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Survival and end-of-life aspects among subjects on long-term noninvasive ventilation

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ABSTRACT

Background: The need for noninvasive ventilation (NIV) is commonly considered a predictor of poor survival, but life expectancy may vary depending on the underlying disease. We studied the factors associated with decreased survival and end-of-life characteristics in an unselected population of subjects starting NIV.

Methods: We conducted a retrospective study including 205 subjects initiating NIV from 1/1/2012-31/12/2015 who were followed up until 31/12/2017.

Results: The median survival time was shorter in subjects needing help with activities of daily living than in independent subjects (hazard ratio (HR) for death 1.7, 95% CI 1.2–2.6, $P = 0.008$) and was also shorter in subjects on long-term oxygen therapy (LTOT) than in those not on LTOT (HR for death 2.8, 95% CI 1.9–4.3, $P < 0.001$). There was marked difference in survival according to the disease necessitating NIV, and subjects with amyotrophic lateral sclerosis or interstitial lung disease seemed to have the shortest survival. The two most common diseases resulting in the need for NIV were chronic obstructive pulmonary disease (COPD) and obesity hypoventilation syndrome (OHS). The median survival time was 4.4 years in COPD subjects, but the median survival time was not reached in subjects with OHS (HR for death COPD vs. OHS: 3.2, 95% CI 1.9–5.5, $P < 0.001$). Most of the deceased subjects (55.6%) died in the hospital, while only 20.0% died at home. The last hospitalization admission leading to death occurred through the emergency room in 44.4% of the subjects.

Conclusions: Survival among subjects starting NIV in this real-life study varied greatly depending on the disease and degree of functional impairment. Subjects frequently died in the hospital after admission through the emergency department. A comprehensive treatment approach with timely advance care planning is therefore needed, especially for those needing help with activities of daily living and those with both NIV and LTOT.

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Introduction

Chronic hypercapnia commonly occurs in the late stages of pulmonary diseases, such as chronic obstructive pulmonary disease (COPD), some neuromuscular disorders and, by definition, obesity hypoventilation syndrome (OHS) [1]. It has been shown that the treatment of hypoventilation with noninvasive ventilation (NIV) in patients with OHS [2] or amyotrophic lateral sclerosis (ALS) [3,4] improves survival [5], reduces sleepiness and decreases daytime $PaCO_2$ [6]. Although the overall benefit of long-term NIV for patients with COPD is under debate, the use of NIV has been shown to improve survival and reduce readmissions among patients with persistent hypercapnia after acute exacerbation of COPD [7]. There are international guidelines for the initiation of NIV in patients with COPD [8,9] and OHS [1,10], but the criteria are not strict, leaving room for clinical judgment. The use of NIV may also be beneficial in patients with hypoventilation due to other diseases, such as thoracic deformation. As the list of diseases causing chronic hypoventilation is long and there are no uniform criteria for the initiation of NIV, the real-life sample of patients initiating NIV is heterogeneous, with different underlying diseases and comorbidities.

End-of-life care and advance care planning are usually recommended if the patient is at considerable risk of dying in the next 12 months [11]. Timely advance care planning improves patient care and decreases unnecessary treatments and hospital

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admissions [12]. In subjects with neuromuscular diseases, such as ALS, hypoventilation is a sign of advanced disease [4]. The overall survival of patients with COPD on NIV is difficult to estimate as a consequence of the substantial impact of comorbidities [13]. As patients treated with NIV form a heterogeneous group, the need for NIV cannot be uniformly used as an indicator of poor prognosis. Therefore, it would be useful to identify relevant prognostic factors to guide the appropriate timing of advance care planning and arrangements for end-of-life care in everyday practice.

Our aim was to identify the factors associated with decreased survival and end-of-life characteristics in subjects in whom NIV was initiated in a real-life setting in an unselected patient population of a respiratory insufficiency clinic.

Materials and methods

Subjects

All subjects who started NIV, excluding 11 subjects with only sleep apnoea, between 1 January 2012, and 31 December 2015, in the respiratory insufficiency unit of Tampere University Hospital were included in this study. Tampere University Hospital provides care for the 530 000 inhabitants of Pirkanmaa County. All the subjects were treated in an acute pulmonary ward or respiratory insufficiency unit at the time of initiation of NIV, and they visited the respiratory insufficiency unit 1–3 months after the initiation of NIV and approximately once or twice per year thereafter. The decision to initiate NIV was made on clinical grounds by the attending pulmonologist, who applied the relevant guidelines [2,4,8,14]. The subjects were followed up until death or 31 December 2017.

Data collection

All the medical records of the subjects were reviewed. The collected information included sex, age, weight, height, living conditions, smoking status, primary diagnoses, information about comorbidities, do not resuscitate orders and decisions regarding end-of-life care. We also collected the results of spirometry and arterial or capillary blood gas analysis and the usage hours and settings of NIV recorded by nurses or doctors. The median daily usage hours from the device memory card were registered at every control for the time period between the previous and current visits. The disease necessitating NIV was defined as the primary disease, while all the other diseases were considered comorbidities. Diagnoses of COPD and OHS were made by the attending physician of the respiratory insufficiency unit in compliance with the current guidelines [1,15]. The Charlson comorbidity index was calculated for the subjects based on the number and severity of their comorbidities [16,17]. A subject was defined as needing help with activities of daily living (ADL) if he or she needed daily help from a family member working as a caregiver, received home care services provided by social services (e.g., dietary services, ablutions, dressing or medication) or permanently resided in a nursing home or a community hospital.

All the death certificates of the subjects who died before 31 December 2017 were reviewed. The collected information included the date and cause of death, place of death, do not resuscitate orders and end-of-life care decisions. An end-of-life care decision was defined as a recorded decision to start comfort-only end-of-life care or symptom-centred palliative care.

Statistical analysis

Almost all of the continuous variables were non-normally distributed based on visual estimation; thus, nonparametric tests were used. Comparisons of categorical variables were performed with the Mann–Whitney U test or Kruskal–Wallis test for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables. The Kaplan–Meier method and Cox regression were used for survival estimation. All comorbidities affecting more than five subjects (hypertension, cardiovascular diseases, diabetes, asthma, previous cancer and sleep apnoea) and age were included in the Cox multivariate analysis conducted in subjects with COPD or OHS. Statistical significance was set at $P < 0.05$. Analyses were performed with IBM SPSS Statistics versions 22.0 and 26.0 (IBM Corp, Armonk, NY).

Ethics consideration

This study was approved by the Regional Ethics Committee of Tampere University Hospital, Finland (approval code R15180/1 December 2015).

Results

A total of 205 subjects started long-term NIV during the study period and were included. The characteristics of the subjects are shown in Table 1. The most common diseases necessitating NIV were COPD and OHS. Three out of eight subjects with ILD initiated NIV with

concomitant LTOT due to hypercapnia ≥8 kPa and five subjects with ILD initiated NIV as part of palliative treatment for dyspnoea. Of the subjects included in the analysis, 135 (65.9%) started NIV during an acute exacerbation or airway infection, but they all fulfilled the criteria for long-term NIV after the resolution of the acute event. Altogether, 62 (30.2%) of all the included subjects and 26 (49.1%) of the subjects with COPD were treated with long-term oxygen therapy (LTOT) concomitantly with NIV. Of all the subjects who discontinued NIV during the follow-up period, 33 (16.1%) subjects discontinued due to lack of motivation or insufficient usage hours (<4 h per 24 h), and 14 (6.8%) subjects did not fulfil the criteria for NIV anymore. Furthermore, of those who discontinued NIV, 29 (60.0%) discontinued it during the first year, 6 (20.7%) of whom had COPD, 17 (58.6%) of whom had OHS and 6 (20.7%) of whom had other diagnoses. The median partial pressure of pCO_2 was 8.1 kPa (IQR 7.0–9.5) at the initiation of NIV, and at the first control, it was reduced to 6.1 kPa (IQR 5.4–6.7). The detailed settings of NIV, usage data and values of pCO_2 are shown in Supplementary Table 1. The most common comorbidities were cardiovascular diseases, hypertension and diabetes. Of all the subjects, 56 (27.3%) needed daily help at home, and 15 (7.3%) permanently resided in a nursing home or a community hospital.

Baseline characteristics in the subjects with COPD, OHS and other diagnoses are presented in Table 2. As expected, subjects with COPD had a more prominent smoking history, while subjects with OHS were more likely to be obese and more often suffered from concomitant sleep apnoea. Of those subjects with OHS, 20 (20.6%) also had mild or moderate COPD as a comorbidity.

Survival

Almost half (43.9%) of the subjects died during the study period. Needing help with ADL was associated with worse survival than being independent (hazard ratio for death (HR) 1.7, 95% CI 1.2–2.6, $P = 0.008$) (Figure 1(a)). Lung function or discontinuation of NIV therapy were not significantly associated with survival. In the total study sample, subjects who used LTOT concomitantly with NIV had worse survival than those who did not use LTOT (HR 2.8, 95% CI 1.9–4.3, $P < 0.001$) (Figure 1(b)).

There were marked differences in survival between subjects with different diseases, and the median survival was significantly longer in subjects with OHS (median not reached) than in those with COPD (median of 4.4 yrs., IQR 1.4–5.3, $P < 0.001$) (Figure 1(c)). The numbers of subjects in each of the other disease groups were relatively small, and detailed survival data in these groups are presented in Supplementary Figure 1. Survival was shortest in subjects with interstitial lung diseases and ALS.

Due to the small numbers of subjects in other disease groups, Cox multivariate analysis was conducted only in subjects with COPD and OHS (Supplementary Table 2). In subjects with COPD, hypertension (HR 6.4 (95% CI 2.4–-17.2, $P < 0.001$)) and older age (HR 1.1 (95% CI 1.0–1.2, $P = 0.011$)) were significantly associated with worse survival, while diabetes (HR 0.2 (95% CI 0.1–0.6, $P = 0.002$)) and previous cancer (HR 0.1 (95% CI 0.02–0.5, $P = 0.006$)) were associated with longer survival. None of the comorbidities in the survival analysis were associated with the survival time among subjects with OHS.

End-of-life characteristics

Of the subjects who died, 87.8% had do not resuscitate orders, and 43.3% had end-of-life care decisions (Table 3). The do not resuscitate decision was made a median of 199 days before death (IQR 43–642 days), and the medians were 171 days (IQR 35–506), 144 days (IQR 20–665) and 387 days (IQR 97–697) among subjects with COPD, OHS and other diagnoses, respectively ($P = 0.344$). The exact date of the DNR decision was missing in 24 subjects. Fifty-six percent of all the deceased subjects died in the hospital, and one-fifth died at home. Of those who died at the hospital, 86.0% had a do not resuscitate order, and 40.0% had an end-of-life care decision, while these proportions were 83.3% and 38.9%, respectively, among those who died at home. Forty-four percent of the subjects arrived via the emergency department for their last hospital admission before death. There was no difference in do not resuscitate orders or end-of-life care decisions between subjects who arrived via the emergency department for the last hospitalization before death and those who did not. The most common causes of death were COPD and heart disease.

Discussion

In this retrospective study on subjects with NIV due to respiratory insufficiency, the need for help with ADL and simultaneous LTOT were associated with shortened survival, while subjects with COPD had worse survival than those with OHS. Among the comorbidities, hypertension was associated with decreased survival in subjects with COPD. Decisions reflecting the recognition of the approach of the end-of-life period

Table 1. Subject characteristics.

Sex, *n* (%)	
Males	120 (58.5)
Females	85 (41.5)
Age, Median (IQR) y	67.0 (60.3–75.1)
< 65 y, *n* (%)	85 (41.5)
65–75 y, *n* (%)	74 (36.1)
> 75 y, *n* (%)	46 (22.4)
Body mass index, Median (IQR) (kg/m^2)*	33.2 (25.5–43.3)
<18.5, *n* (%)	11 (5.5)
18.5–24.9, *n* (%)	35 (17.5)
25.0–29.9, *n* (%)	32 (16.0)
30.0–34.9, *n* (%)	29 (14.5)
35.0–39.9, *n* (%)	33 (16.5)
>40.0, *n* (%)	60 (30.0)
Need for help with ADL, *n* (%)	
No	134 (65.4)
Yes	71 (34.6)
Smoking status, *n* (%)	
Never-smoker	69 (33.7)
Ex-smoker	89 (43.4)
Smoker	46 (22.4)
Not known	1 (0.5)
Pack years, Median (IQR) y	30.0 (15.0–50.0)
FEV_1 †	
Median (IQR) L	1.23 (0.86–1.83)
Median (IQR) % of predicted	45.5 (33.0–59.0)
FVC ‡	
Median (IQR) L	2.30 (1.60–2.78)
Median (IQR) % of predicted	61.0 (49.0–71.5)
FEV_1/FVC, Median (IQR) ‡	0.67 (0.48–0.77)
pCO_2, Median (IQR) kPa	8.2 (7.1–9.6)
Primary disease that caused the need for NIV, *n* (%)	
Obesity hypoventilation syndrome	97 (47.3)
COPD	53 (25.9)
Amyotrophic lateral sclerosis	10 (4.9)
Other neurological disease than amyotrophic lateral sclerosis	17 (8.3)
Thoracic deformity	14 (6.8)
Interstitial lung diseases	8 (3.9)
Other §	6 (2.9)
Comorbidities, *n* (%)	
Hypertension	127 (62.0)
Cardiovascular diseases	117 (57.1)
Sleep Apnea	87 (42.4)
Diabetes	85 (41.5)
Asthma	48 (23.4)
COPD	26 (12.7)
Cancer	31 (15.1)
Neurological diseases	20 (9.8)
Renal diseases	19 (9.3)
Rheumatic diseases	15 (7.3)
Others	99 (48.3)
No comorbidities	12 (5.9)
Charlson Comorbidity Index, Median (IQR)	1.0 (1.0–2.0)

* Data missing in five subjects due to being confined to bed (tetraplegia, multiple sclerosis, spinocerebellar ataxia or otherwise poor general condition (2)).

† Data missing in 20 subjects: lack of co-operation (tetraplegia, muscle dystrophy or subject didn't understand instructions because of e.g. Alzheimer's disease) in ten subjects and spirometry was not conducted in nine subjects as the disease was not a lung disease and missing values in one subject.

‡ Data missing in 40 subjects: only microspirometry available (20) and same reasons as for FEV_1† (20)

§ Consisting of central hypoventilation due to opioids (n = 1), bronchiolitis obliterans (n = 1), severe asthma (n = 1), tracheobronchomalacia (n = 1), vocal cord dysfunction (n = 1), chronic pleuritis (n = 1)

IQR, interquartile range; ADL, activities of daily living; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; pCO_2, partial pressure of carbon dioxide; NIV, noninvasive ventilation; COPD, chronic obstructive pulmonary disease

were commonly made, but many of the subjects still died in the hospital.

The median survival time in subjects with COPD (4.4 yrs.) was slightly better than that identified in a study by Blankenburg et al. (3.9 yrs.), while a relatively long survival of OHS subjects was found in both studies[18]. Subjects with other diagnoses showed very variable prognoses in our study. Furthermore, there were very limited numbers of subjects in these groups, precluding the drawing of firm conclusions. However, subjects with amyotrophic lateral sclerosis and interstitial lung disease had poor survival, which is in line with previous studies [19,20]. Among subjects with chronic hypoventilation, those with COPD, amyotrophic lateral sclerosis and interstitial lung diseases could benefit from timely advance care planning.

To our knowledge, this is the first study to evaluate the association between needing help with ADL and survival in subjects with NIV. Impairment in ADL has been previously shown to affect survival in the general elderly population [21], and patients with COPD have more difficulties with ADL than those without COPD [22]. However, those previous studies did not report the usage of NIV. Coping with ADL should be assessed among patients needing domiciliary NIV because needing help with ADL is common and is associated with worse survival.

Most of the subjects starting NIV, especially those with OHS, had several comorbidities, of which cardiovascular diseases, hypertension, diabetes and sleep apnoea were the most common. In contrast to the findings in some previous studies, cardiovascular diseases were not associated with decreased survival among subjects with COPD in our study [13,23,24]. However, hypertension was associated with poor survival in subjects with COPD in our results. In a previous study by Mannino et al., hypertension was common in subjects with at least severe COPD; hypertension was only slightly associated with impaired survival, while cardiovascular disease had a larger effect on survival [24]. We suggest that subjects with hypertension could actually have undiagnosed cardiovascular disease and a higher risk of cardiovascular events. Subjects with COPD and diabetes or previous non-metastatic cancer had better survival than those without. This somewhat unexpected finding might be due to better health behaviours in subjects with diabetes and cancer survivors. Although our results may also be partly due to the lack of power or coincident results related to multiple statistical testing, they highlight the need for comprehensive care of patients treated with

Table 2. Subject characteristics in subjects with COPD, obesity-hypoventilation syndrome or other diagnoses as the cause for initiation of noninvasive ventilation.

	COPD	OHS	Others	P-value
Total, *n*	53	97	55	
Sex, *n* (%)				
Males	35 (66.0)	56 (57.7)	29 (52.7)	0.364
Females	18 (34.0)	41 (42.3)	26 (47.3)	
Age, Median (IQR) y	69.0 (63.7–73.9)	66.3 (58.4–75.1)	65.9 (58.9–76.7)	0.523
< 65 y, *n* (%)	18 (34.0)	42 (43.3)	25 (45.5)	0.194
65–75 y, *n* (%)	25 (47.2)	35 (36.1)	14 (25.5)	
>75 y, *n* (%)	10 (18.9)	20 (20.6)	16 (29.1)	
Body mass index, Median (IQR) (kg/m^2)*	25.9 (21.4–31.2)	43.5 (37.4–48.8)	25.5 (21.5–28.9)	<0.001
<18.5, *n* (%)	7 (13.2)	0 (0.0)	4 (7.8)	
18.5–24.9, *n* (%)	16 (30.2)	0 (0.0)	19 (37.3)	
25.0–29.9, *n* (%)	13 (24.5)	0 (0.0)	19 (37.3)	
30.0–34.9, *n* (%)	11 (20.8)	14 (14.6)	4 (7.8)	
35.0–39.9, *n* (%)	6 (11.3)	24 (25.0)	3 (5.9)	
>40.0, *n* (%)	0 (0.0)	58 (60.4)	2 (3.9)	
Need for help with ADL, *n* (%)				
No	40 (75.5)	72 (74.2)	22 (40.0)	<0.001
Yes	13 (24.5)	25 (25.8)	33 (60.0)	
Smoking status, *n* (%)				
Never-smoker	0 (0.0)	40 (41.2)	29 (52.7)	<0.001
Ex-smoker	30 (56.6)	35 (36.1)	24 (43.6)	
Smoker	23 (43.4)	21 (21.6)	2 (3.6)	
Not known	0 (0.0)	1 (1.0)	0 (0.0)	
Pack years, Median (IQR) y	45.0 (35.0–54.0)	25.0 (10.0–40.0)	15.0 (7.0–30.0)	<0.001
FEV_1 †				
Median (IQR) L	0.81 (0.68–1.06)	1.65 (1.13–1.98)	1.27 (0.94–2.11)	<0.001
Median (IQR) % of predicted	29.0 (21.0–40.0)	53.0 (43.0–62.3)	47.0 (33.5–66.5)	<0.001
FVC ‡				
Median (IQR) L	2.44 (2.00–2.74)	2.27 (1.72–2.84)	1.66 (1.20–2.53)	0.012
Median (IQR) % of predicted	66.0 (55.0–77.0)	62.0 (52.0–73.0)	51.0 (39.0–66.0)	0.002
FEV_1/FVC, Median (IQR) ‡	0.41 (0.27–0.50)	0.70 (0.63–0.77)	0.77 (0.67–0.89)	<0.001
pCO_2, Median (IQR) kPa	8.4 (7.9–10.4)	8.6 (7.4–10.0)	7.3 (6.2–8.6)	<0.001
Comorbidities, *n* (%)				
Hypertension	28 (52.8)	71 (73.2)	28 (50.9)	0.007
Cardiovascular diseases	32 (60.4)	60 (61.9)	25 (45.5)	0.124
Diabetes	18 (34.0)	56 (57.7)	11 (20.0)	<0.001
COPD		20 (20.6)	5 (9.1)	0.001
Asthma	11 (20.8)	25 (25.8)	12 (21.8)	0.745
Sleep Apnoea	6 (11.3)	72 (74.2)	9 (16.4)	<0.001
Neurological diseases	2 (3.8)	10 (10.3)	8 (14.5)	0.164
Renal diseases	5 (9.4)	9 (9.3)	5 (9.1)	1.000
Rheumatic diseases	3 (5.7)	6 (6.2)	6 (10.9)	0.545
Cancer	8 (15.1)	16 (16.5)	7 (12.7)	0.824
Others	22 (41.5)	53 (54.6)	24 (43.6)	0.221
No comorbidities	4 (7.5)	0 (0.0)	8 (14.5)	<0.001
Charlson Comorbidity Index, Median (IQR)	1.0 (0.0–2.0)	2.0 (1.0–3.0)	1.0 (0.0–2.0)	0.001

* Data missing in five subjects due to being confined to bed (tetraplegia, multiple sclerosis, spinocerebellar ataxia or otherwise poor general condition (2)).
† Data missing in 20 subjects: lack of co-operation (tetraplegia, muscle dystrophy or subject didn't understand instructions because of e.g. Alzheimer's disease) in nine subjects and spirometry was not conducted in ten subjects as the disease was not a lung disease and missing values in one subject.
‡ Data missing in 40 subjects: only microspirometry available (20) and same reasons as for FEV_1† (20)
COPD, chronic obstructive pulmonary disease; OHS, obesity hypoventilation sdr; IQR, interquartile range; ADL, activities of daily living; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; pCO_2, partial pressure of carbon dioxide; COPD, chronic obstructive pulmonary disease

NIV, with a focus on comorbidities and not just hypoventilation.

The subjects in this study were adherent to NIV, with a median of 6 h. Our results are in line with those of the study by Blankenburg et al., although the discontinuation percentages in subjects with COPD and OHS in our study were slightly lower [18]. Moreover, discontinuation was not associated with survival in the subjects in the current study, even though discontinuation has previously been shown to be associated with worse survival in subjects with OHS [25]. Our finding might be related to the tendency of subjects with milder disease and better prognosis to perceive less subjective gain from the treatment, making them more likely to discontinue NIV, although again, the lack of a significant association between survival and the discontinuation of NIV may also be due to the relatively small study population. In our study, the decrease in pCO_2 after the initiation of NIV was quite good even with relatively low pressures, especially in subjects with COPD, compared to what is usually recommended [26,27], and this might be related to

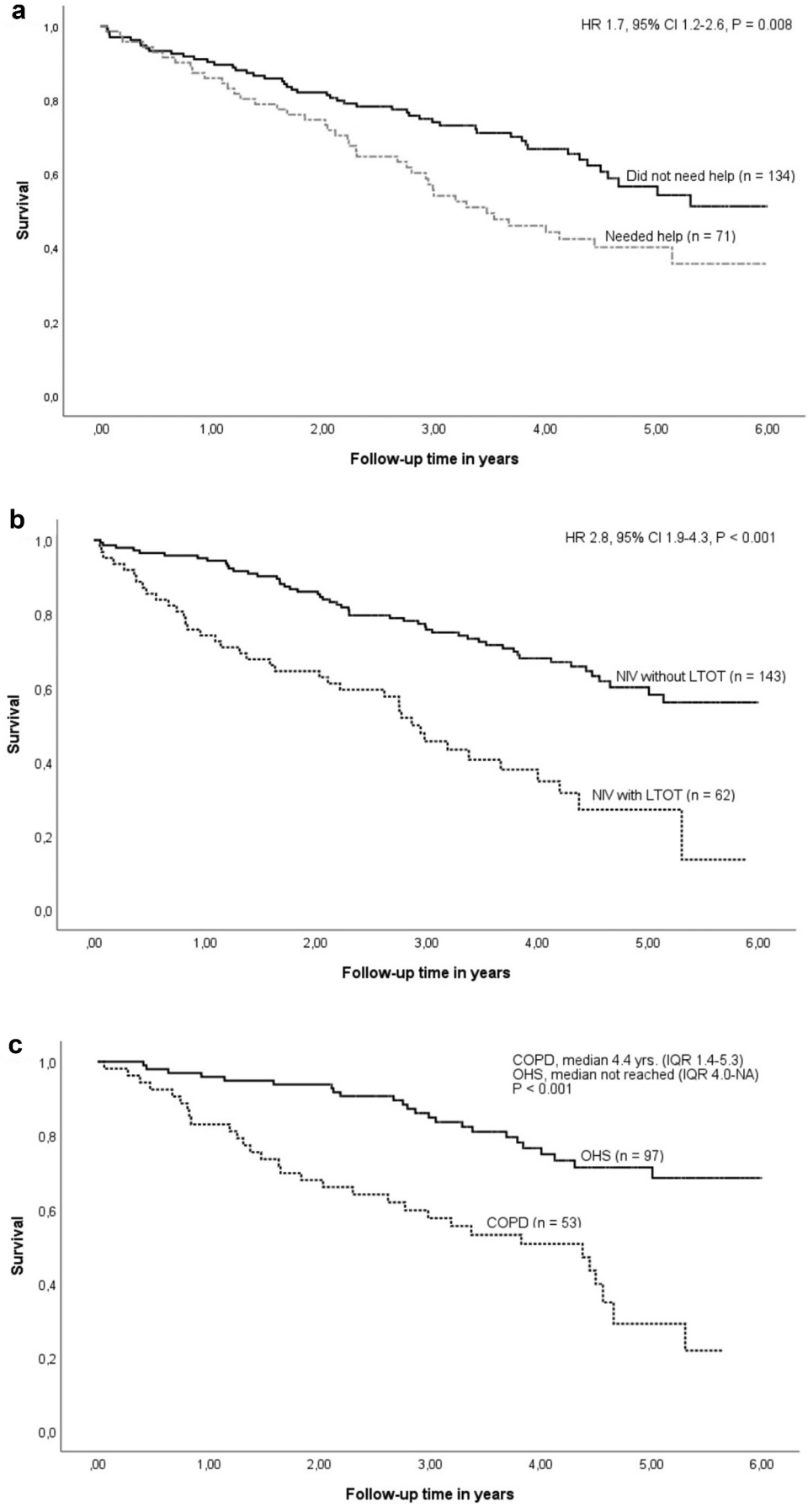

Figure 1. Kaplan-Meier survival curve for overall survival in the total study sample according to the need for assistance with activities of daily living (A), according to the concomitant use of long-term oxygen therapy with NIV (B) and after the initiation of noninvasive ventilation according to the primary diagnosis for noninvasive ventilation in subjects with OHS and COPD (C).NIV, noninvasive ventilation; LTOT, long-term oxygen therapy; HR; hazard ratio; COPD, chronic obstructive pulmonary disease; OHS, obesity hypoventilation syndrome; IQR, interquartile range; NA, not available.

Table 3. Characteristics related to end-of-life among the deceased subjects according to primary diagnosis.

	COPD	OHS	Others	P-value
Total, *n*	53	97	55	
Died before 31.12.2017, *n* (% of all)	31 (58.5)	24 (24.7)	35 (63.6)	<0.001
DNR decision before death, *n* (%) †	30 (96.8)	18 (75.0)	31 (88.6)	0.053
End-of-life care decision before death, *n* (%)	12 (38.7)	11 (45.8)	16 (45.7)	0.814
Place of death, *n* (%)				
Hospital	17 (54.8)	17 (70.8)	16 (45.7)	0.907
Home	7 (22.6)	3 (12.5)	8 (22.9)	
Nursing home	3 (9.7)	1 (4.2)	3 (8.6)	
Hospice	2 (6.5)	2 (8.3)	4 (11.4)	
Emergency	2 (6.5)	1 (4.2)	3 (8.6)	
Not known	0 (0.0)	0 (0.0)	1 (2.9)	
Cause of death, *n* (%)				
COPD	23 (74.2)	2 (8.3)	1 (2.9)	<0.001
Heart diseases	4 (12.9)	9 (37.5)	4 (11.4)	
Interstitial lung disease	0 (0.0)	0 (0.0)	8 (22.9)	
Cancer	4 (12.9)	3 (12.5)	3 (8.6)	
Neurological diseases	0 (0.0)	1 (4.2)	13 (37.1)	
Chronic respiratory failure	0 (0.0)	4 (16.7)	1 (2.9)	
Pneumonia or other infection	0 (0.0)	1 (4.2)	1 (2.9)	
Other	0 (0.0)	4 (16.7)	4 (11.4)	
Admission through the emergency for the last hospitalization before death, *n* (%)	13 (41.9)	11 (45.8)	16 (45.7)	0.941

† 39 (49.4%) had also end-of-life care decision
COPD, chronic obstructive lung disease; OHS, obesity hypoventilation sdr; DNR, do not resuscitate

the fact that NIV was initiated in approximately 60% of subjects in an acute setting.

In the total study sample, those subjects needing LTOT in addition to NIV had worse survival than those who did not need LTOT, and this was also found when subjects with COPD and OHS were analysed separately. This is to be expected, as being hypercapnic is a sign of a pathological process that decreases gas exchange. To our knowledge, there have been no previous studies assessing whether the use of LTOT is associated with survival in patients with COPD who also use NIV. In contrast, a previous study by Murphy et al. showed that survival was better in subjects with concomitant NIV with LTOT than in subjects with only LTOT after the acute exacerbation of COPD [7]. However, our results are in line with those of one previous study by Priou and colleagues, in which hypoxemia among patients with OHS and NIV was also associated with worse survival than the absence of hypoxemia [28].

Our study showed that the majority of the deceased subjects had do not resuscitate orders, which is in line with the findings in the study by Raskin et al. [29]. However, only half of our subjects had end-of-life care decisions, although our numbers are higher than those previously reported by European respiratory care units [30]. Many of the subjects in this study died in the hospital, and only one-fifth of them died at home, which was also found in a study by Gruneir et al. [31]. In contrast, 85% of the 60 patients with advanced COPD died at home or in the palliative care unit in a recent study by Gainza-Miranda et al., highlighting the different practices in the arrangements of palliative care in the context of advanced respiratory insufficiency [32]. In addition, almost half of the subjects arrived via the emergency room for their last hospitalization prior to death in our study. When discussing do not resuscitate orders with a patient, the physician should also consider broader advance care planning discussions, including arrangements for end-of-life care, to avoid unnecessary hospitalization before death.

More than half of the subjects with COPD died in our study; thus, the management of these subjects should focus on slowing down the progression of COPD. In contrast, we found that comorbidities were a common cause of death in subjects with OHS, as shown in previous studies [25,33]. This highlights the importance of a comprehensive therapeutic approach to comorbidities in patients with OHS.

Strengths and limitations

The strength of the study is the unselected subject sample with NIV, which means that the findings provide practical information to physicians caring for similar patients. Due to the retrospective nature of the study, consistent baseline settings of NIV were lacking, and the criterion for the initiation of NIV slightly differed due to the heterogeneity of the subject population and the clinical decisions made by the attending pulmonologist. A minority of the subjects with OHS (20/97) also had COPD, but none of them had severe obstruction, and hypoventilation was thus considered to be primarily due to OHS. Due to missing lung function tests, the association

between FEV_1/FVC and survival could not be analysed. The need for assistance with ADL was defined by using strict criteria, ensuring an accurate definition of those who needed help, although the criteria might have excluded subjects with minor impairment.

Conclusions

Survival in a real-life sample of subjects with NIV varied depending on the primary disease, need for help with ADL and use of LTOT. In addition, hypertension in subjects with COPD was associated with shortened survival. Most of the subjects died in the hospital after being admitted through the emergency department, although most of them had a do not resuscitate order or end-of-life care decision. Among patients treated with NIV, a comprehensive treatment approach with timely advance care planning is needed, and clinicians should pay attention to the underlying primary diagnosis, functional impairment and comorbidities.

Disclosure statement

The authors declare that there are no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Data availability statement

Data available on request from the authors

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