Respiratory Medicine 177 (2021) 106291

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: http://www.elsevier.com/locate/rmed

Non-invasive ventilation at home improves survival and decreases healthcare utilization in medicare beneficiaries with Chronic Obstructive Pulmonary Disease with chronic respiratory failure

William D. Frazier [a,*], Richard Murphy [b], Emma van Eijndhoven [b]

[a] Viemed Healthcare Inc, United States
[b] PRECISIONheor, United States

ARTICLE INFO

Keywords:
Chronic obstructive pulmonary disease
Chronic respiratory failure
Non-invasive ventilation
Survival
Mortality
Healthcare utilization

ABSTRACT

Background: Patients with Chronic Obstructive Pulmonary Disease with chronic respiratory failure (COPD-CRF) experience high mortality and healthcare utilization. Non-invasive home ventilation (NIVH) is increasingly used in such patients. We examined the associations between NIVH and survival, hospitalizations, and emergency room (ER) use in COPD-CRF Medicare beneficiaries.

Materials and methods: Retrospective cohort study using the Medicare Limited Data Set (2012–2018). Patients receiving NIVH within two months of CRF diagnosis (treatment group) were matched on demographic and clinical characteristics to patients never receiving NIVH (control group). CRF diagnosis was identified using ICD-9-CM/ICD-10-CM codes. Time to death, first hospitalization, and first ER visit were estimated using Cox regressions.

Results: After matching, 517 patients receiving NIVH and 511 controls (mean age: 70.6 years, 44% male) were compared. NIVH significantly reduced risk of death (aHR: 0.50; 95%CI: 0.36–0.65), hospitalization (aHR: 0.72; 95%CI: 0.52–0.93), and ER visit (aHR: 0.48; 95%CI: 0.38–0.58) at diagnosis. The NIVH risk reduction became smaller over time for mortality and ER visits, but continued to accrue for hospitalizations. One-year post-diagnosis, 28% of treated patients died versus 46% controls. For hospitalizations and ER visits, 55% and 72% treated patients experienced an event, respectively, versus 67% and 92% controls. The relative risk reduction was 39% for mortality, 17% for hospitalizations, and 22% for ER visits. Number needed to treat were 5.5, 9, and 5 to prevent a death, hospitalization, or ER visit one-year post-diagnosis, respectively.

Conclusion: NIVH treatment is associated with reduced risk of death, hospitalizations, and ER visits among COPD-CRF Medicare beneficiaries.

1. Introduction

Chronic obstructive pulmonary disease (COPD) affects approximately 7% of the adult population in the U.S [1]. It is the third leading cause of death and is responsible for an estimated 120,000 deaths annually [2]. Furthermore, COPD is the primary diagnosis for approximately 1.5 million emergency room (ER) visits and 700,000 hospitalizations each year. Patients who develop chronic respiratory failure as a consequence of COPD (COPD-CRF) are at a high risk of poor health outcomes, with one international cohort of clinically stable COPD-CRF patients showing a three-year mortality of nearly 20% [3].

COPD-CRF has no known cure, and treatment is primarily supportive. Interventions such as non-invasive ventilation at home (NIVH) are sometimes used to mitigate the adverse outcomes seen in patients with COPD-CRF, including the risk of death. For example, a randomized controlled trial conducted in 2014 showed that NIVH decreased mortality in COPD-CRF patients when compared to patients receiving standard treatment [4]. Several additional studies have reported decreased healthcare utilization in patients who receive NIVH compared to other therapies, such as oxygen therapy alone [4–10]. Furthermore, a meta-analysis published in 2020 concluded that NIVH reduced hospitalizations in COPD-CRF, but did not find that NIVH reduced mortality [11].

Despite the data demonstrating the effectiveness of NIVH for patients

* Corresponding author. 150 Butler Drive Ridgeland, MS, 39157, United States.
E-mail address: wfrazier@viemed.com (W.D. Frazier).

https://doi.org/10.1016/j.rmed.2020.106291
Received 19 November 2020; Received in revised form 22 December 2020; Accepted 23 December 2020
Available online 30 December 2020

with COPD-CRF, and despite a recently published national practice guideline supporting the use of NIVH in COPD-CRF patients [12], NIVH remains infrequently used in the U.S. According to an estimate from the Department of Health and Human Services, only 47,000 of the estimated 1.6 million adults in the U.S. diagnosed with COPD-CRF received NIVH in 2017, resulting in an approximate 3% utilization rate [13–15]. One reason for the slow adoption of NIVH may be that older clinical data suggested this therapy had little to no benefit in COPD-CRF patients [16, 17]. Additionally, the benefit of NIVH has largely been shown in European trials and only rarely have improved clinical outcomes been demonstrated in U.S populations.

To develop a greater understanding of the potential benefits of NIVH in a U.S population, we evaluated the association of NIVH with the risk of mortality, hospitalizations, and ER visits in Medicare beneficiaries diagnosed with COPD-CRF.

2. Materials and methods

2.1. Data source

Data from January 1, 2012 through December 31, 2018 reported in the Medicare Limited Data Set (LDS) were used for this study. The LDS contains health care claims data from Medicare Parts A and B for a randomly selected 5% sample of the complete Medicare fee-for-service population [18]. The LDS database does not contain information on retail medication prescriptions from Medicare Part D. Because these data are de-identified in preparation for use by external researchers, review by an Institutional Review Board was not required.

2.2. Study cohorts

We restricted our sample to patients with a CRF diagnosis (ICD-9-CM: 518.53, 518.83, 518.84; CD-10-CM: J95.822, J96.10, J96.11, J96.12, J96.20, J96.21, J96.22) and a COPD diagnosis (ICD-9-CM: 490, 491.0, 491.1, 491.8, 492.0, 492.8, 491.20, 491.21, 491.22, 496; ICD-10-CM: J40, J41.1, J41.8, J42, J43.0, J43.1, J43.2, J43.8, J43.9, J44.0, J44.1, J44.9) made between January 1, 2012 and December 31, 2018. We defined the date of diagnosis for CRF as the first time a medical claim appeared in the Medicare LDS with a CRF ICD-9-CM or ICD-10-CM diagnosis code. This date was used as the start of the analytic period (index date). We used all available data files in the Medicare LDS data set, meaning claims could come from an inpatient visit, an outpatient visit, emergency room visit, a skilled nursing home facility, hospice care, home health care, or a durable medical equipment supplier. Patients were required to have 6 months of continuous Medicare enrollment prior to the index date and a minimum of 12 months of enrollment following the index date, with an exception for subjects who died during the first 12 months post-index. Because NIVH also treats obstructive sleep apnea, patients with a diagnosis of sleep apnea (ICD-9-CM: 327.23; ICD-10-CM: G47.33) at any time during the study were excluded [19]. Patients with evidence of dementia (ICD-9-CM: 290.x, 294.1, 331.2; ICD-10-CM: F00.x–F03.x, F05.1, G30.x, G31.1) in the 6 months pre-index period were also excluded as it has been found that patients with dementia may have difficulty tolerating NIVH [20].

The treatment cohort consisted of all patients identified using the above stated criteria who received NIVH within two months of the index CRF diagnosis. NIVH treatment was identified through billing data (Durable Medical Equipment file) using Healthcare Common Procedure Coding System (HCPCS; pre-2016 HCPCS E0460, E0461, E0464; and post-2016 HCPCS E0466) in the Medicare LDS. The control cohort consisted of all patients meeting the above stated criteria who did not receive NIVH at any time during the study period.

Study cohorts were matched using a propensity score matching (PSM) nearest neighbor (1:1) procedure [21]. The propensity score is the likelihood an individual receives treatment and we calculated it for all individuals in the treatment and control groups as a function of observable clinical and demographic attributes. Each individual in the treatment group was matched to an individual in the control group, based on minimizing the difference in propensity scores. The demographic and clinical factors used in the propensity score matching process included race/ethnicity, gender, age, region of the country, components of the Charlson Comorbidity Index to control for the presence of chronic diseases, total health care spending for the 6 months prior to CRF diagnosis, county-level smoking prevalence, and comorbid hypercapnia when such information was available (only identifiable through ICD-10-CM codes which were introduced in October 2015).

2.3. Outcomes

The pre-specified primary study endpoint was all-cause mortality following CRF diagnosis. Secondary outcomes were time to first hospital admission and time to first emergency room visit. All patients were followed from CRF diagnosis until event occurrence or censored at the end of the study period (December 31, 2018).

2.4. Statistical analysis

We estimated the association of NIVH with survival, time to first hospitalization, and time to first ER visit over the entire study period using Cox regression time-to-event analysis. Our main analyses were performed on the PSM cohorts to estimate the average treatment on the treated effects. We controlled for the same demographic and clinical factors that the cohorts were matched on in the Cox regressions. This is a doubly robust method, as both ways can produce an unbiased estimate of the treatment effect if correctly specified [22].

We tested the assumption of proportional hazards in our Cox models by regressing the Schoenfeld residuals on a time index [23]. Because the semiparametric Cox model assumes that the ratio of the treatment group hazard to the control group hazard is constant over time, a violation of this assumption may yield biased estimates [24]. Since evidence of violation of the proportional hazards assumption was found in our test, we followed standard practice and included a time-by-treatment interaction in the regression equations [25]. This approach results in the simultaneous estimation of two parameters related to the treatment effect: a hazard ratio describing the difference in event rates at the start of the analysis period and a second parameter describing the rate of change in the hazard ratio over time.

Because both the propensity score estimation procedure and the regression models were computed with error, we used a bootstrap procedure to calculate standard errors that incorporate both sources of uncertainty. This approach has previously been demonstrated through simulation to correctly estimate standard errors in two-part models [26].

In addition to reporting hazard ratios, we estimated the risk difference (RD), the relative risk ratio (RRR), and the number needed to treat (NNT) at one-year after index date [27]. After estimating the Cox model, we computed the mean predicted probability of experiencing an event within the first year assuming everyone is untreated ($\bar{p}_{T=0}$), and assuming everyone is treated ($\bar{p}_{T=1}$). The RD was calculated as the difference between these mean predicted probabilities ($\bar{p}_{T=0} - \bar{p}_{T=1}$). The RRR was calculated as the difference divided by the mean predicted probability assuming everyone is untreated ($\frac{\bar{p}_{T=0}-\bar{p}_{T=1}}{\bar{p}_{T=0}}$). The NNT was calculated as the inverse of the RD ($\frac{1}{\bar{p}_{T=0}-\bar{p}_{T=1}}$).

3. Results

3.1. Study sample

Initial sample selection procedures resulted in 517 COPD-CRF patients who used NIVH and who met all study inclusion criteria (treatment group), and an additional 44,281 COPD-CRF patients without evidence of NIVH use (unadjusted control group). Compared to the

unadjusted control group, the treatment group was younger (mean 70.6 years vs. 75.1 years, $p < 0.001$), more likely to reside in the Western US (23% vs. 17%, $p < 0.001$), had lower total healthcare spending in the 6 months pre-index (mean $17,897 vs. $32,370, $p < 0.001$), and had significantly lower rates of comorbidities (Table 1). Following propensity score matching, all 517 treatment group subjects were retained and matched to 511 control subjects. Six members of the treatment group were matched to the same control subjects that were used for other treatment subjects explaining why there are 517 treated patients and only 511 controls. The final groups were balanced on all predictors.

Time-to-event analysis.

Table 2 shows the results of the Cox time-to-event analyses over the entire study period. In the assessment of time to death, NIVH use provided a substantive and significant survival benefit over no NIVH use. Users of NIVH had a 50% lower risk of death at CRF diagnosis compared to comparable patients who did not use NIVH (aHR: 0.502; 95%CI: 0.359–0.646; $p < 0.001$). The magnitude of the mortality reduction seen with NIVH slowly declined over time (decay rate: 1.001; 95%CI: 1.000–1.001; $p < 0.001$), with the largest mortality reduction occurring in the early period following the index date. The risk reduction for mortality provided by NIVH disappeared after approximately 23 months of use. Fig. 1A shows the Cox proportional hazard regression plot for survival.

Table 2
Survival adjusted hazard ratio results.

	Survival	Hospitalization	ER Visit
	PSM model aHR (95%CI)	PSM model aHR (95%CI)	PSM model aHR (95%CI)
NIVH	0.502*** (0.359, 0.646)	0.723*** (0.518, 0.927)	0.481*** (0.381, 0.580)
Rate of decay for NIVH	1.001*** (1.000, 1.001)	0.1000 (0.999, 1.001)	1.001*** (1.000, 1.002)

Abbreviations: CI = Confidence Interval, aHR = Adjusted Hazard Ratio, NIVH = Non-invasive ventilation at home, PSM = Propensity score matching.
***$p < 0.01$.

For time to first hospitalization, NIVH provided a 28% decrease in the risk of subsequent hospitalizations at CRF diagnosis (aHR: 0.723; 95%CI: 0.518–0.927; $p < 0.001$), and this benefit continued to accrue over time (decay rate: 1.000; 95%CI: 0.999–1.000). For the time to first ER visit, patients with NIVH experienced a 52% reduction in the risk of an emergency room visit at CRF diagnosis (aHR: 0.481; 95%CI: 0.381–0.580; $p < 0.001$) The magnitude of the reduction in ER visits slowly decreased over time (decay rate: 1.001; 1.000–1.002; $p < 0.001$) and disappeared after approximately 24.5 months of NIVH use. Fig. 1B and C shows the Cox proportional hazard regression plots for

Table 1
Balance diagnostics.

	Treatment group	Control group (unmatched)	Difference in means *P*-value	Treatment group	Control group (matched)	Difference in means *P*-value
Patient count	517	44,281		517	511	
Age at index date (mean, SD)	70.6 (10.8)	75.1 (10.9)	<0.001	70.6 (10.8)	70.9 (11.5)	0.62
Gender						
Female	56%	56%	0.73	56%	56%	0.77
Male	44%	44%	0.73	44%	44%	0.77
Race						
White	86%	88%	0.20	86%	83%	0.15
Black	8%	8%	0.86	8%	11%	0.18
Asian	2%	1%	0.14	2%	2%	0.49
Hispanic	2%	1%	0.33	2%	2%	0.80
Native American	1%	1%	0.38	1%	1%	0.99
Other/Unknown	1%	1%	0.72	1%	1%	0.99
Region at index date						
North East	13%	16%	0.07	13%	15%	0.43
Midwest	19%	25%	<0.001	19%	19%	0.93
South	46%	42%	0.07	46%	45%	0.84
West	23%	17%	<0.001	23%	22%	0.62
Medical spending 6 months pre-index date (mean, SD)	$17,897 ($23,449)	$32,370 ($50,710)	<0.001	$17,897 ($23,449)	$19,294 ($25,070)	0.32
County-level smoking prevalence at index date (mean, SD)	0.2 (0.04)	0.2 (0.04)	<0.001	0.2 (0.04)	0.2 (0.04)	0.36
Hypercapnia[1]	12%	3%	<0.001	12%	12%	0.95
Charlson Comorbidity Index Comorbidities[2]						
AIDS/HIV	0%	0%	0.51	0%	0%	0.99
Cerebrovascular disease	13%	22%	<0.001	13%	15%	0.38
Congestive heart failure	35%	44%	<0.001	35%	40%	0.13
Chronic pulmonary disease	88%	81%	<0.001	88%	88%	0.90
Diabetes	19%	20%	0.65	19%	22%	0.31
Hemiplegia, paraplegia	4%	4%	0.98	4%	4%	0.84
Any malignancy, except neoplasm of the skin	11%	15%	0.01	11%	11%	0.81
Metastatic solid tumor	3%	7%	<0.001	3%	3%	0.55
Mild liver disease	4%	7%	0.03	4%	5%	0.53
Moderate/severe liver disease	1%	1%	0.17	1%	0%	0.32
Myocardial infarction	8%	16%	<0.001	8%	7%	0.76
Peptic ulcer disease	1%	3%	0.004	1%	1%	0.75
Peripheral vascular disease	19%	31%	<0.001	19%	21%	0.38
Renal disease	14%	28%	<0.001	14%	17%	0.27
Rheumatologic disease	4%	6%	0.11	4%	5%	0.63

Note: (1) Hypercapnia could only be identified through ICD-10-CM codes (introduced in October, 2015); the ICD-9-CM codes do not provide enough detail to identify phenotype. As such, the hypercapnia percentage may be higher in real life than the number presented in this table. (2) We used ICD-9-CM and ICD-10-CM diagnosis codes for all comorbidities included in the Charlson Comorbidity Index as identified by Quan et al. [31]. These comorbidities were present within 6 months prior to index date.

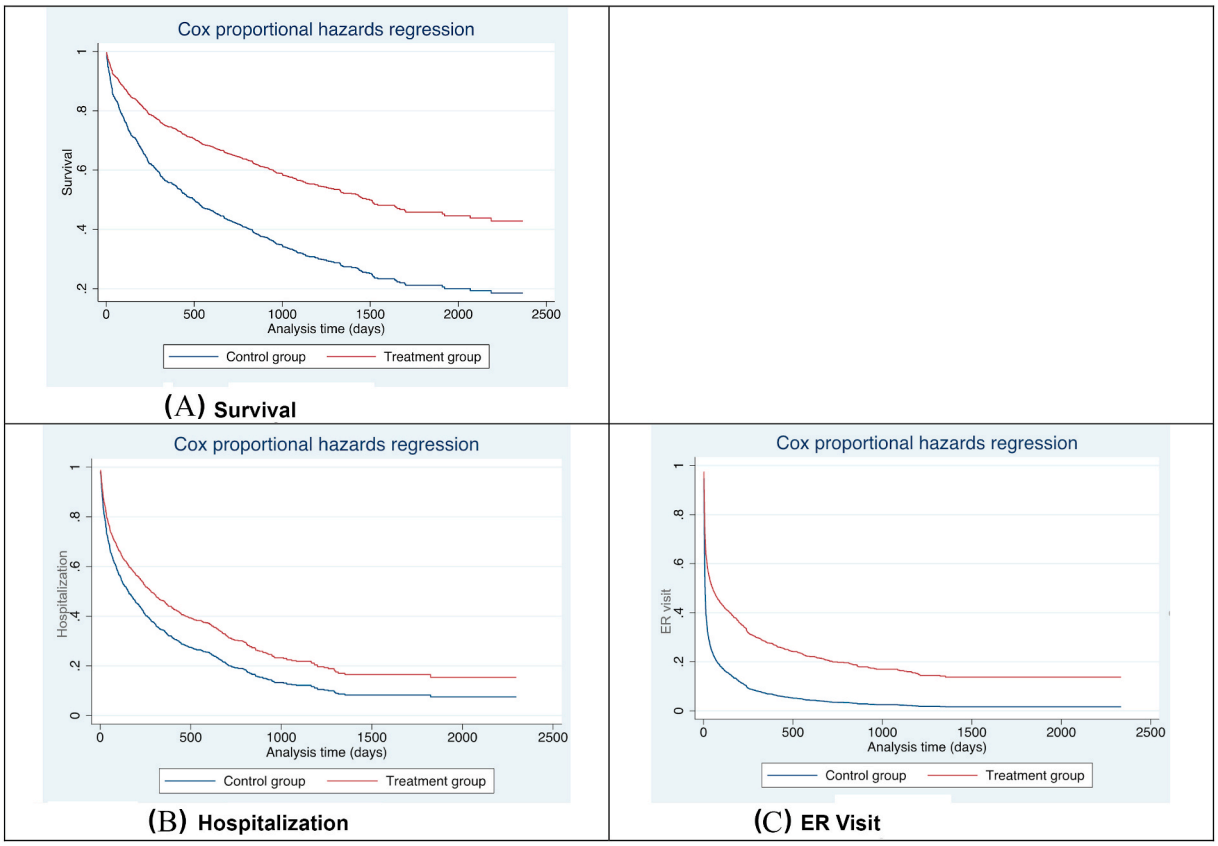

Fig. 1. Cox Proportional Hazards Regressions for A) overall survival, B) time to first hospitalization, C) time to first ER visit.

hospitalizations and ER visits.

The Cox proportional hazards regressions demonstrate reduced mortality, hospitalization, and ER visits for patients with COPD-CRF who are prescribed NIVH compared to their matched controls. These benefits decrease over time for survival and emergency room visits, but remain consistent for hospitalizations.

In the first year following CRF diagnosis, a significantly lower percentage of patients prescribed NIVH died compared to the control group (28% vs. 46%; $p < 0.001$). This difference translates to a one-year RD of 18% and an RRR of 39% for mortality. The NNT to prevent a death at one year was 5.5. For hospitalizations and ER visits in the first year following CRF diagnosis, benefits of NIVH were also observed. Among patients prescribed NIVH, 55% experienced a hospitalization compared to 67% in the control group ($p < 0.001$) resulting in a one-year RD of 11% and RRR of 17% for hospitalizations. The NNT to prevent a first hospitalization was 9. For ER visits, 72% of the NIVH treatment cohort experienced an ER visit compared to 92% of those not using NIVH. This results in a one-year RD of 20%, an RRR of 22% and an NNT to prevent a first ER visit of 5 [see Table 3].

Table 3
Risk difference, relative risk reduction, and numbers needed to treat results.

	Events in treatment group	Events in control group	Risk Difference	Relative Risk Reduction	Number Needed to Treat
Death	28% *** (24.7%, 31.9%)	46% *** (40.9%, 51.0%)	18% *** (12.6%, 23.5%)	39% *** (30.4%, 48.2%)	5.5*** (3.7, 7.4)
Hospitalization	55% *** (50.8%, 59.8%)	67% *** (61.4%, 71.8%)	11% *** (4.8%, 17.9%)	17% *** (8.0%, 26.0%)	9* (-1.0, 18.7)
ER visit	72% *** (68.4%, 75.4%)	92%*** (98.4%, 94.9%)	20%*** (16.2%, 24.3%)	22%*** (17.8%, 26.1%)	5*** (4.0, 5.9)

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

4. Discussion

This is the first study analyzing the effect of NIVH on clinical outcomes in the U.S. Medicare population with COPD-CRF. Analyzing data from 2012 to 2018, we demonstrated that the use of NIVH was associated with statistically significant reductions in mortality, hospitalizations, and ER visits.

Patients with COPD-CRF treated with NIVH within 2 months of CRF diagnosis showed a 50% reduction in risk of death, a 28% reduction in the risks of hospitalizations, and a 52% reduction in the risks of ER visits at CRF diagnosis compared to similar patients not treated with NIVH. While the reduced risk of hospitalization continued to accrue during the entire seven-year study period, the magnitude of the reduction in the risks of mortality and ER visits diminished over time and disappeared after 23 months and 24.5 months respectively.

One year after CRF diagnosis, the results demonstrate an RD of 18% and an RRR of 39% for mortality in patients with COPD-CRF receiving NIVH compared to patients with COPD-CRF who were not treated with NIVH. These results are highly clinically significant, as currently the only COPD-CRF treatment with a larger mortality reduction is smoking cessation [28]. The NNT to prevent a death one year following CRF diagnosis with NIVH was 5.5.

Our results show a RD/RRR for first hospitalization of 11%/17% with an NNT to prevent a hospitalization of 9 one year after CRF diagnosis. For a first ER visit, the RD/RRR was 20%/22%, with a NNT to prevent an ER visit one year following CRF diagnosis of 5. As a hypothetical exercise, we extrapolated these results to the full Medicare Fee-for-Service population and estimated that providing NIVH to the

patients with COPD-CRF could reduce the number of deaths by 135,000 per year, hospitalizations by 64,000 per year, and ER visits by 151,000 per year.

The relatively high mortality rate of patients in this study is to be expected, as over 60% of the patients we observed were initially diagnosed with COPD-CRF while they were hospitalized. Previous literature demonstrated similar mortality risks for COPD patients who required invasive or non-invasive ventilation while hospitalized for an exacerbation [29]. In addition, our study findings are consistent with a randomized controlled trial by Kohnlein et al. which showed the same rapid reduction in mortality among patients with COPD-CRF following the institution of NIVH as was seen in our study [4].

4.1. Limitations

This study has a number of limitations, the most important of which is its retrospective and therefore non-randomized design. We used propensity score matching and included covariates in the regressions to control for potential selection bias introduced by the non-randomized nature of our data. Although the variables included in the matching procedure and as regression controls were carefully selected, we recognize that there are other important variables that might not have been included in this analysis. One important concern was immortal-time bias [9], which we addressed by selecting the shortest window to receiving treatment post index date that allowed for a sample large enough for sufficient analytic power.

As the Medicare LDS does not report on Medicare non-fee for service populations, such as health management organizations or Part C Medicare Advantage Plans, the results of this study should not be generalized to these populations [30]. Additionally, since the level of compliance with prescribed NIVH treatment is not reported in the LDS claims data, we cannot comment as to any correlation between hours of use of NIVH and clinical outcomes.

The limitations of the Medicare LDS also prevented us from determining the diagnostic criteria used by the providers assigning the CRF diagnoses. We do not know the proportion of study subjects that were hypercapnic or hypoxic nor the proportion that had CRF defined by other findings such as pulmonary function test (PFT) abnormalities or clinical characteristics. Hypercapnia was only identifiable through ICD-10-CM diagnosis codes, which were introduced in October 2015. The ICD-9-CM diagnosis codes did not provide enough detail to identify hypercapnia. However, while previous research on the efficacy of NIVH in COPD-CRF has been limited to hypercapnic patients on the assumption that these patients are the most likely to benefit, no studies have been published which investigate this assumption. Our results suggest that clinical benefits are associated with NIVH use in patients diagnosed with COPD-CRF, but our study design and data limitations prevent us from demonstrating that any specific CRF phenotype benefits more from NIVH use than does any other.

An important concern is that the clinical condition of individuals when they received NIVH might affect the results. Since 60% of our sample was hospitalized when the initial diagnosis of CRF was made, our study population cannot be described as clinically stable, and we do not know how many of these patients received invasive or non-invasive ventilation during the hospitalization in which they were diagnosed with CRF.

Lastly, while we attempted to investigate outcomes for patients using bi-level devices (BPAP, HCPCS E0470) or respiratory assist devices (RAD, HCPCS E0471) to treat COPD-CRF, insufficient numbers of cases appeared in the Medicare LDS to allow for statistically meaningful conclusions as to their efficacy. Because of this, our results are specific to NIVH, and should not be generalized to patients with COPD-CRF that are treated with BPAP or RADS.

5. Conclusions

The use of NIVH in Medicare patients diagnosed with COPD-CRF is associated with lower risks of mortality, hospitalizations and ER visits when instituted within two months of CRF diagnosis. The magnitude of the benefit of NIVH diminishes over time for mortality and ER visits, but remains constant for hospitalizations throughout the seven-year study period. Our findings suggest NIVH could be an important treatment option for patients with COPD-CRF, and more patients may benefit from the use of NIVH than the small number currently being prescribed this therapy.

Funding information

This study was funded by Viemed Healthcare Inc. The sponsor provided guidance regarding the target journal for submission, conceptualization and supervision of study, and provided feedback on the manuscript.

CRediT authorship contribution statement

William D. Frazier: Conceptualization, Writing - review & editing, Funding acquisition, Supervision. **Richard Murphy:** Resources, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Emma van Eijndhoven:** Conceptualization, Methodology, Validation, Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Formal analysis, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: EvE and RM are employees of PRECISIONheor, a research firm which has received consulting fees from life science companies, including Viemed Healthcare Inc, the sponsor of this study. WDF is the Chief Medical Officer of Viemed Healthcare Inc, a home healthcare services company that provides non-invasive ventilation at home and is the sponsor of this study. Additionally, WDF reports unrelated consulting fees from Pfizer, Bristol Myers Squibb, Sunovion, Glaxo Smith Klein, and Boehringer Ingleheim.

Acknowledgements

The authors would like to thank Yanmei Liu for her assistance in the construction of the analytic file for this study.

References

[1] National Institutes of Health, Chronic Obstructive Pulmonary Disease (COPD), 2018. https://report.nih.gov/nihfactsheets/ViewFactSheet.aspx?csid=77.
[2] A. Punturieri, T.L. Croxton, G.G. Weinmann, J.P. Kiley, Chronic obstructive pulmonary disease: a view from the NHLBI, Am. J. Respir. Crit. Care Med. 178 (5) (2008) 441–443.
[3] M. Carone, S. Antoniu, P. Baiardi, V.S. Digilio, P.W. Jones, G. Bertolotti, Predictors of mortality in patients with COPD and chronic respiratory failure: the quality-of-life evaluation and survival study (QuESS): a three-year study, COPD 13 (2) (2016) 130–138.
[4] T. Köhnlein, W. Windisch, D. Köhler, A. Drabik, J. Geiseler, S. Hartl, O. Karg, G. Laier-Groeneveld, S. Nava, B. Schönhofer, B. Schucher, K. Wegscheider, C. P. Criée, T. Welte, Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial, the Lancet, Respir. Med. 2 (9) (2014) 698–705.
[5] S. Coughlin, W.E. Liang, S. Parthasarathy, Retrospective assessment of home ventilation to reduce rehospitalization in chronic obstructive pulmonary disease, J. Clin. Sleep Med. 11 (6) (2015) 663–670. JCSM : official publication of the American Academy of Sleep Medicine.
[6] J.A. Galli, J.S. Krahnke, A. James Mamary, K. Shenoy, H. Zhao, G.J. Criner, Home non-invasive ventilation use following acute hypercapnic respiratory failure in COPD, Respir. Med. 108 (5) (2014) 722–728.

[7] P.B. Murphy, S. Rehal, G. Arbane, S. Bourke, P.M.A. Calverley, A.M. Crook, L. Dowson, N. Duffy, G.J. Gibson, P.D. Hughes, J.R. Hurst, K.E. Lewis, R. Mukherjee, A. Nickol, N. Oscroft, M. Patout, J. Pepperell, I. Smith, J. R. Stradling, J.A. Wedzicha, M.I. Polkey, M.W. Elliott, N. Hart, Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial, Jama 317 (21) (2017) 2177–2186.
[8] M. Weir, N. Marchetti, A. Czysz, N. Hill, F. Sciurba, P. Strollo, G.J. Criner, High intensity non-invasive positive pressure ventilation (HINPPV) for stable hypercapnic chronic obstructive pulmonary disease (COPD) patients, chronic obstructive pulmonary diseases (Miami, Fla 2 (4) (2015) 313–320.
[9] L. Zhou, X. Li, L. Guan, J. Chen, B. Guo, W. Wu, Y. Huo, Z. Zhou, Z. Liang, Y. Zhou, J. Tan, X. Chen, Y. Song, R. Chen, Home noninvasive positive pressure ventilation with built-in software in stable hypercapnic COPD: a short-term prospective, multicenter, randomized, controlled trial, Int. J. Chronic Obstr. Pulm. Dis. 12 (2017) 1279–1286.
[10] M.L. Duiverman, J.M. Vonk, G. Bladder, J.P. van Melle, J. Nieuwenhuis, A. Hazenberg, H.A.M. Kerstjens, J.F.M. van Boven, P.J. Wijkstra, Home initiation of chronic non-invasive ventilation in COPD patients with chronic hypercapnic respiratory failure: a randomised controlled trial, Thorax 75 (3) (2020) 244–252.
[11] M.E. Wilson, C.C. Dobler, A.S. Morrow, B. Beuschel, M. Alsawas, R. Benkhadra, M. Seisa, A. Mittal, M. Sanchez, L. Daraz, S. Holets, M.H. Murad, Z. Wang, Association of home noninvasive positive pressure ventilation with clinical outcomes in chronic obstructive pulmonary disease: a systematic review and meta-analysis, Jama 323 (5) (2020) 455–465.
[12] M. Macrea, S. Oczkowski, B. Rochwerg, R.D. Branson, B. Celli, J.M. Coleman 3rd, D.R. Hess, S.L. Knight, J.A. Ohar, J.E. Orr, A.J. Piper, N.M. Punjabi, S. Rahangdale, P.J. Wijkstra, S. Yim-Yeh, M.B. Drummond, R.L. Owens, Long-Term noninvasive ventilation in chronic stable hypercapnic chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 202 (4) (2020) e74–e87. An Official American Thoracic Society Clinical Practice Guideline.
[13] C.H. Martinez, D.M. Mannino, F.A. Jaimes, J.L. Curtis, M.K. Han, N.N. Hansel, A. A. Diaz, Undiagnosed obstructive lung disease in the United States. Associated factors and long-term mortality, Ann. Am. Thorac. Soc. 12 (12) (2015) 1788–1795.
[14] J. Sullivan, V. Pravosud, D.M. Mannino, K. Siegel, R. Choate, T. Sullivan, National and state estimates of COPD morbidity and mortality - United States, 2014-2015, chronic obstructive pulmonary diseases (Miami, Fla 5 (4) (2018) 324–333.
[15] Department of Health and Human Services Office of the Inspector General (Personal Communication), 2020.
[16] F.M. Struik, Y. Lacasse, R. Goldstein, H.A. Kerstjens, P.J. Wijkstra, Nocturnal non-invasive positive pressure ventilation for stable chronic obstructive pulmonary disease, Cochrane Database Syst. Rev. 6 (2013).
[17] A. Tissot, S. Jaffre, F. Gagnadoux, M. Levaillant, F. Corne, S. Chollet, F.X. Blanc, F. Goupil, P. Priou, W. Trzepizur, A. Magnan, Home non-invasive ventilation fails to improve quality of life in the elderly: results from a multicenter cohort study, PloS One 10 (10) (2015), e0141156.
[18] Research Data Assistance Center, Medicare Limited Data Set (LDS) Quarterly Claims and Enrollment Data, 2016. https://www.resdac.org/articles/medicare-limited-data-set-lds-quarterly-claims-and-enrollment-data.
[19] J.M. Marin, J.B. Soriano, S.J. Carrizo, A. Boldova, B.R. Celli, Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome, Am. J. Respir. Crit. Care Med. 182 (3) (2010) 325–331.
[20] J.P. Janssens, E. Cicotti, J.W. Fitting, T. Rochat, Non-invasive home ventilation in patients over 75 years of age: tolerance, compliance, and impact on quality of life, Respir. Med. 92 (12) (1998) 1311–1320.
[21] M. Caliendo, S. Kopeinig, Some practical guidance for the implementation of propensity score matching, J. Econ. Surv. 22 (1) (2008).
[22] M.J. Funk, D. Westreich, C. Wiesen, T. Stürmer, M.A. Brookhart, M. Davidian, Doubly robust estimation of causal effects, Am. J. Epidemiol. 173 (7) (2011) 761–767.
[23] D. Schoenfeld, Partial residuals for the proportional hazards regression model, Biometrika 69 (1) (1982) 239–241.
[24] K.R. Hess, Graphical methods for assessing violations of the proportional hazards assumption in cox regression, Stat. Med. 14 (15) (1995) 1707–1723.
[25] J.M. Box-Steffensmeier, B.S. Jones, Event History Modeling: A Guide for Social Scientists, Cambridge University Press, Cambridge, 2004.
[26] P.C. Austin, D.S. Small, The use of bootstrapping when using propensity-score matching without replacement: a simulation study, Stat. Med. 33 (24) (2014) 4306–4319.
[27] P.C. Austin, Absolute risk reductions and numbers needed to treat can be obtained from adjusted survival models for time-to-event outcomes, J. Clin. Epidemiol. 63 (1) (2010) 46–55.
[28] R. Strassmann, B. Bausch, A. Spaar, J. Kleijnen, O. Braendli, M.A. Puhan, Smoking cessation interventions in COPD: a network meta-analysis of randomised trials, Eur. Respir. J. 34 (3) (2009) 634–640.
[29] P.K. Lindenauer, K. Dharmarajan, L. Qin, Z. Lin, A.S. Gershon, H.M. Krumholz, Risk trajectories of readmission and death in the first year after hospitalization for chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 197 (8) (2018) 1009–1017.
[30] N. Brennan, C. Ornstein, A.B. Frakt, Time to release Medicare advantage claims data, Jama 319 (10) (2018) 975–976.
[31] H. Quan, V. Sundararajan, P. Halfon, A. Fong, B. Burnand, J.C. Luthi, L. D. Saunders, C.A. Beck, T.E. Feasby, W.A. Ghali, Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data, Med. Care 43 (11) (2005) 1130–1139.