Investigation of chronic obstructive pulmonary disease patients discharged without home mechanical ventilation after in-hospital use of acute non-invasive ventilation

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Abstract

In stable hypercapnic chronic obstructive pulmonary disease (COPD) patients, clear benefits have been shown on long-term non-invasive positive pressure ventilation (NPPV) use, targeting reduction of hypercapnia. In contrast, the effectiveness of continuing NPPV at home after acute NPPV during hospitalization is controversial. To evaluate the prognosis and clinical course of patients with COPD who used acute NPPV during hospitalization but not after discharge, we conducted a retrospective, single-center, chart review on patients admitted because of an acute exacerbation of COPD, who used NPPV during hospitalization between December 2010 and March 2014. Of 50 patients, 25 patients were excluded due to insufficient follow-up and death during hospitalization. 18 patients continued using NPPV after discharge, while 7 patients did not. The average $PaCO_2$ on discharge was 62.0 mmHg in patients who used NPPV after discharge and 51.2 mmHg in patients who did not. Percentage of patients who developed an exacerbation after discharge was 61.0% and 42.9%, respectively. Median survival, event-free survival, and rate of acute exacerbation between the two groups were not significantly different. $PaCO_2$-matched comparison revealed no significant difference in median survival and event-free survival between the patients with NPPV and without NPPV after discharge. $PaCO_2$ before discharge or NPPV usage after discharge was not related to the acute exacerbation after discharge. COPD patients treated with acute NPPV in hospital did not continue NPPV after discharge when $PaCO_2$ got lower. In these patients prognosis was not significantly different from those with chronic NPPV. The doctors' judgment of discontinuing NPPV when $PaCO_2$ has improved in hospital is feasible for COPD patients.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a disease characterized by chronic progressive obstructive ventilatory disturbance.[1] When COPD progresses, patients develop respiratory failure due to impaired diffusion and ventilation-perfusion mismatch and sometimes hypercapnia with ventilation failure due possibly to respiratory muscles fatigue.[2] Once patients with COPD develop respiratory failure, two-year survival rate was reported as 30-40 %.[3]

For patients with hypercapnia in the course of acute exacerbation of COPD, use of non-invasive positive pressure ventilation (NPPV) proved effective for decreasing mortality, endotracheal intubation, and hospital stay with accumulating evidences.[4-11] Although performing NPPV for stable hypercapnic COPD patients improves physiologic parameters as hypercapnia, exercise tolerance at six-minute walk distance, and QOL,[12-14] evidence is weak for improving survival.[15-17] Köhnlein et al reported in 2014 that targeting marked reduction of hypercapnia for stable hypercapnia COPD patients improved survival compared to the non-intervention group.[19]

In contrast, the effectiveness of continuing NPPV at home after acute NPPV during hospitalization is controversial.[20-23] To evaluate the prognosis and clinical course of patients with COPD who used acute NPPV during hospitalization but not after discharge, we conducted a retrospective, single-center, chart review on patients admitted because of an acute exacerbation of COPD, who used NPPV during hospitalization.

2. Material & Methods

2.1. Patients

There were 478 patients who were admitted to this hospital and used NPPV for respiratory failure from December 2010 to March 2014. Four hundred and twenty-nine patients were excluded because their respiratory failure resulted from other underlying cardiopulmonary diseases, such as prior pulmonary tuberculosis, congestive heart failure or sleep apnea syndrome. Thus, 49 patients with acute exacerbation (AE) of COPD were selected. Thirteen patients were excluded due to insufficient follow-up and 11 patients due to death during hospitalization. The remaining 25 patients were analyzed in this study. Of the 25 patients who met inclusion criteria, 18 patients continued NPPV after discharge (NPPV group) while 7 patients did not continue after discharge (non-NPPV group).

2.2. Diagnosis of AE-COPD

COPD patients with a post-bronchodilator forced expiratory volume in the first second (FEV1)/forced vital capacity (FVC) ratio of < 0.70 [24] were

included in the study. We did not distinguish COPD from Asthma-COPD overlap syndrome. Acute exacerbations of COPD (AE-COPD) was defined as an acute worsening of respiratory symptoms that results in additional therapy.[24]

2.3. Study protocol

This study retrospectively analyzed medical records in this center. We reviewed age, sex, overall survival (OS), Event-free survival (EFS), Gold stage, $PaCO_2$, and ventilator settings and assessed these parameters between patients with NPPV after discharge and patients without NPPV after discharge. EFS was defined as the period from discharge to readmission due to AE-COPD. The observation period was more than two years (until March 2016). This study met compliance with the standards of the Declaration of Helsinki and the current ethical guidelines, and was approved by the institutional ethics committee.

2.4. Statistical analysis

OS and EFS curves were calculated by the Kaplan-Meier method and compared using the log-rank test. OS was calculated from the first admission due to AE-COPD until death from any cause or the last follow-up. Mean $PaCO_2$ on discharge was calculated by Welch-t test. Data were analyzed using GraphPad Prism ver.5.02. Two-tailed P values of < 0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

The characteristics of the patients are shown in Table 1. There were several differences in the baseline characteristics of the two groups. The mean age of the non-NPPV group was 8.0 years older than the with NPPV group which was statistically significant (p=0.0214). There was a higher proportion of female distribution in the non-NPPV group. $PaCO_2$ on admission tended to be higher in non-NPPV group (p=0.0721). IPAP on admission and EPAP on admission were similar in both groups (p=0.5513 and 0.9066, respectively).

3.2. Comparison of OS and EFS with and without NPPV after discharge

OS was 827 days in patients with NPPV after discharge and 537 days in patients without, indicating no significant difference (p=0.88) (Figure 1). EFS was 501 days in patients who used NPPV after discharge and 537 days in patients who did not, which was not significantly different (p=0.72) (Figure 2). The average $PaCO_2$ on discharge in patients with NPPV (62.0±13.9 mmHg) was significantly higher than that in patients without using NPPV after discharge (51.2±6.2) mmHg (p=0.0021).

Table 1. Baseline characteristics of patients.

	With NPPV(n=18)	Without NPPV(n=7)	p-value
Age	72.5(5.3)	80.5(5.7)	0.0214
Men/Women	16/2	4/3	0.0748
Gold stage I+II/III+IV	1/17	1/6	0.490
LTOT use −/+	5/13	3/4	0.640
Smoking status(py)	81.7(37.6)	59.4(33.0)	0.1985
pH on admission	7.274(0.077)	7.256(0.068)	0.590
$PaCO_2$ on admission	88.4(24.2)	108.9(22.7)	0.0721
PaO_2 on admission	85.6(35.2)	86.0(38.7)	0.984
IPAP on admission	11.2(3.3)	12.2(3.2)	0.551
EPAP on admission	4.4(1.3)	4.5(0.84)	0.907
IPAP on discharge	10.8(3.1)	N/A	N/A

Notes: All results are expressed as the mean (standard deviation).

Abbreviations: LTOT, long-term oxygen therapy; py, pack-years; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PaO_2, partial pressure of oxygen in arterial blood; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure; N/A, not applicable

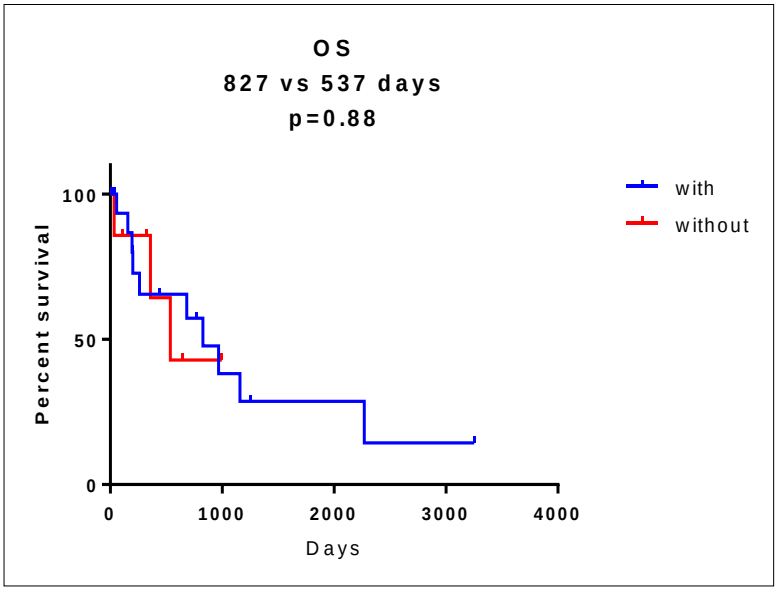

Figure 1. Overall survival (OS) difference between patients discharged with and without NPPV

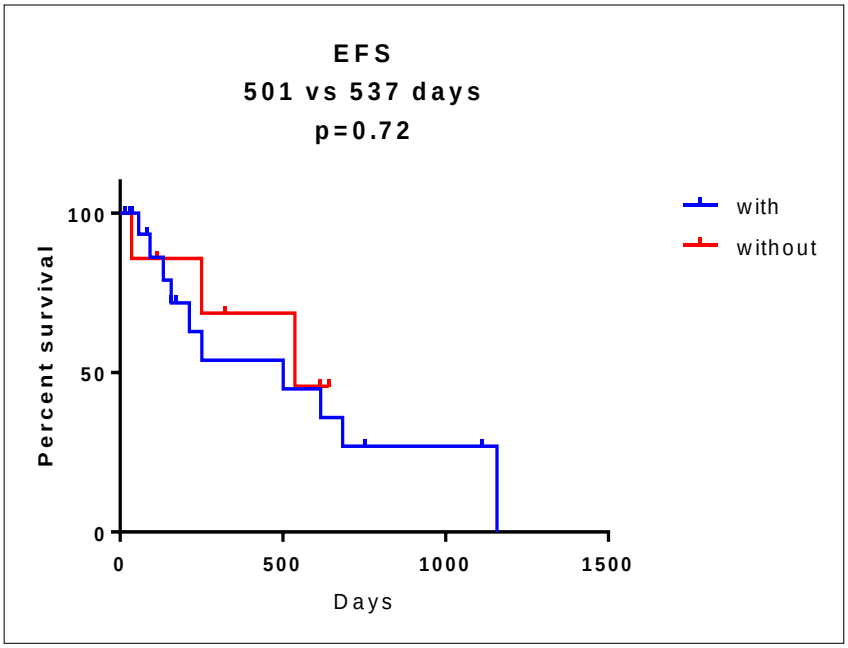

Figure 2. Event-free survival (EFS) difference between patients discharged with and without NPPV

3.3. Comparison of OS and EFS with and without NPPV after discharge analyzed in $PaCO_2$-matched patients

We, thus, compared $PaCO_2$-matched OS and EFS. We selected 9 patients discharged with NPPV, whose $PaCO_2$ at the time of discharge was in the lower half of the group. Mean $PaCO_2$ of these patients discharged with NPPV (51.5±3.5 mmHg) was properly matched with that of patients without NPPV (51.5±6.2 mmHg). Neither OS (p=0.95) (Figure 3) or EFS (p=0.67) (Figure 4) was significantly different between the two $PaCO_2$-matched groups.

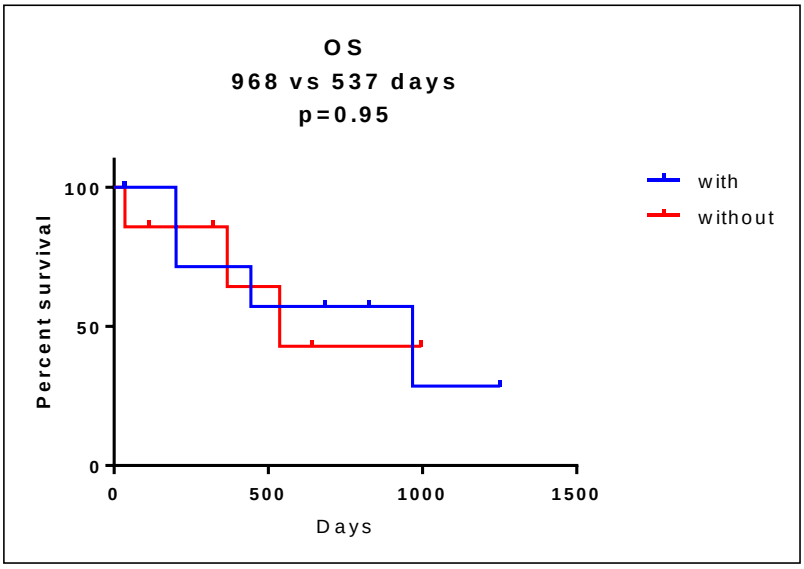

Figure 3. $PaCO_2$-matched OS differences between the patients discharged with and without NPPV

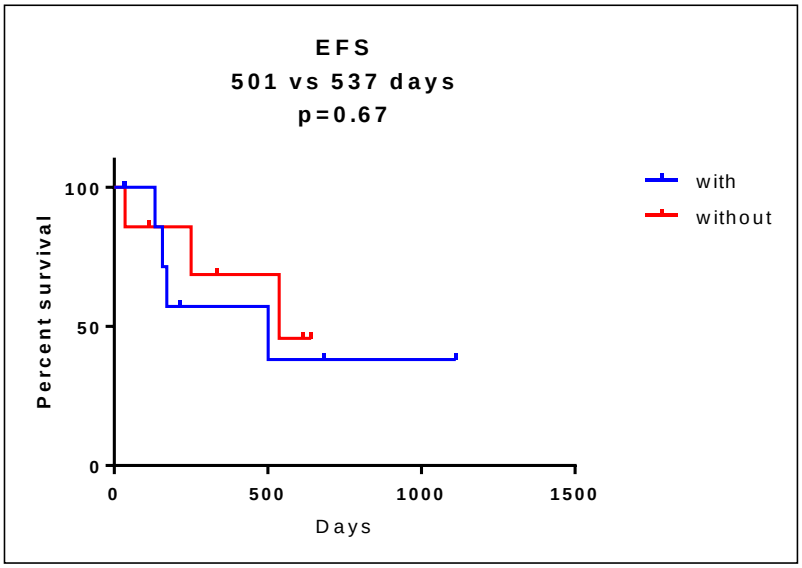

Figure 4. $PaCO_2$-matched EFS differences between the patients discharged with and without NPPV.

3.4. Difference in OS and EFS in patients with NPPV after discharge depending on $PaCO_2$ on discharge

Then, we divided patients discharged with NPPV into 2 groups, low $PaCO_2$ group (n=9) and high $PaCO_2$ group (n=9). OS (p=0.82) (Figure 5) or EFS (p=0.73) (Figure 6) was not significantly different between the two groups. Higher $PaCO_2$ on discharge was not a risk factor for. There was not a significant difference in survival or rehospitalization among low and high $PaCO_2$ group with NPPV, and non-NPPV group.

3.5. Comparison of risk for rehospitalization between NPPV group and non-NPPV group

Percentage of patients who developed an exacerbation after discharge was 67% and 29%, respectively (p=0.085) (Figure 7), suggesting patients discharged without NPPV tended to show less AEs than those with NPPV. There was no significant difference of mean $PaCO_2$ on discharge between patients with and without acute exacerbation after discharge (p=0.66).

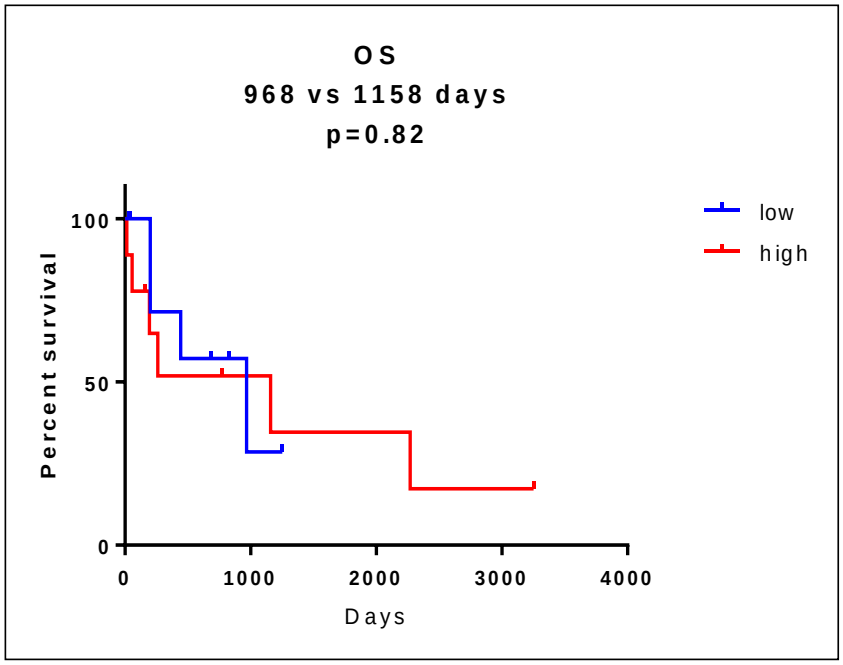

Figure 5. OS differences of patients discharged with NPPV between high $PaCO_2$ group and low $PaCO_2$ group

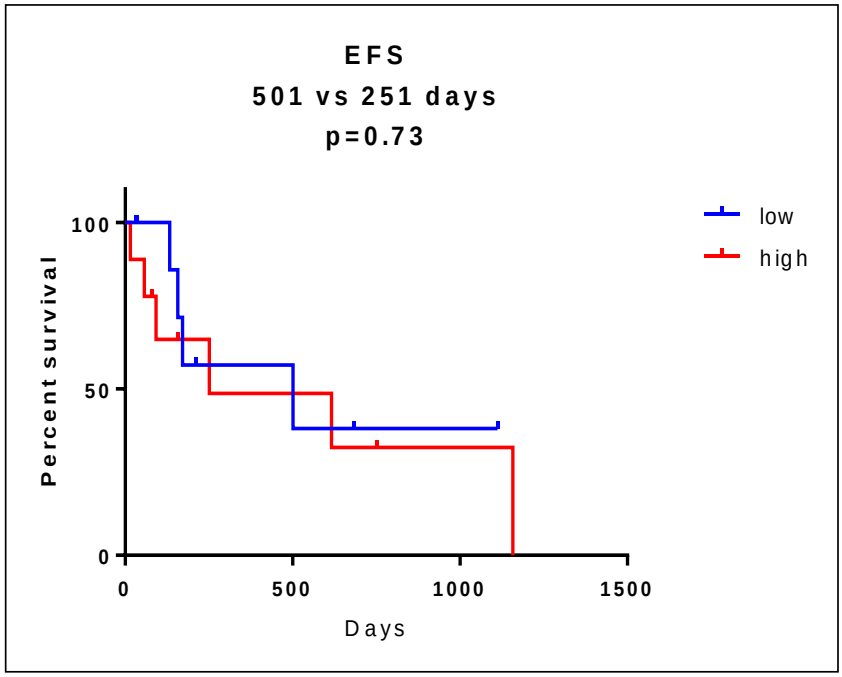

Figure 6. EFS differences of patients discharged with NPPV between high $PaCO_2$ group and low $PaCO_2$ group

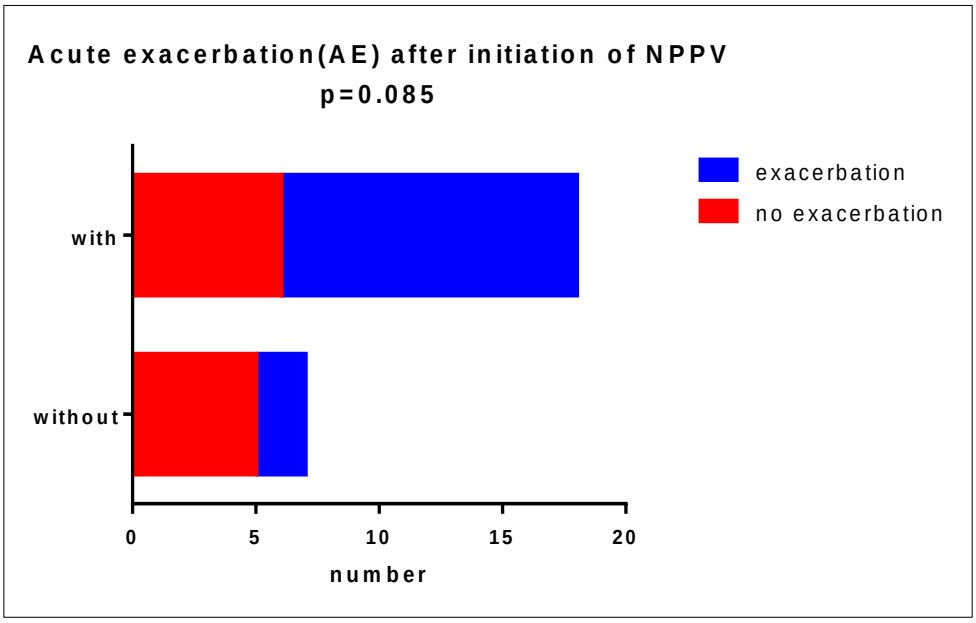

Figure 7. Difference of acute exacerbation after discharge between patients discharged with and without NPPV.

4. Discussion

In this study, we first hypothesized that more patients in the non-NPPV group would be rehospitalized after in-hospital use of NPPV for acute exacerbation of COPD, so that we could determine the risk factors which predict quick rehospitalization. However, survival or rehospitalization was not significantly different between patients with and without NPPV. We then suspected that the reason for the no difference might be because of lower $PaCO_2$ on discharge of patients without NPPV compared with that of patients with NPPV. Contrary to our suspicion, $PaCO_2$-matched comparison of OS and EFS did not exhibit significant difference between patients discharged with and without NPPV. In addition, there was no significant difference of OS and EFS depending on $PaCO_2$ in patients discharged with NPPV.

To our surprise, patients discharged without NPPV tended to show less AEs than those with NPPV. This result indicated that not only $PaCO_2$ at the time of discharge but other unknown factors affected doctors' decisions of using or not using NPPV after discharge. Although the factors were not clarified in this study, we could suppose there are unknown risk factors for AE-COPD and rehospitalization for these patients included in this study.

This study suggested that doctors tended to discontinue NPPV after discharge for patients with lower $PaCO_2$, in accordance with guidelines.[24] The choice of discontinuing NPPV when $PaCO_2$ improved in hospital was not a risk factor for rehospitalization or survival. Our study also suggested that $PaCO_2$ was not the only factor for the decision of NPPV continuation since doctors might discontinue NPPV for the more stable patients, resulting in less admission for the patients without NPPV.

In 2010-2014 before the study published by Köhnlein T et al.[19], we used inspiratory positive airway pressure (IPAP) of ~11cmH_2O for the acute and chronic NPPV because of fear of pneumothorax and patients' intolerance. While randomized trials[15-18] between 2000-2010 indicated that NPPV did not significantly reduce hypercapnia or improve long-term survival when low-intensity NPPV was adopted, Köhnlein et al.[19] reported that the mean IPAP 21.6 cmH_2O significantly reduced hypercapnia and resulted in improved overall survival in patients with hypercapnic COPD. Our study showed significant reduction of $PaCO_2$ in the acute phase of the clinical course but did not reveal improvement in OS, and EFS in the chronic phase after discharge. The fact that the mean IPAP (10.8 cmH_2O on discharge) of this investigation was lower than the study (21.6 cmH_2O[19]) might be the reason for no significant difference.

In 2011, Funk et al.[13] performed a study investigating 26 consecutive COPD

patients with acute hypercapnic respiratory failure requiring NPPV, who were randomized to continue or discontinue NPPV after their exacerbation. Mean time to clinical worsening was 162±40 days in the withdrawal group and 391±36 days in the ventilation group. Although clinical worsening was different from EFS, patients in this study stayed without readmission for a longer period without NPPV. We considered it was because of the lower $PaCO_2$ on discharge (51.5 cmH_2O).

The study had some limitations. Since it was a retrospective, single-center study, the sample size was small. There were only 7 patients in the non-NPPV group. It could be the reason for the non-significant differences in the statistical analyses. Therefore, our main findings need to be confirmed in a large prospective study. Another concern was IPAP. Lower IPAP might reduce the OS and EFS in the NPPV group, leading to no difference in the comparisons between patients with and without NPPV. Although patients' intolerance and fear of pneumothorax could have prevented higher IPAP studies in Japan, we should test the efficacy and safety with our patients.

5. Conclusions

We concluded that the doctors' judgment of discontinuing NPPV when $PaCO_2$ has improved in hospital after acute NPPV was feasible and not inferior to continuing NPPV for the management of COPD patients.

6. Declaration of interest

The authors declare no conflicts of interest associated with this manuscript.

7. References

1. American Thoracic Society. A statement of the committee on therapy; Chronic obstructive lung disease. *Am Rev Respir Dis* 1965;92:513-8.

2. Begin P, Grassino A. Inspiratory muscle dysfunction and chronic hypercapnia in chorni obstructive pulmonary disease. *Am Rev Respir Dis* 1991;143:905-12.

3. Foucher P, Baudouin N, Merati M, Pitard A, Bonniaud P, Reybet-Degat O, *et al*. Relative survival analysis of 252 patients with COPD receiving long-term oxygen therapy. *Chest* 1998;113:1580.

4. Meyer TJ, Hill NS. Noninvasive positive pressure ventilation to treat respiratory failure. *Ann Intern Med* 1994;120:760-70.

5. Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation—a consensus conference report. *Chest* 1999;116:521-34.

6. British Thoracic Society Standards of Care Committee. Non-invasive ventilation in acute respiratory failure. *Thorax* 2002;57:192-211.

7. Bott J, Carroll MP, Conway JH, Keilty SEJ, Ward EM, Brown AM, *et al*. Randomised controlled trial of nasal ventilation in acute ventilator failure due to chronic obstructive airway disease. *Lancet* 1993;341:1555-7.

8. Brochard L, Mancebo J, Wysocki M, Lofaso F, Conti G, Rauss A, *et al*. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995;333:817-22.

9. Kramer N, Meyer TJ, Meharg J, Cece RD, Hill NS. Randomised, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. *Am J Respir Crit Care Med* 1995;151:1799-806.

10. Plant PK, Elliott MW. Chronic obstructive pulmonary disease *9: management of ventilator failure in COPD. *Thorax* 2003;58:537-42.

11. Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicenter randomized controlled trial. *Lancet* 2000;355:1931-5.

12. Windisch W, Kostic S, Dreher M, Virchow JC Jr, Sorichter S. Outcome of patinents with stable COPD receiving controlled noninvasive positive pressure ventilation aimed at a maximal reduction of $PaCO_2$. *Chest* 2005;128:657-62.

13. Funk GC, Breyer MK, Burghuber OC, Kink E, Kirchheiner K, Kohansal R, *et al*. Long-term non-invasive ventilation in

COPD after acute-on-chronic respiratory failure. *Respir Med* 2011;105:427-34.

14. Windisch W. Impact of home mechanical ventilation on health-related quality of life. *Eur Respir J* 2008;32:1328-36

15. Clini E, Sturani C, Rossi A, Viaggi S, Corrado A, Donner CF, *et al*. The Italian Multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. *Eur Respir J* 2002;20:529-38.

16. Casanova C, Celli BR, Tost L, Soriano E, Abreu J, Velasco V, *et al*. Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. *Chest* 2000;118:1582-90.

17. McEvoy RD, Pierce RJ, Hillman D, Esterman A, Ellis EE, Catcheside PG, *et al*. Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomized controlled trial. *Thorax* 2009;64:561-66.

18. Dreher M, Storre JH, Schmoor C, Windisch W. High-intensity versus low-intensity non-invasive ventilation in patients with stable hypercapnic COPD: a randomized crossover trial. *Thorax* 2010;65:303-08.

19. Köhnlein T, Windisch W, Kohler D, Drabik A, Geiseler J, Hartl S, *et al*. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicenter, randomized, controlled clinical trial. *Lancet Respir Med* 2014;2:698-705.

20. Jones SE, Packham S, Hebden M, Smith AP. Domiciliary nocturnal intermittent positive pressure ventilation in patients with respiratory failure due to severe COPD: long-term follow up and effect on survival. *Thorax* 1998;53:495-8.

21. Duiverman ML, Wempe JB, Bladder G, Vonk JM, Zijistra JG, Kerstjens HA, *et al*. Two-year home-based nocturnal noninvasive ventilation added to rehabilitation in chronic obstructive pulmonary disease patients: a randomized controlled trial. *Respir Res* 2011;12;112.

22. Windisch W, Haenel M, Storre JH, Dreher M. High-intensity non-invasive positive pressure ventilation for stable hypercapnic COPD. *Int J Med Sci* 2009;6:72-6.

23. Galli JA, Krahnke JS, James MA, Shenoy K, Zhao H, Criner GJ. Home non-invasive ventilation use following acute hypercapnic respiratory failure in COPD. *Respir Med* 2014;108:722-8.

24. Global initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. www.goldcopd.org

