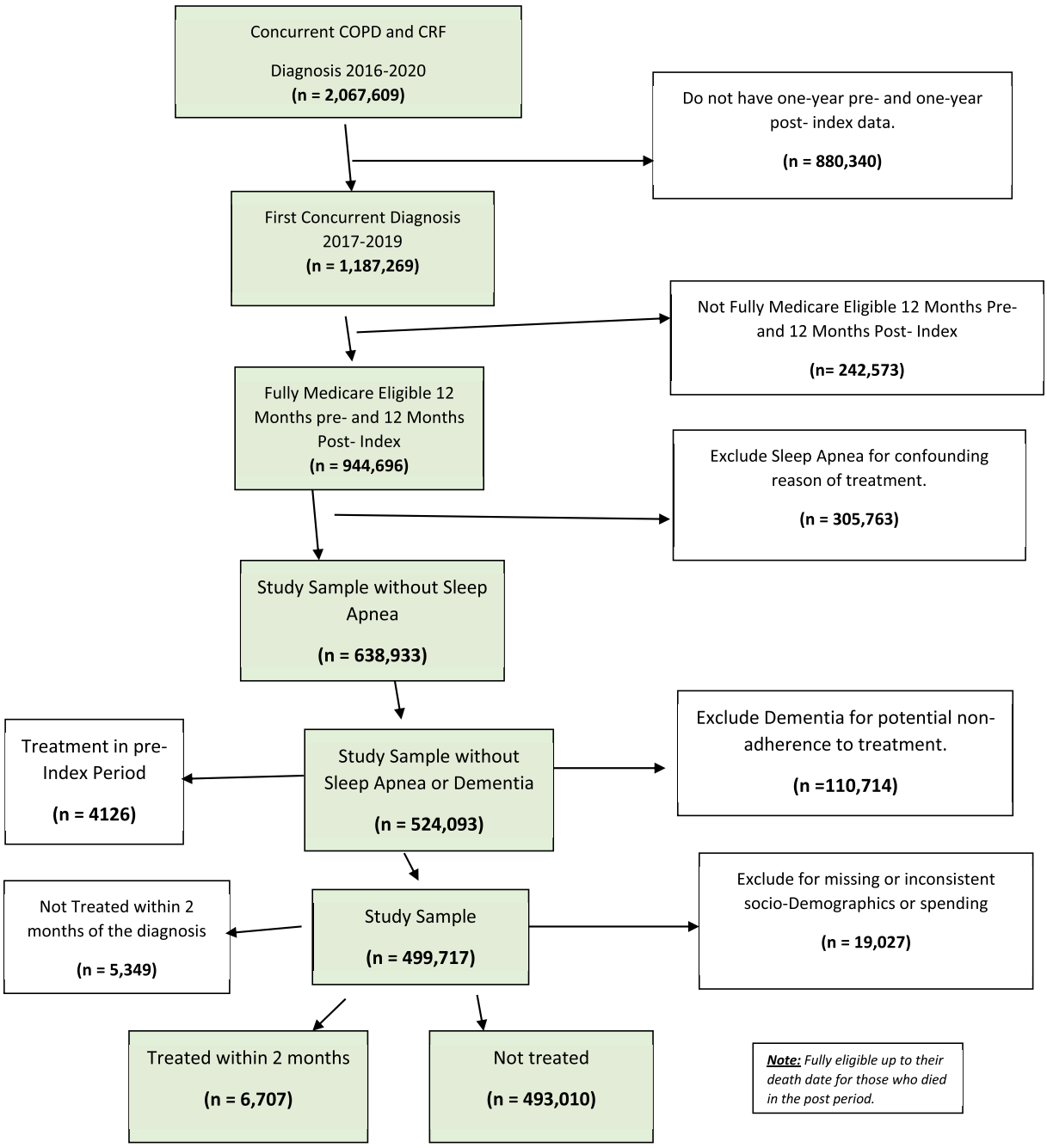

Fig. 1A. Flow chart of patients who met inclusion/exclusion criteria for the study population.

Table 1A
Patient Characteristics by CRF Phenotype

Characteristics	CRF Phenotype			All	P-values
	Hypercapnia	Hypoxia	Unspecified		
Patient count	**80,000**	**316,564**	**103,153**	**499,717**	
Age	74.18±10.72	76.28±10.30	75.49±10.94	75.78±10.53	0.0001
Female	57.03%	56.67%	55.66%	56.50%	0.0001
Race-White	87.08%	89.95%	86.10%	88.70%	0.0001
Race-Black	8.48%	6.21%	8.90%	7.10%	0.0001
Race-Asian	1.08%	0.86%	1.31%	1.00%	0.0001
Race-Hispanic	1.09%	0.97%	1.48%	1.10%	0.0001
Race-American Indian/Pacific Islander	0.76%	0.71%	0.65%	0.70%	0.0188
Race-Other	1.52%	1.30%	1.56%	1.40%	0.0001
Dual Medicare/Medicaid	30.99%	23.63%	28.90%	25.90%	0.0001
ESRD	4.47%	4.55%	6.07%	4.90%	0.0001
Inpatient Index	45.85%	36.89%	31.05%	37.10%	0.0001
Region1: CT, ME, MA, NH, RI, VT	4.81%	5.27%	3.98%	4.90%	0.0001
Region2: NY, NJ, PR	8.03%	6.38%	9.20%	7.20%	0.0001
Region3: DE, MD, DC, WV, VA, PA	11.04%	10.29%	10.64%	10.50%	0.0001
Region4: NC, SC, TN, FL, GA, AL, KY, MS	24.05%	22.69%	25.08%	23.40%	0.0001
Region5: MI, MN, OH, IL, IN, WI	18.57%	18.12%	16.48%	17.90%	0.0001
Region6: TX, LA, AR, OK, NM	12.62%	12.21%	13.41%	12.50%	0.0001
Region7: MO, KS, IA, NE	5.97%	6.23%	4.48%	5.80%	0.0001
Region8: ND, UT, SD, WY, CO, MT	2.45%	4.76%	2.70%	4.00%	0.0001
Region9: NV, AS, AZ, CA, GU, HI, MIS	8.90%	10.13%	11.84%	10.30%	0.0001
Region10: AK, ID, OR, WA	3.57%	3.91%	2.17%	3.50%	0.0001
Myocardial Infarction	17.51%	18.73%	21.18%	19.00%	0.0001
Malignancy, Except Neoplasm of Skin	20.67%	25.85%	24.84%	24.80%	0.0001
Cerebrovascular Disease	22.70%	24.86%	28.50%	25.30%	0.0001
Congestive Heart Failure	46.38%	45.64%	49.94%	46.60%	0.0001
Chronic Pulmonary Disease	82.84%	85.65%	85.97%	85.30%	0.0001
Diabetes	35.42%	33.90%	38.71%	35.10%	0.0001
Diabetes with Complications	21.85%	21.57%	24.60%	22.20%	0.0001
Hemiplegia, Paraplegia	4.43%	3.43%	5.13%	3.90%	0.0001
Metastatic Solid Tumor	6.26%	8.81%	8.03%	8.20%	0.0001
Mild Liver Disease	9.61%	10.26%	11.77%	10.50%	0.0001
Moderate/Severe Liver Disease	1.54%	1.55%	2.06%	1.70%	0.0001
Peptic Ulcer Disease	3.82%	3.84%	4.83%	4.00%	0.0001
Peripheral Vascular Disease	38.58%	41.36%	44.01%	41.50%	0.0001
Renal Disease	29.88%	33.21%	36.97%	33.50%	0.0001
Rheumatologic Disease	6.30%	7.79%	7.96%	7.60%	0.0001
AIDS/HIV	0.43%	0.37%	0.49%	0.40%	0.0001
Chronic Hypercapnia	100.00%	0.00%	0.00%	16.00%	0.0001
Chronic Hypoxia	0.00%	100.00%	0.00%	63.30%	0.0001
Log(Prior 12 Months Total Spending)	9.65±1.57	9.79±1.41	10.03±1.41	9.82±1.44	0.0001

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