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Full Length Research Paper

NIV in COPD and OHS patients: Predictors of short and long term survival

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Abstract

Acute Exacerbations of Chronic Hypercapnic Respiratory Failure (CHRF) are associated with increased mortality during hospitalization and after hospital discharge. The aim of the study was to estimate short and long term survival in patients hospitalized for acute respiratory failure. 177 patients (100 Chronic Obstructive Pulmonary Disease, COPD and 77 Obesity Hypoventilation Syndrome, OHS) hospitalized for acute respiratory failure and treated with Non Invasive Ventilation (NIV) were enrolled. 2 year survival was evaluated in all patients and predictors of survival not only during hospitalization but in the period after, were explored. Survival during hospitalization in the COPD group was 94%, while there were no deaths in the OHS group. Increased age (B 0.132, p=0.02) and the level of hypercapnia (B -0.159, p=0.018) were significant predictors of survival in COPD group. 2-year survival in both groups was affected by the use of NIV (p<0.001 for both groups), while in COPD group sex (B -1.248, p=0.036) and FEV_1/FVC (B 0.096, p=0.005) were additional predictors. Patients presenting with acute respiratory failure due to COPD or OHS, can be effectively treated in a regular ward with NIV. Receiving NIV at home directly after hospital discharge can prolong survival.Word count 197.

Keywords: Acute hypercapnic respiratory failure, chronic hypercapnic respiratory failure, COPD, OHS, NIV, survival.

INTRODUCTION

Patients with Chronic Hypercapnic Respiratory Failure (CHRF) have a particularly poor prognosis, although the role of hypercapnia per se is not clear, as most data refer to patients with mild to moderate hypercapnia during Long Term Oxygen Therapy (LTOT) (Aidaet al., 1998; Nizet et al., 2005). Acute Exacerbations of CHRF are associated with increased mortality not only during hospitalization but in the period after discharge as well.

Exacerbations of Chronic Obstructive Pulmonary Disease (COPD) is the fourth leading cause of death. Estimates of inpatient mortality range from 4-30%, but patients admitted due to Acute Respiratory Failure (ARF) experience a higher rate, in particular elderly patients with co-morbidities (up to 50%) and those requir-ing Intensive Care Unit (ICU) admission (11-26%) (Patil et al., 2003). On the other hand, obesity has been found to be a factor having a negative effect on ICU outcomes (longer duration of mechanical support and ICU stay)(Nowbar et al., 2004). Patients with Obesity Hypoventilation Syndrome (OHS) (a syndrome defined by the presence of obesity and daytime hypercapnia) are heavy users of health care resources and have a high mortality rate when presenting with acute respiratory failure (Berg et al., 2001; Perez de Llano et al., 2005).

Patients with COPD and OHS have increased mortality after hospital discharge.(Nowbaret al., 2004) The use of NIV on a long term basis has been proven the gold standard of treatment of CHRF in patients with restrictive disorders and neuromuscular diseases. In patients with COPD and OHS the use of NIV is not yet recommended unequivocally. There is however evidence that NIV can improve physiologic outcomes and quality of life in both groups (Tsolaki et al., 2001; Windisch, 2008).

The aim of the present retrospective study was to evaluate survival in patients with COPD and OHS when

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presenting with acute respitratory failure, as well as to estimate survival of these patients, either treated with NIV or not, after hospital discharge in a period of two years. Finally, this study explores the factors associated with survival in both groups of patients.

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MATERIALS AND METHODS

This study was conducted in the Pulmonary Department of University Hospital of Larissa from January 2009 to April 2011. All patients with COPD and OHS admitted with acute or acute on chronic respiratory failure were selected retrospectively to enter the study.

COPD was defined according to ATS/ERS guidelines (1995). The group of OHS consisted of patients with obesity (BMI> 30 kgr/m2), presenting with hypercapnic respiratory failure with no other profound explanation.(Olsonet al., 2005,Weitzenblumet al., 2002) Patients with thoracic or neuromuscular disorders leading to hypoventilation were excluded.

Patients were included if they presented at the Emergency Department with 1). Clinical signs and symptoms of acute respiratory distress: worsening dyspnea, respiratory rate of more than 24 breaths per minute, use of accessory muscles of respiration. 2). Hypercapnic respiratory failure (acute or chronic) with PaCO2 > 50 mmHg. Patients were excluded if they met any of the following criteria: respiratory arrest, medically unstable condition (hypotension, uncontrolled cardiac ischemia/arrythmia), inability to protect airway (stuporous or comatose patient), unwilling patient to cooperate.

Non Invasive ventilation was delivered via the portable non invasive ventilator VPAP III ST (ResMed, Sydney, Australia), via a full face mask (UltraMirage, Sydney, Australia). The positive pressures set at the beginning of NIV's application were IPAP:15 mmHg, EPAP: 5 mmHg and were then gradually adjusted according to the patient's ability to tolerate, patient- ventilator synchrony, alleviation of dyspnea and the use of accessory respiratory muscles, and the correction of arterial blood gases. Supplemental oxygen was delivered so as to provide saturation of 88-92%. Patients used the non invasive ventilator for 18-20 hours during the first day of the ventilation, reducing the total hours of ventilator use to 8-10 thereafter.

NIV failure was defined as inability to ventilate the patient despite adjustments in NIV's parameters (uncontrolled elevation of PaCO2, comatose patient, pH< 7.20)

Primary outcome was the survival of patients, presenting with decompensation of respiratory failure, while receiving NIV during hospitalization. Patients who had agreed to receive the ventilator at home comprised the NIV group, while all the others comprised the control group. Patients with poor compliance (daily use of NIV < 6h/24h) were excluded from the analysis. All the patients were contacted after two years at home by a study nurse. Survival was estimated for COPD and OHS patients. Parameters associated with survival of patients both during hospitalization and in the two years following discharge, were evaluated.

RESULTS

NIV was initiated in 177 patients (100 COPD patients – 77 OHS patients) who presented with decompensation of respiratory failure. There were no deaths during hospitalisation in the OHS group. In the COPD group eleven patients (6%) failed to improve with NIV application. Six patients were intubated and treated in the ICU and the rest five died. These were patients with end stage COPD and, in agreement with their families, it was decided not to be intubated. The patients who were transmitted in the ICU died as well. Therefore, 89 COPD patients and all 77 patients were followed up for two years.

Demographic data are presented in Table 1.

Parameters associated with NIV failure during hospitalization in COPD patients

Concerning COPD patients, cox regression model indicated that NIV failure during hospitalization was associated with age. On the contrary for COPD patients with pH<7.35 NIV failure was associated with lower levels of pCO_2 at hospitalization before the application of NIV (Table 2).

Two years mortality for COPD and OHS patients

During the period of two years after the initial hospitalization, 18 COPD patients died. From these patients, 8 COPD patients had received NIV at home. Two year mortality was associated with sex and the use of NIV at home (Table 3). Survival between patients who received NIV at home compared with those who did not receive NIV at home differed significantly ($p<0.0001$). Independently, for patients with NIV at home after discharge, two year mortality was associated with sex, and FEV_1/FVC ratio at stable condition, whereas none of the parameters associated with NIV model, IPAP or EPAP, were associated with mortality. Furthermore, for COPD patients who received NIV at home, there was no difference in survival when they were stratified according to NIV model. Kaplan-Meier curves for COPD patients are shown in Figures 1 and 2.

In the OHS group, 10 patients had died two years after the initial hospitalization. From these patients two had received NIV at home. In this group, two year mortality was associated with the use of NIV at home (Table 3).

Table 1. Demographic data.

	COPD patients	OHS patients	Total	p value
N	100	77	177	
Sex (M/F)	79/21	41/36	120/57	
Age (Years)	71.0 (66.0-76.0)*	67 (56.8-73.0)*	69.0 (61.0-75.0)	0.0252
BMI (Kg/m^2)	30.0 (25.0-34.0)*	42.0 (40.0-48.2)*	35.4 (29.0-42.3)	<0.0001
Glucose (mg/dl)	113.5 (99.0-149.5)	121.0 (100.0-149.5)	119.0 (99.0-149.0)	0.9606
ESS	12 (9.8-18.0)*	18.0 (14.0-20.0)*	15.0 (12.0-18.0)	0.0002
pO_2 (mmHg)(Hospitalization)	55.0 (47.8-63.3)	56.0 (48.0-62.0)	56.0 (48.0-62.5)	0.9733
pCO_2 (mmHg)(Hospitalization)	61.0 (54.1-69.0)	59.0 (53.0-68.0)	59.0 (53.0-68.0)	0.7110
pH (Hospitalization)	7.35 (7.32-7.41)	7.38 (7.31-7.42)	7.36 (7.32-7.42)	0.7745
pO_2 (mmHg) (Discharge)	65.0 (59.0-73.0)	65.0 (59.0-70.0)	65.0 (59.0-72.0)	0.8497
pCO_2 (mmHg) (Discharge)	47.5 (44.0-53.1)	47.0 (43.0-50.0)	47.0 (44.0-52.0)	0.4166
pH (Discharge)	7.43 (7.41-7.45)	7.44 (7.42-7.46)	7.43 (7.41-7.46)	0.0984
FEV_1 (%pred)	34.5 (25.3-44.9)*	59.0 (39.0-67.5)*	41.5 (30.0-60.3)	<0.0001
FVC (%pred)	44.0 (34.0-53.0)*	58.0 (42.8-68.3)*	48.0 (38.5-61.0)	<0.0001
FEV_1/FVC (%pred)	58.0 (48.0-65.0)*	78.0 (72.0-86.0)*	67.0 (56.0-78.0)	<0.0001
AHI (apneas/hour)	13.5 (4.0-24.5)	16.8 (9.6-35.1)	16.0 (7.0-28.4)	0.425
Hospitalization (days)	10.0 (7.0-14.0)	10.0 (7.0-15.0)	10.0 (7.0-15.0)	0.8135
NIV at home (%)	71 (79.8%)	57 (74.0%)	128 (72.3%)	0,4828
BiPAP Model (S / ST)	48/23	20/37		
IPAP (cmH_2O)	17.0 (15.0-18.0)*	18.0 (17.0-20.0)*	17.4 (16.0-19.0)	0.0002
EPAP (cmH_2O)	5.0 (5.0-6.0)*	6.4 (6.0-7.0)*	6.0 (5.0-6.6)	<0.0001
Two year survival (%)	71 (79.8%)	67 (87.0%)		

*Statistically significant differences
BMI: Body mass index, ESS: Epworth sleepiness scale, FEV_1: Forced expiratory volume at the 1st second, FVC: Forced vital capacity, AHI: Apnea hypopnea index, IPAP: Inspiratory positive airway pressure, EPAP: Expiratory positive airway pressure

Table 2. Parameters associated with NIV failure during hospitalization for COPD patients.

	B	SE	Odds Ratio	95% CI	p value
Overall					
Age	0.132	0.057	1.141	1.021-1.274	0.020
pH <7.35					
pCO_2 (mmHg)(Hospitalization)	-0.159	0.067	0.853	0.748-0.973	0.0118

SE: Standard error, CI: Confidence interval

Table 3. Parameters associated with 2 year survival in COPD and OHS patients after discharge.

	B	SE	Odds Ratio	95% CI	p value
COPD patients					
Sex	1.248	0.596	0.287	0.089-0.924	0.036
FEV_1/FVC	-0.096	0.034	1.100	1.029-1.176	0.005
NIV at Home	2.180	0.624	0.113	0.033-0.384	<0.0001
OHS patients					
NIV at Home	3.049	0.907	0.047	0.008-0.280	0.047

FEV_1/FVC: Forced expiratory volume at 1st second to forced vital capacity ratio, NIV: Non invasive ventilation

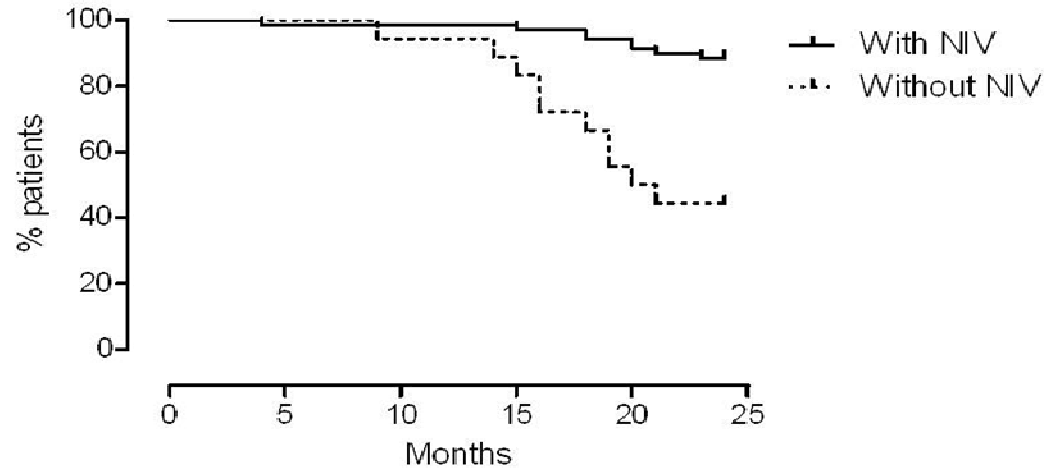

Figure 1. Two years survival of COPD patients with or without NIV at home.

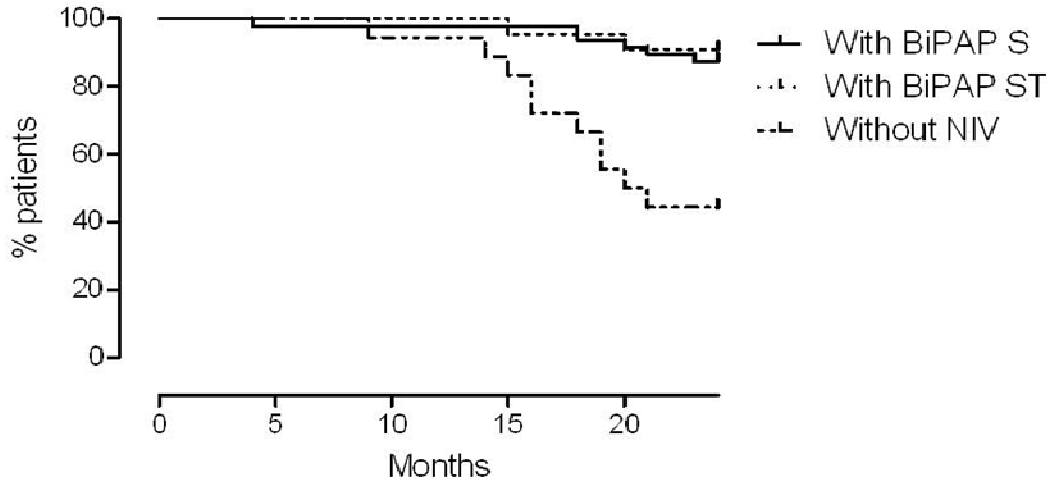

Figure 2. Two years survival of COPD patients with or without NIV at home according to NIV model.

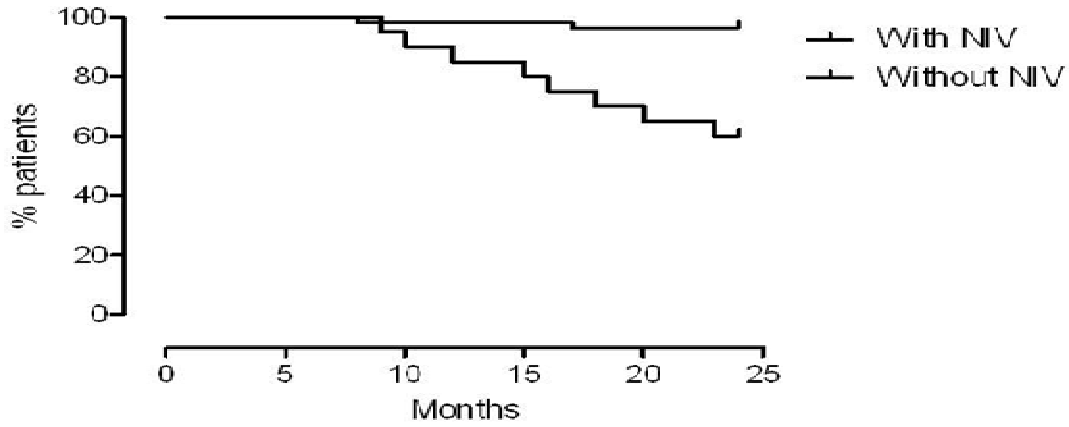

Figure 3. Two years survival of OHS patients with or without NIV at home.

Survival between OHS patients who received NIV at home compared with those who did not receive NIV at home differed significantly ($p<0.0001$). Kaplan-Meier curve for these patients is shown in Figure 3.

DISCUSSION

The present retrospective study aimed to evaluate survival of patients presenting with acute decompensation of respiratory failure not only during hospitalization but on a long term basis as well. We also tried to evaluate the predictors which favor prolonged survival. Mortality in the COPD group was 6% during hospitalization and it was associated with age and the degree of hypercapnia at presentation, while there were no deaths in the OHS group during hospitalisation. 2 year survival in the whole COPD group was 79.8% and 87% was the survival in the OHS group. Patients who received NIV had better survival in both groups.

The role of NIV in the acute management of Hypercapnic Respiratory Failure in COPD patients is well established (Brochard et al., 1995; Plant et al., 2000). Compared to standard medical therapy alone the application of NIV improves survival, reduces the need for endotracheal intubation and the rate of complications and shortens length of stay in hospital and in ICU (Lightowler et al., 2003). In patients with moderate exacerbation (7.25<pH<7.35) NIV lowers intubation rates while in patients with pH>7.35 the use of NIV can shorten the length of hospitalization (Lightowler et al., 2003; Pastaka et al., 2007; Plant et al., 2000). For patients presenting with pH< 7.25, the use of NIV is associated with increased rates of failure, but it seems that it does not affect overall mortality, while patients finally treated successfully with NIV have lower rates of complications (Nava et al., 2006; Pastaka et al., 2007). It seems that older patients with COPD have increased mortality. Increased age has been previously found a poor prognostic factor affecting survival in patients treated with NIV on a long term basis, although NIV is an efficacious modality in the elderly (Farrero et al., 2007; Laub et al., 2007). Life expectancy is decreased when older patients are hospitalized for acute respiratory failure. Moreover, this group probably has more concomitant end stage diseases (not only concerning the respiratory system but other systems as well, such as cardiovascular). Often, these patients have a poor prognosis if they are intubated. However, a trial of NIV should be applied in this group.

Moreover, in the subgroup of COPD patients presenting with pH<7.35, survival was affected by the level of hypercapnia at presentation. Specifically, there was a negative correlation between the levels of PaCO2 and survival, meaning that the more hypercapnic the patients were, the better they went. This finding at first sight seems controversial. Patients with decompansation of chronic respiratory failure seem to have an advantage over patients with acute respiratory failure. In the second case acidosis can not only be explained by the degree of hypercapnia. One possible explanation is that metabolic acidosis plays a crucial role, which reflects the extent of sepsis involved and tissue hypoxia. Patients with elevated base excess seem to benefit from application of NIV in the long term (Budweiser et al., 2007). Base excess reflects the ability of the kidneys to compensate respiratory acidosis as well as the time of the onset of respiratory failure.

Concerning the OHS group all the patients were treated effectively with NIV. There was not noted any case with NIV failure. Early mortality in OHS patients hospitalized for acute respiratory failure is increased (Nowbar et al., 2004). Earlier case series of hospitalized patients with severe OHS reported a mortality rate approaching 50% including cases of sudden deaths (MacGregor et al., 1970). They also present high rates of ICU admissions (40%) (Nowbar et al., 2004). NIV is a modality which has been proved to be successful in treating patients with OHS who present with acute respiratory failure. It can unload respiratory muscles, improve clinical symptoms and prevent further worsening of respiratory failure demanding intubation (Perez de Llano et al., 2005).

Survival is prolonged in patients who receive NIV after hospitalization for acute respiratory failure compared to patients who return home with usual therapy (long term oxygen therapy). Patients with OHS showed a survival rate of 87% (96.5% for patients on NIV, 60% for patients without NIV). In patients with OHS a randomized controlled trial appears unethical because it cannot be argued that patients with OHS benefit from NIV. Moreover, patients with OHS presents increased mortality (46%) when untreated, compared to patients who receive NIV at home (Perez de Llano et al., 2005). Patients with OHS are heavy users of health care services and have increased hospitalization rates compared to morbidly obese eucapnic patients (Berg et al., 2001). Furthermore, when a group of patients with OHS was discharged, they showed excess mortality (23%) after 18 months compared with patients with obesity but without hypercapnia. Although our study is retrospective in design, there is clear evidence that the use of domiciliary NIV in patients with OHS after they have been hospitalized for acute respiratory failure can improve survival.

Survival in COPD patients after two years of domiciliary use of NIV was 88.8% which is in accordance with that referred in the literature (Budweiser et al., 2007; Budweiser et al., 2007; Budweiser et al., 2007), while 2 year survival of COPD after an episode of acute exacerbation is 44.5%. The major indication for prescription of NIV at home for patients with COPD is the presence of hypercapnic respiratory failure, provided that the presence of hypercapnia has been assessed while the patient is in stable condition (1999). Unfortunately, patients with COPD are usually first diagnosed with hyperacapnic respiratory failure when they present at hospital with an acute exacerbation (Chu et al., 2004). Patients who survived after an episode of Acute Hypercapnic Respiratory failure requiring the use of NIV

have high risk of readmission rates and life threatening events. In this study, we followed up patients with COPD who were offered NIV at home after their hospitalization for Acute Respiratory Failure. Patients who finally agreed to receive NIV at home presented increased survival compared to patients who continued with oxygen at home. Chung et al., reported a 2 year survival rate of 52% in COPD patients receiving NIV at home after they had been hospitalized for acute respiratory failure. Patients included in the study by Chung et al., had more severe respiratory failure on presentation (as indicated by a lower pH value (7.24 vs 7.35) and higher PaCO2 values (84.7 vs 61 mmHg), while they had worse PaCO2 values at discharge (52 vs 47.5 mmHg). Moreover, the patients included in our study had higher BMI values [28 kg/m2 (27-30) vs 24.9 kg/m2 (5.8)] (Chung et al). It seems that hypercapnic COPD patients with increased BMI, is a distinct subgroup with different survival rates than the cachectic COPD phenotype. BMI has been found to be a major predictor of survival in hypercapnic COPD patients (Chung et al). Values of <25 kg/m2 have been associated with worse prognosis. In patients with severe COPD requiring LTOT higher values of BMI were gradually linked to a better longer term outcomes (Chailleux et al., 2003; Schols et al., 1998).

In the COPD group, women seem to have worse survival. The disease course in women is different. Women show a faster rate of FEV1 decline, more hospitalizations, more dyspnea and increased mortality.(Ohar et al) This could be explained by the increased susceptibility of women in COPD, meaning increased prevalence of the disease in smokers.(Ohar et al) It has previously been found that women have increased annual death rate compared to men (11% versus 5%) and are at increased risk of death due to COPD-related comorbidities (Machado et al., 2006; Nilsson et al., 2001). We have found that when women are hospitalized with Acute Respiratory Failure, they have increased mortality rates. Moreover patients with an increased FEV1/FVC show increased mortality. One could expect that patients with more obstruction would have worse prognosis. It seems that patients' weak muscle tone, depicted by a lower FVC, reflects the chronically fatigued respiratory muscles which results in respiratory failure. Progressive weight loss and generalized skeletal muscle wasting, collectively known as pulmonary cachexia syndrome is well recognized in COPD. It is not affected by the degree of airway obstruction but it is directly correlated with an increased mortality (Prescott et al., 2002). An increased FEV1/FVC ratio, could therefore indicate, in patients having previously been diagnosed with COPD, respiratory muscle fatigue.

Moreover, when patients with COPD were stratified according to NIV model (S or ST mode), there was no difference in survival. Concerning NIV parameters, none was found to be a significant factor concerning survival. It seems that ventilator mode (meaning the spontaneous or timed mode) has no effect on patients' survival. Both modes can be used effectively. In a recent randomized crossover study comparing the effects of high intensity versus low intensity NIV applied in COPD patients with hypercapnic respiratory failure found that the major determinant for maintaining alveolar ventilation was the IPAP setting (Dreher et al). Appling high levels of Inspiratory pressures, effective ventilation can be achieved without providing a back up respiratory rate, especially in patients with COPD patients.

Our study, of course is not without limitations. The primary limitation of our trial is its retrospective design. There is no information about the cause of death in any patient, but this was not the intention in the present study. Secondly, there was a selection bias. Patients who received NIV at home were those who accepted to use it on a long term basis. All the patients who refused NIV's use constituted the control group. Patients in the control group received usual medication for their disease and oxygen therapy at home. The denial to use NIV did not mean intrinsic incompliance of these patients. Concerning follow up visits, all the patients were seen on three month intervals.

In conclusion, patients who present with acute decompensation of chronic respiratory failure due to COPD or OHS, can be effectively treated in a regular ward with NIV. Receiving NIV at home directly after hospital discharge can prolong survival. It seems that the prescription of NIV at home does not have to be strictly when patients are in stable condition. Patients can be prescribed NIV at home after hospitalization for acute respiratory failure with a survival benefit.

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