Original Article

Efficacy of domiciliary noninvasive ventilation on clinical outcomes in posthospital chronic obstructive pulmonary disease patients: a meta-analysis of randomized controlled trials

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Background: As newly emerging evidence was given, we conducted a meta-analysis of randomized controlled trials (RCTs) with the following objectives: (I) to evaluate the effect of long-term noninvasive ventilation (NIV) on posthospital chronic obstructive pulmonary disease (COPD) patients with respiratory failure in mortality, blood gas, exacerbation frequency; (II) to distinguish different follow-up length of long-term NIV and its effect on these outcomes.

Methods: We tried to conduct and report this meta-analysis in accordance with the Cochrane Handbook (version 5.1.0) by searching the PubMed, Embase, Cochrane Library, and Chinese Biomedical Literature for RCTs in humans through April 2020. Studies comparing treatment effects of domiciliary NIV with control therapy in posthospital COPD patients were conducted, and at least one of the following parameters were reviewed: mortality, gas exchange, and exacerbation frequency.

Results: Five studies with 419 subjects were identified. The exacerbation frequency significantly decreased in patients who received domiciliary NIV [weighted mean difference (WMD) –1.74, 95% CI: –2.90 to –0.57, P=0.004]. No significant difference was found in mortality, partial pressure of arterial oxygen (PaO_2), $PaCO_2$, and pH. Subgroup analysis of $PaCO_2$ showed that domiciliary NIV of 3 months was most likely to decrease $PaCO_2$, but not significant (WMD –2.95, 95% CI: –6.11 to 0.21, P=0.07).

Discussion: The results indicate that domiciliary NIV decreases the exacerbation frequency of posthospital COPD patients, but may not improve mortality or gas exchange. Further studies are needed to evaluate the benefit of domiciliary NIV on COPD patients.

Keywords: Chronic obstructive pulmonary disease (COPD); meta-analysis; domiciliary NIV; mortality; gas change; exacerbation frequency

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common chronic lung disease, which is predicted to be the 3rd leading cause of death by 2020 (1). COPD has induced huge burden globally because of the increasing morbidity and mortality, especially in developing countries. The destruction of gas-exchanging surfaces of the alveolar, called emphysema, is the main pathological

changes of COPD. As disease progresses, hypoxemia and hypercapnia are the common gas exchange abnormalities. Meanwhile, airflow limitation contributes to the high possibility of exacerbations and death (2-4). Oxygen therapy and ventilation support are essential steps on improve hypoxemia and hypercapnia. Goals of COPD management are reducing the risk of exacerbations and minimizing the negative impact of exacerbations.

The applying of noninvasive mechanical ventilation (NIV) is considered priority to treat acute respiratory failure in hospitalized AECOPD patients (5). Evidence showed that NIV could improve mortality during hospitalization and reduce the use of endotracheal intubation (6,7). Mild acidosis (pH 7.30–7.35) patients were most likely to benefit from NIV during acute hypercapnic respiratory failure (5). There is insufficient evidence to support long-term NIV in non-acute COPD patients so far (8,9), including blood gas, mortality, lung function and so on. As shown in the ECLIPSE cohort, prior hospital admission of AECOPD was associated with the highest risk of a new hospitalization (2). Therefore, the beginning time of using NIV might have effect on the outcomes. In recent years, several randomized controlled trials (RCTs) concerning posthospital AECOPD patients have been published.

As newly emerging evidence was given, we conducted a meta-analysis of RCTs with the following objectives: (I) to evaluate the effect of long-term NIV on posthospital COPD patients with respiratory failure in mortality, blood gas, exacerbation frequency; (II) to distinguish different subgroups of long-term NIV and its effect on these outcomes. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/apm-20-2017).

Methods

Literature search

We attempted to conduct and report this meta-analysis in accordance with the Cochrane Handbook (version 5.1.0) by searching the PubMed, Embase, Cochrane Library, and Chinese Biomedical Literature for RCTs in humans through April 2020. We used search terms “Pulmonary Disease, Chronic Obstructive,” or “COPD,” in combination with “noninvasive ventilation” and “randomized controlled trial.” No restrictions were imposed. In addition, we reviewed the reference lists of retrieved studies and recent reviews. We did not contact authors of original studies for additional information. No attempt was made to identify unpublished reports.

Study selection and eligibility criteria

Study selection was based on an initial screen of identified abstracts or titles and the second screen of full-text articles. Studies were considered eligible if they met the following criteria: (I) the study design was a RCT; (II) posthospital COPD patients were included (post-hospital COPD is defined as those who has clear evidence that treatment with NIV in a study after hospitalization (due to acute exacerbation or acute hypercapnia). Usually, refer to those who have acute exacerbation within 4 weeks); (III) domiciliary noninvasive ventilation (NIV) was used in the intervention group, and usual care was used in the control group; (IV) measurement of mortality, gas exchange, or exacerbation frequency. First, two reviewers independently screened titles and abstracts of the studies according to eligibility criteria. And if the studies met the eligibility criteria, full texts were reviewed for further selection. Two reviewers’ results were compared, and disagreements were resolved by discussion.

Data extraction

We recorded study characteristics as follows: (I) name of the first author, publication year, and country of origin; (II) study design; (III) number of cases; (IV) length of follow-up; (V) main characteristics of the subjects; (VI) interventions; (VII) outcomes. Two reviewers (XH and LJL) independently performed the literature search, study selection, and data extraction. Any disagreements were resolved by discussion.

Statistical analysis

Our main analysis focused on the different outcomes of intervention on posthospital COPD patients. The risk of bias was assessed based on the Cochrane Handbook. Mean and variance was extracted from the article directly or concerted from median, range, and the size of a sample (10). The relative risk (RR) and weighted mean difference (WMD) were used as the common measure of association across different studies (11,12). Review Manager (version 5.3.5) was used to analyze the results and assess the intervention efficacy (13). The risk of bias in individual

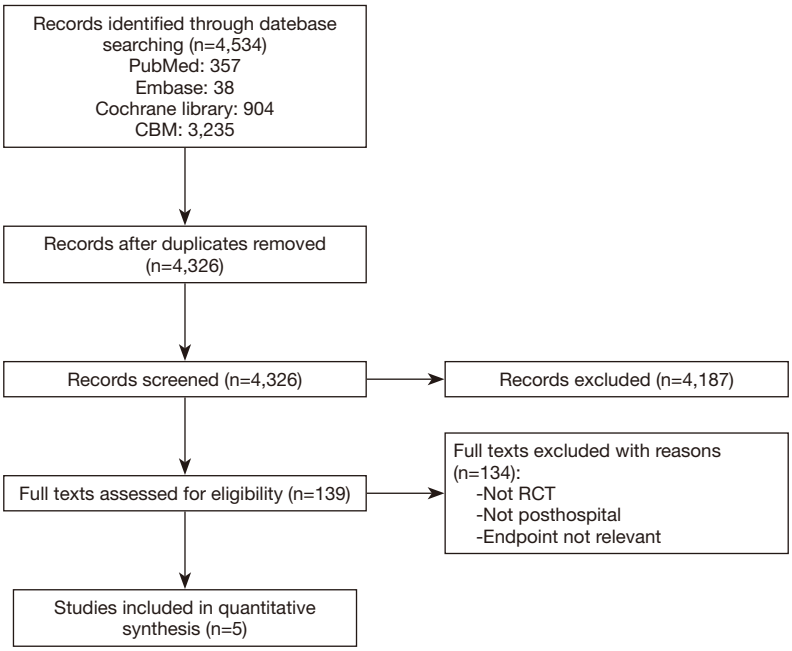

Figure 1 Flow chart of the study selection.

studies was assessed using this software following the PRISMA statement. A random efficacy model was used in the case of significant heterogeneity among studies. RR with 95% confidence interval (95% CI) was computed for discontinuous variable; WMD with 95% CI was calculated for continuous variable. Homogeneity of RRs was evaluated by *Q* statistic (significance level at P<0.1) and I^2 statistic (12). For I^2 statistic, $I^2<25\%$, $25\%\leq I^2<50\%$ or $I^2\geq 50\%$ corresponds to the low, moderate or high significance of heterogeneity, respectively. We conducted subgroup analysis stratified by follow-up length. We also conducted a sensitivity analysis to investigate the influence of a single study on the overall risk estimate by omitting one study in each turn.

Results

Literature search and study characteristics

A flow chart showing the study selection is presented in *Figure 1*. Five studies met the eligible criteria after our complete review. The characteristics of these studies are presented in *Table 1*. These RCTs studies were published between 2007 and 2017. Two studies were conducted in China (14,15), one in Belgium (16), one in Netherland (17), and one in England (18). Two studies were multicenter RCTs (17,18), and three studies were single-center RCTs (14-16). The number of patients enrolled in the original studies ranged from 40 to 201, with a sum of 419. Of them, 211 were in NIV intervention, and 208 of them were in the control group. The follow-up ranged from 6–24 months. 3 studies reported 12 months, 1 reported 6 months, 1 reported 24 months. The risk of bias assessment (including selection bias, performance bias, detection bias, attrition bias, reporting bias, etc.) was shown in *Figure 2*. All the studies claimed RCTs, but De Backer's study didn't show the randomized method. De Backer's and Xiang's study were assessed unclear risk of allocation concealment. Only Cheung reported a blinded intervention to participants. Two studies clearly described the blinding of outcome assessment. Three studies were assessed a high risk of attrition bias. De Backer's study was a high risk of reporting bias, as only one time point result was reported.

Mortality

Three studies reporting mortality were summarized in *Figure 3*. Results from three studies on mortality were consistent, with most showing no relation with intervention. The summary RR comparing domiciliary NIV with control treatment was 0.87 (95% CI: 0.59–1.28), with low heterogeneity (P=0.49, I^2=20%).

Table 1 Characteristics of the included studies

Study	Location	Trial type	Patients recruited	Population (n) randomized (treatment/control)	Length of follow-up	Main characteristics of the subjects	Intervention (I/C)	Main outcomes	Baseline mean value (I/C)	NIV settings at endpoint IPAP/EPAP (cmH_2O)	Initial NIV settings IPAP/EPAP (cmH_2O)	Time of daily use
Murphy *et al.*, 2017	England	Multi-center RCT	Patients admitted with acute decompensated hypercapnic exacerbations of COPD requiring acute noninvasive ventilation were screened for eligibility at least 2 weeks after resolution of decompensated acidosis (arterial pH >7.30) and within 4 weeks of attaining clinical stability	116 (57/59)	12 months	FEV1 <50% predicted, $PaCO_2$ >53 mmHg	Home oxygen therapy + NIV/home oxygen therapy alone	Time to readmission or death, mortality, exacerbation frequency, $PaCO_2$, PaO_2, dyspnea, HRQL, St George's Respiratory Questionnaire	PaO_2 48/48 mmHg, $PaCO_2$ 59/59 mmHg, pH 7.4/7.4, admissions per year not shown	24/4	18/4	NIV: a minimum of 6 hours nightly; OT: at least 15 hours daily
Struik *et al.*, 2014	Netherlands	Multi-center RCT	COPD patients who were admitted to hospital with ARF and treated with ventilatory support	201 (101/100)	12 months	FEV1 <50% predicted, $PaCO_2$ >6 kPa	NIV + LTOT/LTOT	Time to readmission or death, lung function, arterial blood gas, survival, admission and exacerbation rates, HRQL	PaO_2 59.25/56.25 mmHg, $PaCO_2$ 59.25/57.75 mmHg, pH 7.38/7.39, admissions per year 2/2	21/5.2	14/4	NIV: at least 5 hours per night; LTOT: at least 15 hours daily
De Backer *et al.*, 2011	Belgium	Single center RCT	Hospitalized patients after acute hypercapnic COPD exacerbations, were hospitalized due to an exacerbation	15 (10/5)	6 months	FEV1 <50% predicted, $PaCO_2$ >45 mmHg	NIV/no NIV, no details about LTOT	Arterial blood gas, functional imaging of the lungs, lung function tests (static and dynamic lung volumes, diffusion), exercise tolerance	PaO_2 59/65 mmHg, $PaCO_2$ 55.4/ 52.4 mmHg, pH not shown, admissions per year not shown	Not shown	Not shown	NIV: at least 5 hours a day
Cheung *et al.*, 2010	China	Single center RCT	COPD patients who were admitted to acidosis hospital with ARF and treated with ventilatory support	47 (23/24)	12 months	$PaCO_2$ >6 kPa	NIV/CPAP, LTOT if appropriate	Time to recurrent AHRF, readmission, compliance, severe adverse event, arterial blood gas, all-cause mortality	PaO_2 not shown, $PaCO_2$ 57.75/54.75 mmHg, pH 7.4/7.4, admissions per year not shown	10–20/5	Not shown	NIV/CPAP for 8 h during sleep every night
Xiang *et al.*, 2007	China	Single center RCT	Severe COPD patients who were admitted due to AECOPD with type II respiratory failure	40 (20/20)	24 months	FEV1 <50% predicted, $PaCO_2$ ≥55 mmHg	NIV + LTOT/LTOT	Mortality, arterial blood gas, severe adverse event, severe exacerbations (readmission), compliance	PaO_2 55/54 mmHg, $PaCO_2$ 59.2/58.8 mmHg, pH not shown, admissions per year 3.7/3.6	16–20/2–4	Not shown	NIV: at least 8 hours per day; LTOT: at least 15 hours daily

RCT, randomized controlled trial; NIV, noninvasive ventilation; COPD, chronic obstructive pulmonary disease; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure; CPAP, continuous positive airway pressure; LTOT, long-term oxygen therapy.

Gas exchange

All studies reported gas exchange data. Results from four studies on PaO_2 were inconsistent, with most showing no difference with domiciliary NIV. The summary WMD of PaO_2 comparing domiciliary NIV with control treatment was 2.48 (95% CI: −3.24 to 8.20), with high heterogeneity (P=0.40, I^2=81%, *Figure 4*). Results from five studies on $PaCO_2$ were also inconsistent at the endpoint. The summary WMD of PaCO2 comparing domiciliary NIV with control treatment was −4.42 (95% CI: −10.63 to 1.78), with high heterogeneity (P=0.16, I^2=93%, *Figure 5*). Only two studies included pH values. Results from two studies on pH were consistent. The summary WMD of pH comparing domiciliary NIV with control treatment was 0.01 (95% CI: −0.00 to 0.02), with no evidence of heterogeneity (P=0.13, I^2=0%, *Figure 6*).

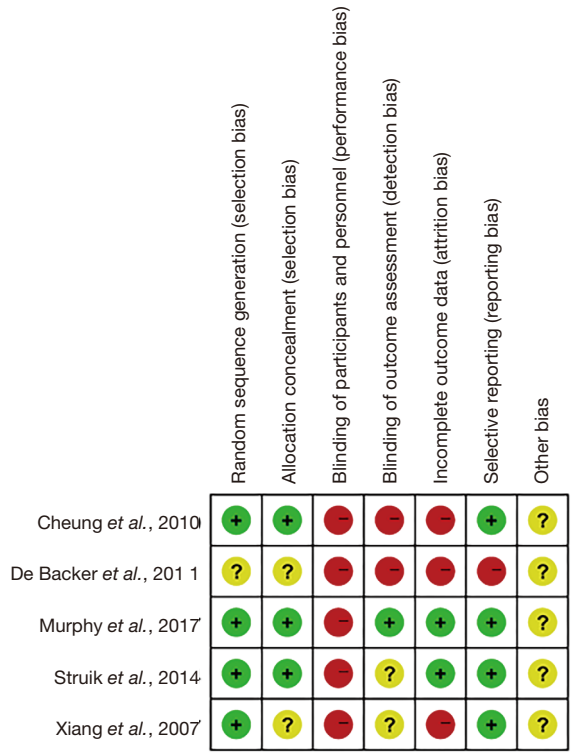

Figure 2 Risk of bias summary. +, low summary risk; ?, unclear risk; −, high risk.

Exacerbation frequency

Three studies reporting mortality were summarized in *Figure 7*. Results from three studies on exacerbation frequency were consistent. The summary WMD comparing domiciliary NIV with control treatment was −1.74 (95% CI: −2.90 to −0.57), with high heterogeneity (P=0.004, I^2=75%, *Figure 7*).

Subgroup and sensitivity analysis

The results of $PaCO_2$ subgroup analysis were presented in *Figure 8*, which were stratified by duration of follow-up. Two studies showed the data of 3 months, three studies each of 6 months and 12 months. Of all the subgroups, the summary WMD of $PaCO_2$ comparing domiciliary NIV with control treatment was similar in total. For 3 months, the summary WMD was −2.95 (95% CI: −6.11 to 0.21), with no evidence of heterogeneity (P=0.07, I^2=0%). Results from two studies on $PaCO_2$ were consistent, with both showing decrease with domiciliary NIV in 3 months. Similar data was shown in 12 months subgroup, which was −1.72 (95% CI: −4.14 to 0.70), with no evidence of heterogeneity (P=0.16, I^2=0%). The result in 6 months seemed inverse relation, which was 0.38 (95% CI: −2.92 to 3.69), with no evidence of heterogeneity (P=0.82, I^2=0%).

The sensitivity analysis was to investigate whether a single study have influence on the overall risk estimate by

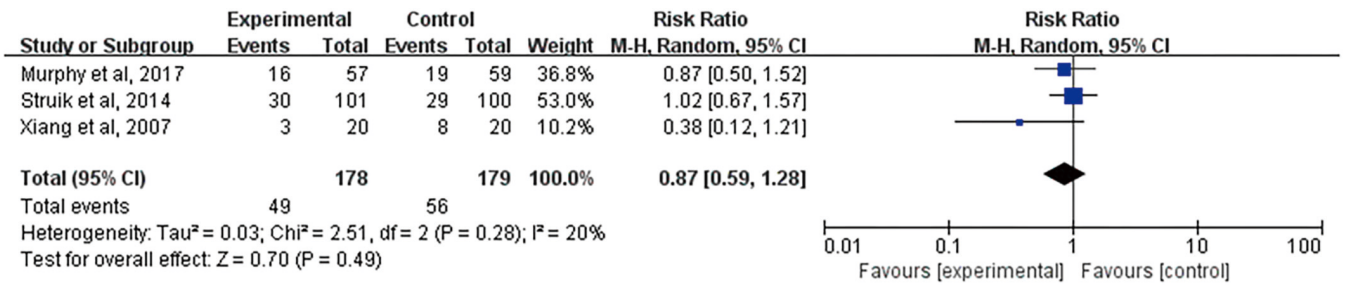

Figure 3 Mortality forest plot. Experimental, domiciliary NIV; control, usual care.

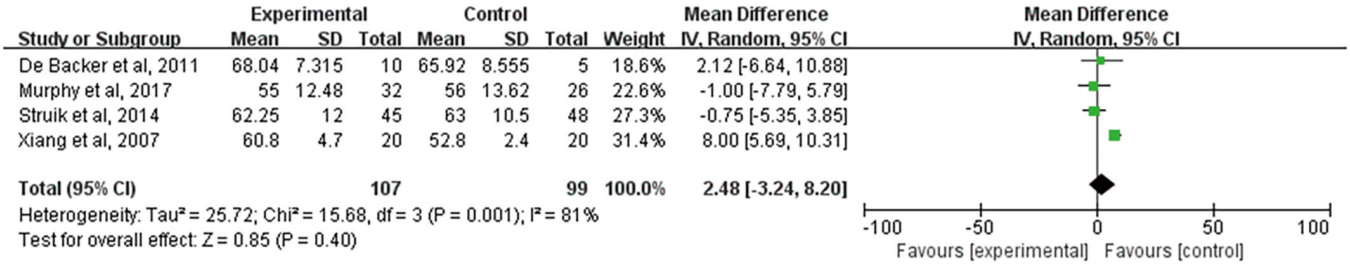

Figure 4 PaO_2 forest plot. Experimental, domiciliary NIV; control, usual care.

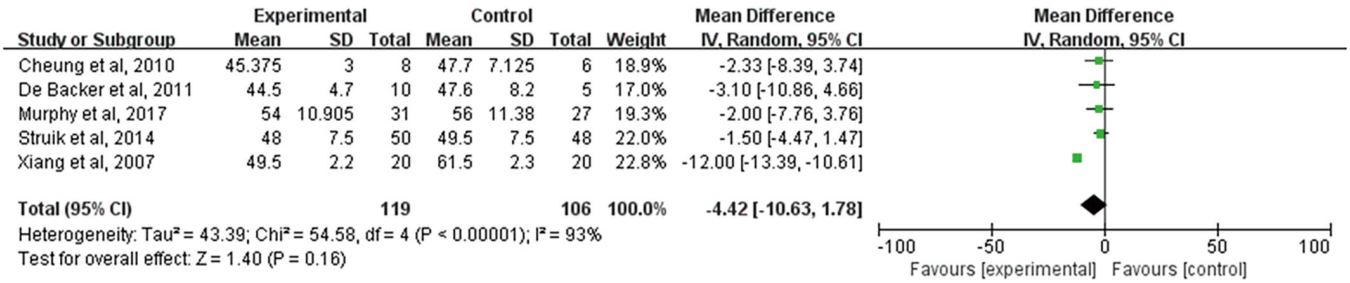

Figure 5 $PaCO_2$ forest plot. Experimental, domiciliary NIV; control, usual care.

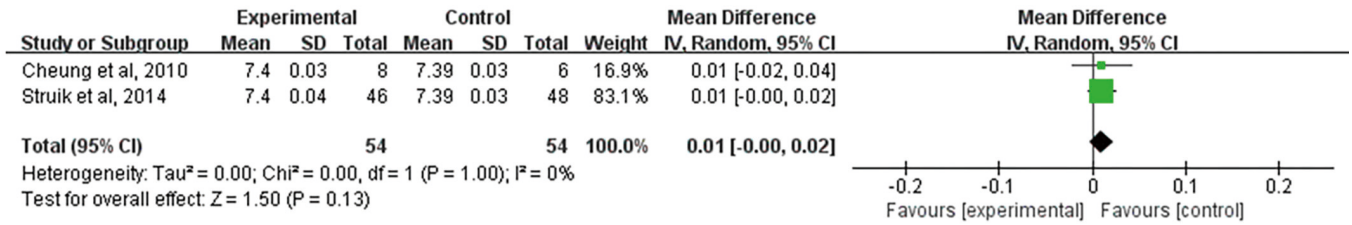

Figure 6 pH forest plot. Experimental, domiciliary NIV; control, usual care.

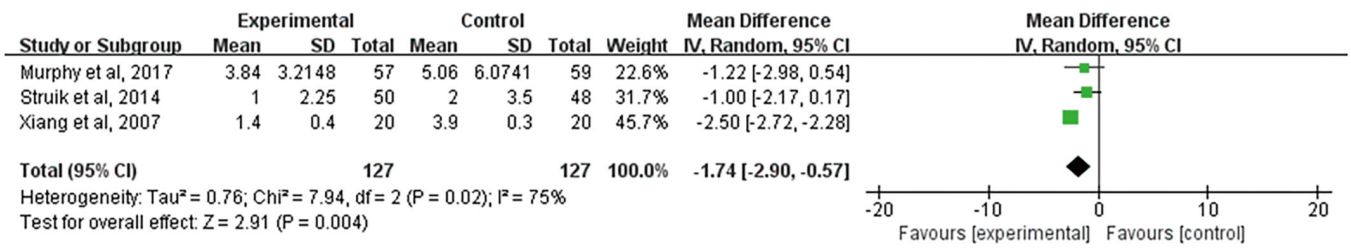

Figure 7 Exacerbation frequency forest plot. Experimental, domiciliary NIV; control, usual care.

omitting one single study in turn. For mortality, PaO_2, $PaCO_2$, and exacerbation frequency, the heterogeneity was attributed to one study (15). When omitting this study, the I^2 turned to 0% in the above analysis, and the overall P value remained similar. Two reviewers went through this study again and found that there was no reason to exclude the study. For mortality, after omitting this study, the result changed from (WMD =0.87, 95% CI: 0.59–1.28, P=0.49,

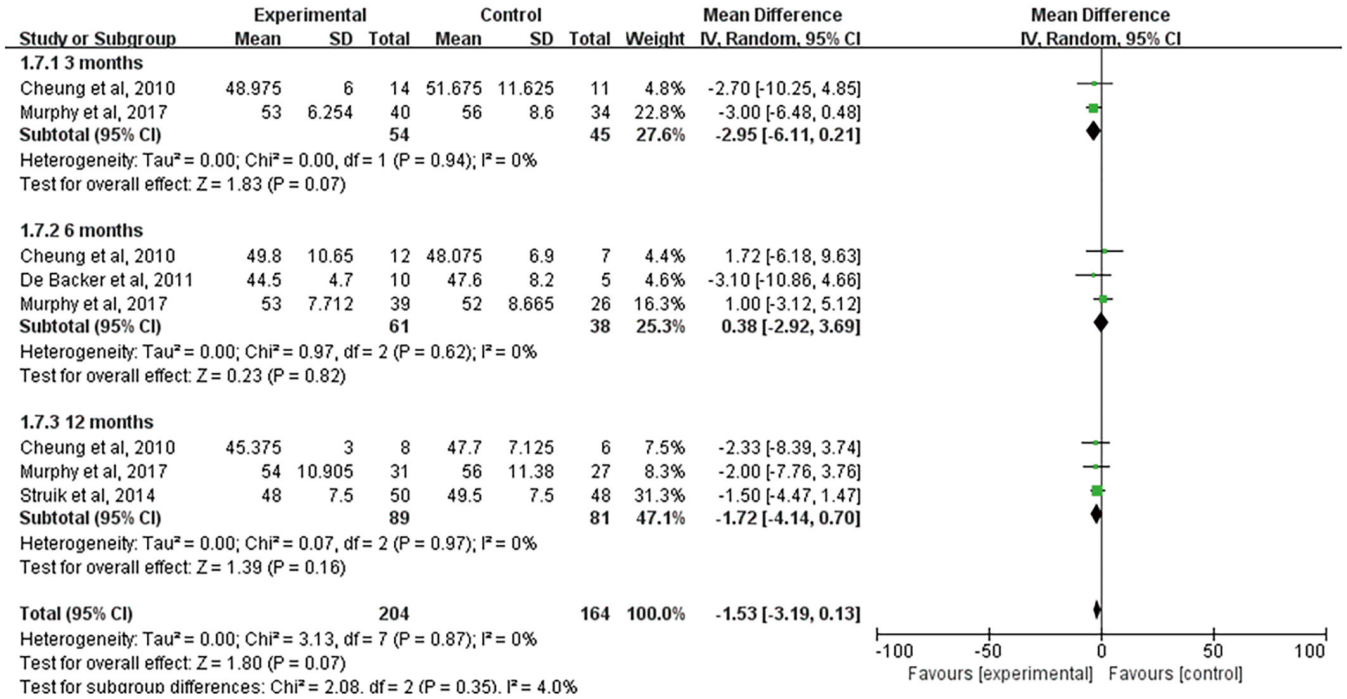

Figure 8 Subgroup analysis of $PaCO_2$ based on follow-up durations. Experimental, domiciliary NIV; control, usual care.

I^2=20%) to (WMD =0.96, 95% CI: 0.69–1.35, P=0.83, I^2=0%). For PaO_2, after omitting this study, the result changed from (WMD =2.48, 95% CI: −3.24 to 8.20, P=0.4, I^2=81%) to (WMD =−0.36, 95% CI: −3.85 to 3.13, P=0.84, I^2=0%). For $PaCO_2$, after omitting this study, the result changed from (WMD =−4.42, 95% CI: −10.63 to 1.78, P=0.16, I^2=93%) to (WMD =−1.84, 95% CI: −4.15 to 0.47, P=0.12, I^2=0%). For exacerbation frequency, after omitting this study, the result changed from (WMD =−1.74, 95% CI: −2.90 to −0.57, P=0.004, I^2=75%) to (WMD =−1.07, 95% CI: −2.04 to −0.09, P=0.03, I^2=0%).

Discussion

It is recognized that recurrent exacerbations leading to short-term readmission and increased all-cause mortality are associated with the initial hospitalization for an acute episode of deterioration (1). So, the treatment and management of posthospital COPD patients with acute exacerbation were essential. The applying of NIV is strongly recommended to treat acute respiratory failure in hospitalized AECOPD patients (1,5). Besides, the present meta-analysis of RCT studies supports a significant inverse association between NIV and $PaCO_2$, as well as mortality in stable hypercapnic COPD patients (9). It usually takes 2 months to reach a stable stage. It was reported that the 28-day COPD readmission rate was around 20% (19). Whether patients could benefit from the early starting of long-term NIV has been an urgent clinical question.

In our current meta-analysis, five RCTs were included with 419 posthospital COPD patients. The mortality, gas exchange, and exacerbation frequency were analyzed between the domiciliary NIV and control treatments. The exacerbation frequency significantly decreased in patients who received domiciliary NIV (WMD −1.74, 95% CI: −2.90 to −0.57, P=0.004). The result was consistent with Murphy's data (18), which is the latest posthospital RCT so far. Meanwhile, no significant difference was found in mortality, PaO_2, $PaCO_2$, and pH. Unlikely with the meta-analysis of stable COPD, domiciliary NIV couldn't decrease $PaCO_2$ for long-term effects in posthospital COPD patients. The subgroup analysis of $PaCO_2$ showed that domiciliary NIV of 3 months was most likely decrease $PaCO_2$, but still not significant (WMD −2.95, 95% CI: −6.11 to 0.21, P=0.07). In Murphy's study, there was significant improvement in hypercapnia during the follow-up duration of 6 weeks and 3 months. The long-term effect on the improvement of gas exchange may need to be evaluated.

Sensitivity analysis showed that Xiang's study (15) was the origin of heterogeneity in mortality, PaO_2, $PaCO_2$, and exacerbation frequency. In this analysis, the left studies present great homogeneity by omitting Xiang's study. We reviewed Xiang's study again, found there was no reason to delete this study. The reason that attributes to the heterogeneity may be the small number and significant results.

In the disease progression, COPD was punctuated by acute exacerbations. The management of exacerbation in COPD patients is the most critical part of disease management. Based on GOLD 2020, one of the goals is to minimize the negative impact of current exacerbation and to prevent subsequent events. For the first part, we have enough evidence to support our current treatment for AECOPD or COPD with acute hypercapnia, including the early use of NIV in hospital, corticosteroids, bronchodilators. Since the readmission is still higher than imagine (19), the management of posthospital is in the spotlight. Gavish *et al.* (20) reported that early follow-up (within one month) following discharge should be undertaken when possible and has been related to less exacerbation-related readmissions. Additional follow-up at three months is recommended to ensure return to a stable clinical state and permit a review of the patient's symptoms, lung function, and where possible the assessment of prognosis using multiple scoring systems such as BODE (21). There is no doubted that patients could benefit from frequent follow-up. But in developing countries like China, the density of physicians (total number per 1,000 population) is far lower compared with developed countries (22). Early follow-up may not be able to accomplish in every hospital, especially those not teaching hospital. In this case, our findings may provide evidence for the use of long-term NIV in COPD patients after acute hypercapnia.

There are several limitations in this study. First, this study includes a high degree of heterogeneity. However, our sensitivity analysis indicated that after omitting one study I^2 became 0%. Deleting that study will not change the result. Second, we didn't attempt to identify unpublished papers. This may contribute to a publication bai. Third, the small numbers of RCTs were another limitation of this meta-analysis. Further studies are needed to confirm our findings. Fourth, better double-blind and sham masks should be taken into consideration in the clinical trials of NIV in the future. The traditional sham device with no pressure could result in the increasing of $PaCO_2$. Unlikely pills, both patients and physicians can figure out positive pressure and zero pressure. The lack of double-blind practice is potential limitation in all NIV trials, and leads to performance and detection bias.

In summary, the results indicate that domiciliary NIV decreases the exacerbation frequency of posthospital COPD patients, but may not improve mortality and gas exchange. However, the analyses were based on small numbers of studies regarding posthospital AECOPD patients. Further studies are needed to evaluate the benefit of domiciliary NIV on COPD patients.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-2017). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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