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Review Article

Effects of long-term non-invasive ventilation in stable chronic obstructive pulmonary disease: a systematic review of 16 randomized controlled trials

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Abstract: Background: The benefits of non-invasive ventilation (NIV) in chronic obstructive pulmonary disease (COPD) have been debated for many years due to the conflicting results observed in these patients. The aim of this meta-analysis was to assess the long-term effects of NIV in stable patients with COPD. Methods: The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and CINAHL databases were searched. Randomized, controlled trials and crossover studies were included. Mortality, hospitalization, gas exchange, exercise tolerance, heath-related quality of life (HRQoL), lung function and sleep efficiency were used as outcome measurements. These outcomes were pooled to yield mean differences (MDs), standardized mean differences (SMDs) and risk differences (RDs). Results: Fourteen randomized controlled trials and two crossover studies were included. Compared with the control group, NIV significantly affected partial pressure of oxygen in the blood ($MD_{short\ term}$ 4.72, [2.66, 6.78]; $MD_{long\ term}$ 2.34, [1.21, 3.47]) and partial pressure of carbon dioxide in the blood in long time ($MD_{long\ term}$ -4.55, [-7.49, -1.62]). Compared to control group, the risk difference of mortality in long term group of NIV was -0.06 [-0.12, -0.01]. Three of the six long-term studies exerted significant effects during hospitalization, whereas one of the short-term studies demonstrated no significant effects. Two of the four short-term studies and all three long-term studies demonstrated no significant effects on HRQoL. Conclusion: NIV exerted no clinically or statistically significant effects on gas exchange, exercise tolerance, HRQoL, death, lung function or sleep efficiency in patients with stable COPD when utilized for less than 3 months. It might significantly improve blood gases, exercise tolerance and lung function after six months. However, long term NIV efficacy for stable COPD remains uncertain in terms of mortality and readmission. Long-term follow-up data of such patients is needed to reconfirm the benefits of NPPV.

Keywords: Non-invasive ventilation, chronic obstructive pulmonary disease, systematic review

Introduction

According to *World Health Statistics 2014*, chronic obstructive pulmonary disease (COPD) was a leading cause of years of life lost (YLL) worldwide as of 2012 [1]. COPD has been associated with declining lung function, sleep-disordered breathing and nocturnal hypoventilation [2], which increased the risks of death, disability and hospitalization [3, 4]. There are several treatments available to patients with COPD [5-9], including pharmacotherapy, surgery, and lung transplantation. However, only long-term oxygen therapy (LTOT) has been recommended as a routine treatment for COPD patients [10, 11]. Non-invasive ventilation (NIV) allows overloaded respiratory muscles to rest, improves gas exchange, and resets the central respiratory drive in patients with hypercapnia, without invading the airway [12, 13]. Strong evidence exists that illustrates the benefits of NIV in treating acute respiratory failure [14, 15]; however, the benefits of NIV in the setting of stable COPD have been unclear due to the conflicting results noted by various studies [16, 17]. Some randomized controlled trials have described the beneficial effects of NIV with regard to dyspnea, partial pressure of carbon dioxide in the blood ($PaCO_2$) and health-related quality of life (HRQoL) [18-22]. However, one systematic review demonstrated that nocturnal NIPPV exerted no clinically or statistically significant

effects in patients with stable COPD [23]. Although there is insufficient evidence to recommend NIV for routine use in patients with stable COPD, there is a consensus that patients with COPD are most likely to benefit from NIV [24]. Because several new studies have been published, providing an up-to-date systematic review of this new treatment approach is necessary. We hoped that our research would provide new evidence regarding NIV in the setting of COPD.

Materials and methods

Studies inclusion criteria for this review

Randomized controlled trials (RCTs) and randomized crossover studies comparing NIV with other therapeutic approaches to treating patients with stable COPD were included. Participants in the NIV group received NIV, which was administered via nasal cannula or facemask for more than 3 weeks, although these patients also had the option of receiving more conventional forms of management. Patients in the control group received the same treatment as the NIV group, but did not receive NIV. Primary outcomes included death, hospitalization, $PaCO_2$, partial pressure of oxygen in the blood (PaO_2), six-minute walking distance (6MWD), and HRQoL. Secondary outcomes included forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), maximal inspiratory pressure (PImax), maximal expiratory pressure (PEmax), sleep efficiency and dyspnea.

Studies exclusion criteria for this review

A study will be excluded if patients in exacerbations of COPD or with respiratory failure. We also excluded studies if NPPV was used in intensive care unit or during walking or physical training.

Literature search

The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and CINAHL were systematically searched. We searched all of the databases, beginning with the database's inception and ending on March 27, 2014 (we update search strategy on March 1, 2015). We also searched clinicaltrials.gov to find registered clinical trials. The search strategy was included in the supplement.

Selection of studies

Two of the review authors (HLF, LR) independently assessed all of the abstracts. Full papers were retrieved and read in detail if the abstracts were selected by both review authors, and disagreements were resolved via discussion with a third review author (SJT).

Risk of bias assessment

Two of the review authors (SJT and SGD) independently assessed the risk of bias of each study. We used the Cochrane Collaboration tool provided in the Cochrane Handbook for Systematic Reviews of Interventions [25] to assess the risk of bias in RCTs. We considered random sequence generation, allocation concealment, blinding of participants, personnel and outcome measurements, incomplete outcome data, selective outcome reporting, and other sources of bias, such as the prognostic balance between the treatment groups. We judged each domain as having a 'high', 'low' or 'unclear' risk of bias. Disagreements were resolved via discussion. If ten or more studies were included to perform meta-analyses for one outcome, funnel plots were inspected.

Data collection

Two of the review authors (HLF and SJT) collected information from eligible trials on studies characteristics (study design, sample size, arms, length of follow-up, funding sources), patient characteristics (sex, age, FEV_1, $PaCO_2$, and BMI), interventions, NIV setting, outcomes, and numbers of patients included for analyses in each arm. We collated all of the data into one study when many reports appear to be related to the same trial. If outcome data were reported at different follow-up time points, we collated the results from the article utilizing the longest follow-up period. The differences in mean changes between the test and control groups were defined as treatment effects. If changes from baseline (change score) were not available, final values were used as effect measurements.

Statistical analysis

Meta-analysis was performed when it is possible and the outcomes were appropriate. Results from both periods of a crossover trial were used

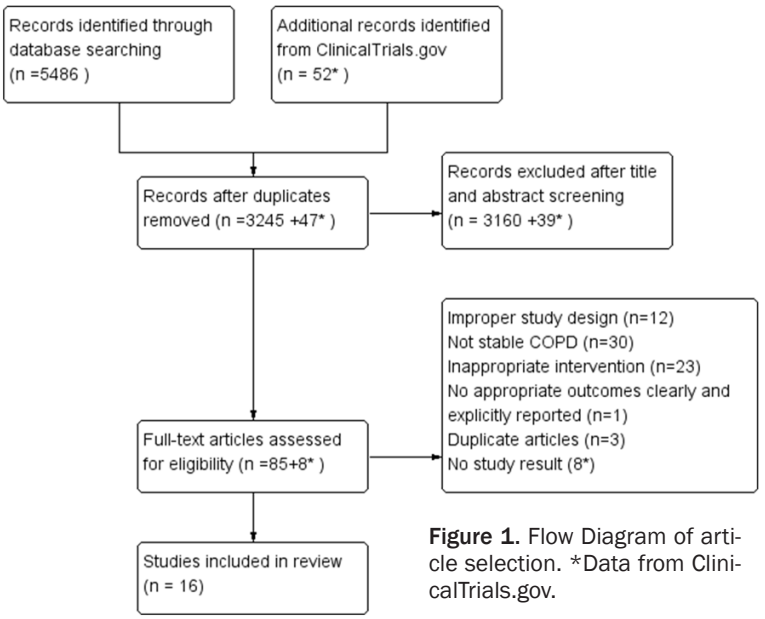

Figure 1. Flow Diagram of article selection. *Data from ClinicalTrials.gov.

unless there were carryover effects from one period to another. The generic inverse variance method [26] was used to perform meta-analysis that combed parallel and two-period crossover trials. A random-effects model was used for high heterogeneity, whereas a fixed effect model was used for low heterogeneity. The χ^2 test and the I^2 test were used to assess heterogeneity among the studies. We reported mean treatment effects and associated 95% confidence intervals. P<0.05 was considered statistically significant. Subgroup analyses were used to reduce heterogeneity, and we hypothesized that patient received NIV for a long time or more, higher levels of IPAP (inspiratory airway pressure) or patients with more hypercapnia might receive greater benefits. We used Review Manager 5.1 to combine the date. We reported the results according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (PRISMA).

Results

Our search yielded 3245 relevant articles and 52 registered clinical trials. After screening the titles and abstracts, we selected 85 articles and 8 trials for full text selection. Sixteen studies were included following the full text screening (**Figure 1**). The characteristics of the included studies were included in **Table 1**. Fourteen studies were parallel RCTs, and two studies had crossover designs.

Five studies lasted for periods of less than three months and were classified as 'short term', whereas eleven studies were classified as 'long term', because their durations were longer than six months. Twelve studies were funded by public foundations [18-22, 29-34, 37, 38], whereas two studies [28, 35] were funded by industrial companies. The risks of bias for the included studies are included in **Table 2**.

Arterial blood gas tension

For short-term follow-up, three studies reporting final $PaCO_2$ values [32, 34, 35] and two studies reporting changes in $PaCO_2$ from baseline [31, 33] were included in the meta-analysis. The meta-analysis demonstrated differences in $PaCO_2$ between the NIV and standard care groups within 3 months (MD 0.81 mmHg, 95% CI -3.18 to 4.81) that were not statistically significant, as shown in **Figure 2**. As shown in **Figure 3**, two studies reporting final PaO_2 values [32, 35] and two additional studies reporting changes in PaO_2 from baseline [31, 33] were included in the meta-analysis, demonstrating significant improvements in the NIV group (MD 4.72 mmHg, 95% CI 2.66 to 6.78).

For long-term follow-up, eight studies reporting final $PaCO_2$ values [18-20, 22, 27-29, 36] and three studies [30, 37, 38] reporting changes in $PaCO_2$ were combined in the meta-analysis (**Figure 2**). There were significant differences between the NIV and standard care groups (MD -4.55 mmHg, 95% CI -7.49 to -1.62). As shown in **Figure 3**, eight studies [18, 22, 27, 28, 30, 36-38] measuring PaO_2 values were included in the meta-analysis, noting improvements in PaO_2 in the NIV group compared with the standard care group (MD 2.34 mmHg, 95% CI 1.21 to 3.47, I^2=82%). However, there were no significant if the study Xiang 2007 were excluded (MD 0.56 mmHg, 95% CI -0.74 to 1.86), and heterogeneity were reduced by 55% (I^2=27%).

Six-minute walking distance

For short-term follow-up, two studies [33, 34] involving 49 patients were combined, and dif-

Table 1. Characteristics of included studies

Author (year)	Countries	Design	Trial duration	Interventions	IPAP/EPAP (cm H_2O)	Total NO.	NO. male	Mean age (y)	FEV_1 (L)	$PaCO_2$ (mmHg)	BMI (kg/m^2)
Bhatt (2013)	USA	RCT	6 months	NPPV *vs.* standard treatment	15/5	30	20	69	30% pred	42.1	24.8
Backer (2011)	Belgium	RCT	6 months	NIV + pharmacological treatment *vs.* pharmacological treatment	NR	15	10	66	29.8% pred	54.4	NR
Duiverman (2011)	Netherlands	RCT	2 years	NIPPV + rehabilitation vs. rehabilitation	23/6	56	33	62	0.84	51.0	27.1
Funk (2010)	Austria	RCT	12 months	NIV *vs.* stop NIV	20/5	26	15	63	0.79	93.5	25.6
McEvoy (2009)	Australian	RCT	5 years	NIV + LTOT *vs.* LTOT	13/3	144	94	68	0.59	53.5	25.5
Sin (2007)	Canada	RCT	3 months	NIMV + standard medical therapy *vs.* sham + standard medical therapy	15.5/4	23	10	65	0.86	44.2	27.2
Chiang (2004)	Taiwan	RCT	6 months	NNPPV + standard treatment *vs.* standard treatment	11.8/4.5	37	19	64	0.5	48.7	22.4
Clini (2002)	Italian	RCT	2 years	NPPV + LTOT *vs.* LTOT	14/2	90	69	65	29.2% pred	54.8	25.5
Casanova (2000)	Spain	RCT	1 year	NPPV + standard treatment vs. standard treatment	12/4	52	43	66	0.85	52.0	25.0
Garrod (2000)	England	RCT	8 weeks	NPPV + exercise training *vs.* exercise training	16/4	45	NR	65	0.92	45.6	NR
GAY (1996)	USA	RCT	3 months	NNV *vs.* sham NNV	10/2	35	10	69	0.67	51.8	24.6
Jones (1995)	UK	Crossover	3 months	NPSV + LTOT *vs.* LTOT	18/2	18	15	69	0.86	55.8	25.3
Strumpf (1991)	USA	Crossover	3 months	NNV + standard treatment vs. standard treatment	15/4	23	19	61	0.56	49.0	NR
Struik (2014)	Netherland	RCT	1 year	NIV *vs.* standard treatment	14/4	201	93	64	0.66	58.1	24.7
Köhnlein (2014)	Germany	RCT	1 year	NPPV *vs.* standard treatment	21.6/4.8	195	121	63	26.7% pred	58.1	24.7
Xiang (2007)	China	RCT	2 years	NPPV *vs.* standard treatment	16~20/2~4	40	31	70	0.59	59.0	20.7

*NPPV: Noninvasive Positive Pressure Ventilation; NIPPV: Noninvasive Intermittent Positive Pressure Ventilation; NIV: Noninvasive ventilation; NIMV: Nocturnal Noninvasive (positive) Mechanical Ventilation; NNV: Nocturnal Nasal Ventilation; NPSV: Nasal Pressure Support Ventilation; NNPPV: Nocturnal Nasal Positive Pressure Ventilation; LTOT: Long-term Oxygen Therapy; SWT: shuttle walk test.

Table 2. Quality assessment of included studies

Author (year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Backer 2011 [27]	Low risk	Uncertain	Low risk	Low risk	Low risk	Uncertain	Low risk
Bhatt 2013 [28]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Casanova 2000 [18]	Low risk	Low risk	Low risk	Low risk	Low risk	Uncertain	Low risk
Chiang 2004 [29]	Low risk	Uncertain	Low risk	Low risk	Low risk	Uncertain	Low risk
Clini 2002 [19]	Low risk	Low risk	Low risk	Low risk	Low risk	Uncertain	Low risk
Duiverman 2011 [30]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Funk 2010 [22]	Low risk	Low risk	Low risk	Low risk	Low risk	Uncertain	Low risk
Garrod 2000 [31]	Low risk	Low risk	Low risk	Low risk	Low risk	Uncertain	Low risk
Gay 1996 [32]	low risk	Low risk	Low risk	Low risk	High risk	Uncertain	Low risk
Jones 1995 [33]	Low risk	Low risk	Low risk	Low risk	Low risk	Uncertain	Low risk
McEvoy 2009 [20]	Low risk	low risk	Low risk	Low risk	Low risk	Uncertain	Low risk
Sin 2007 [34]	Low risk	Low risk	Low risk	Low risk	Low risk	Uncertain	Low risk
Strumpf 1991 [35]	Low risk	Low risk	Low risk	Low risk	High risk	Uncertain	Low risk
Xiang 2007 [36]	Low risk	Uncertain	Low risk	Low risk	Low risk	Uncertain	Low risk
Köhnlein 2014 [37]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Struik 2014 [38]	Low risk	Low risk	Low risk	Low risk	Low risk	Uncertain	Low risk

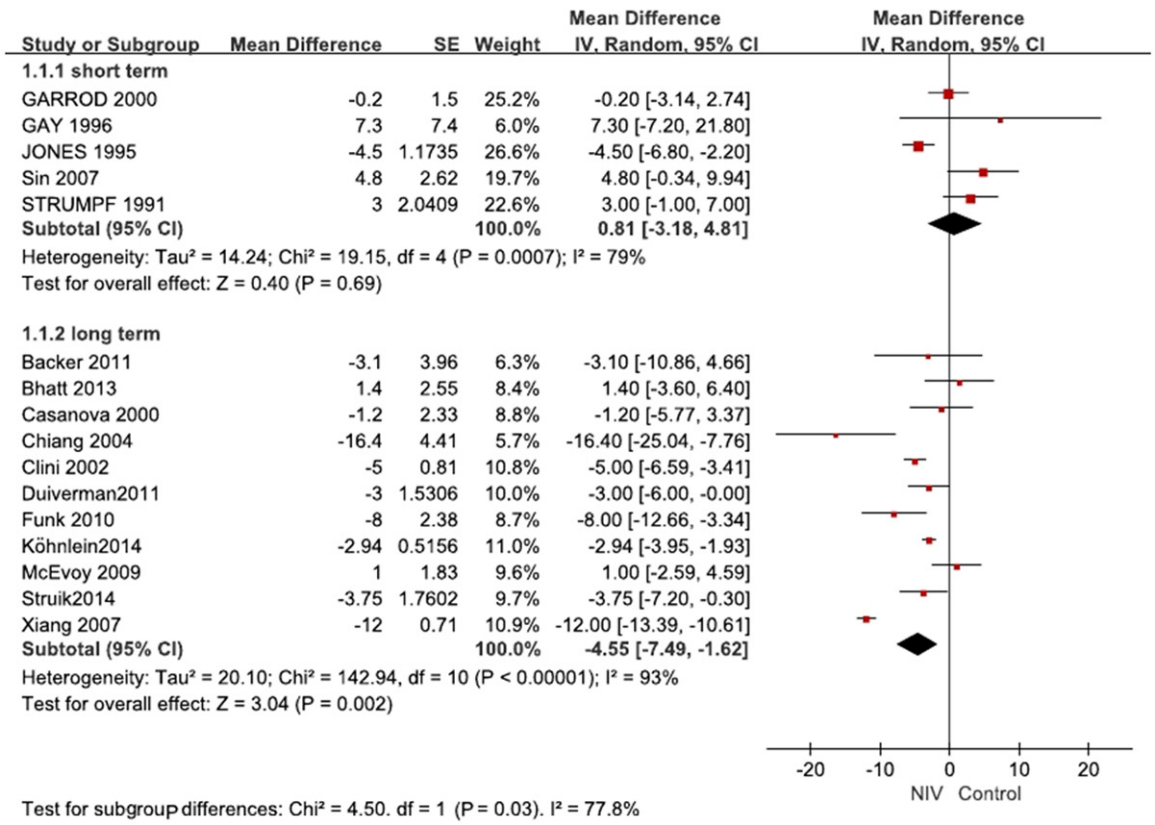

Figure 2. NIV versus control group on outcome of $PaCO_2$.

ferences in 6MWD that were not statistically significant were noted (MD 35.61 m, 95% CI -38.63 to 109.84) (**Figure 4**). Another study by Gay involving ten patients also reported no sta-

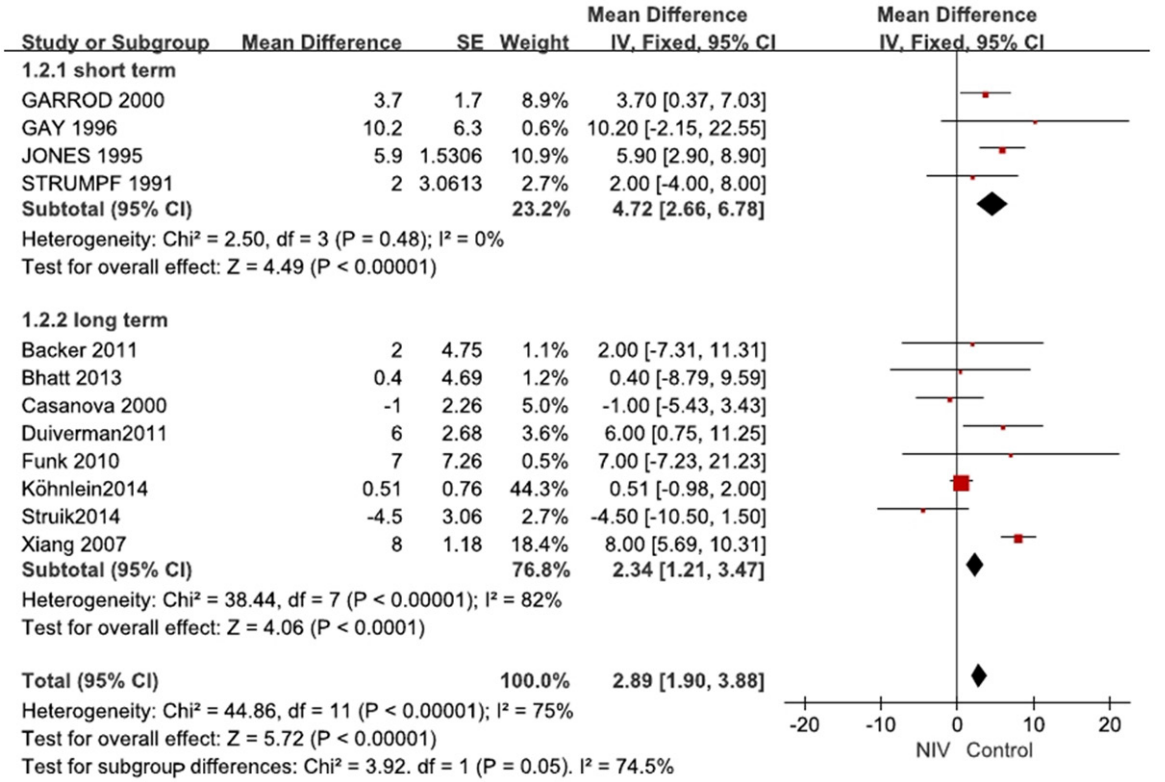

Figure 3. NIV versus control group on outcome of PaO_2.

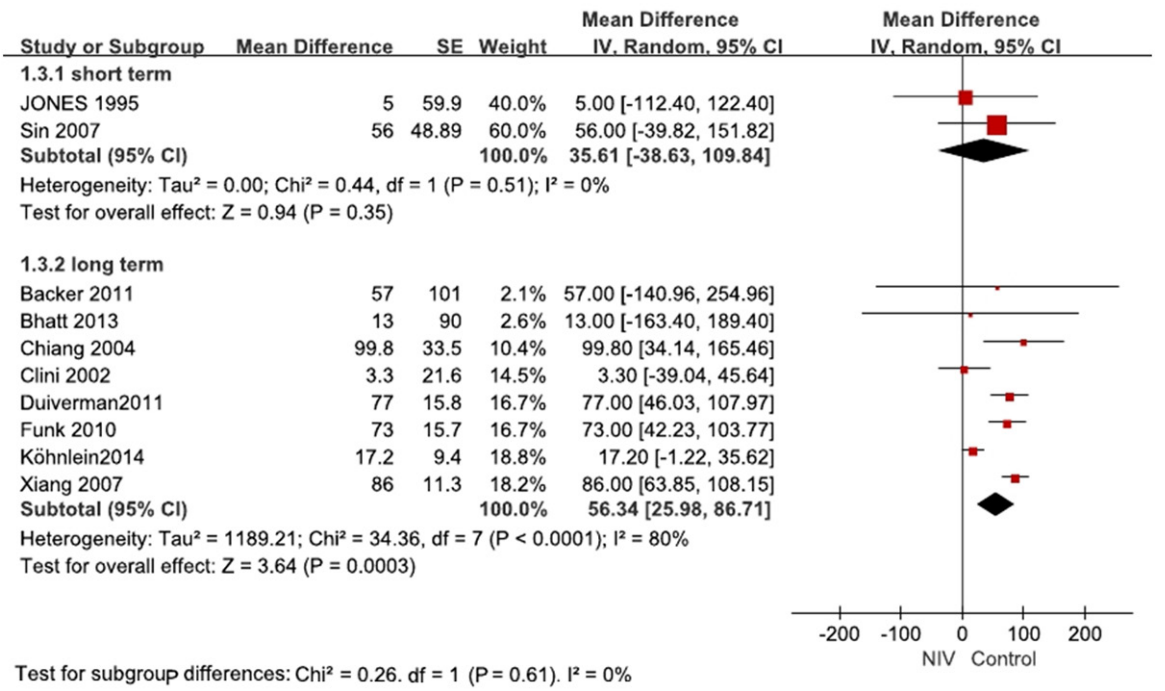

Figure 4. NIV versus control group on 6MWD.

tistically significant effects on 6MWD (MD 7.5 feet, 95% CI -811.54 to 826.54).

For long-term follow-up, eight studies [19, 22, 27-30, 36, 37] were included in a meta-analy-

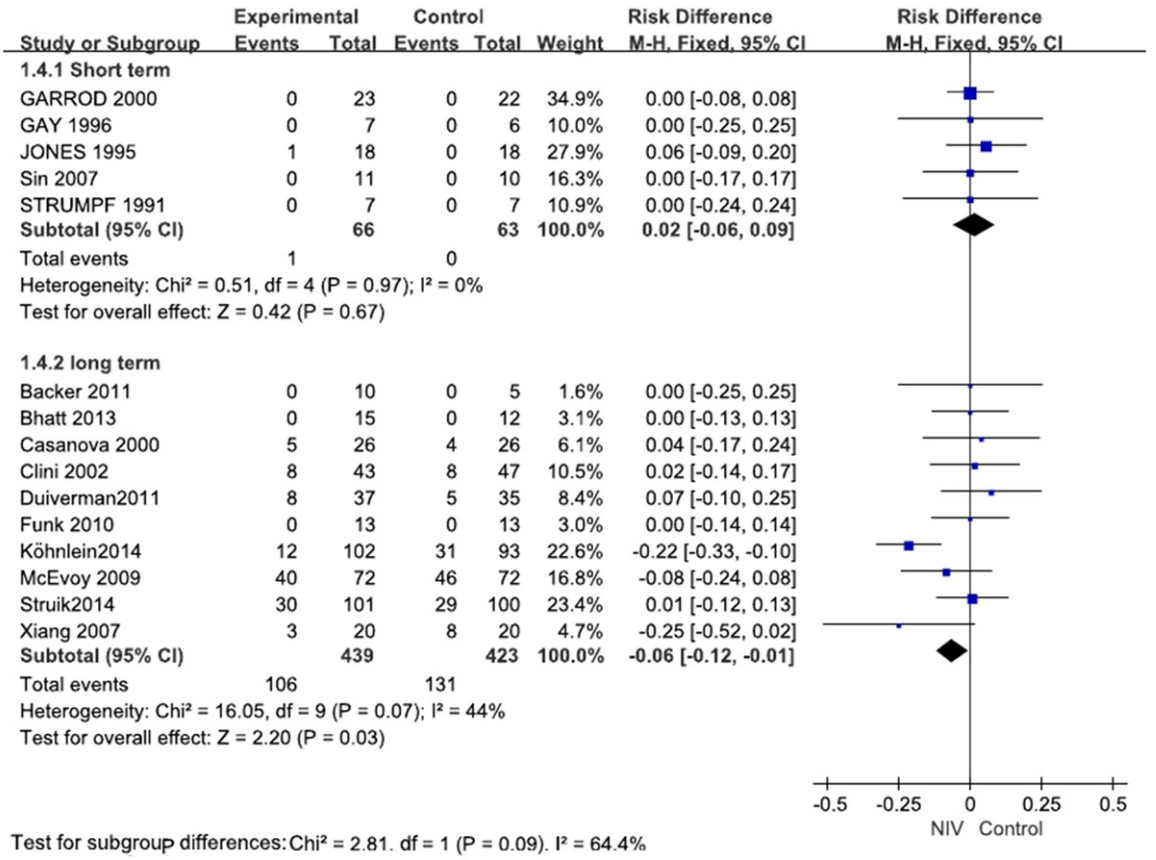

Figure 5. NIV versus control group on death.

Table 3. Hospitalizations in NIV and control groups

Author (year)	Outcomes	Experimental group	Control group	P
McEvoy 2009	Rates	0.032	0.031	P>0.05
Chiang 2004	Δnumber	-2	0.7	P<0.05
	Δtotal stay (days)	-29.4	16	P<0.05
Clini 2002	Δtimes	-45%	+ 27%	P<0.05
	Days spent in hospital	-6.3	+ 0.8	P<0.05
Xiang 2007	Δtimes/year	-2.3	+ 0.3	P<0.05
Strumpf 1991	Number	1	1	P>0.05
Struik 2014	Readmission	56%	57%	P>0.05
	Days spent in hospital	7.0	3.5	P>0.05
Köhnlein 2014	Emergency hospital admissions per patient	2.2	3.1	P>0.05

sis that demonstrated moderate treatment effects on 6MWD (MD 56.34 m, 95% CI 25.98 to 86.71).

Death

For short-term follow-up, five studies [31-35] were included in a meta-analysis, and only one patient died in the NIV group (RD 0.02, 95% CI -0.06 to 0.09), as shown in **Figure 5**.

For long-term follow-up, ten studies [18-20, 22, 27, 28, 30, 36-38] provided data regarding death and demonstrated a little differences (RD -0.06, 95% CI -0.12 to -0.01). Excluding study by Köhnlein, there were no statistically

Table 4. Health status in NIV and control groups

Author (year)	Scales	NIV group	Control group	P
Garrod 2000	ΔCRDQ	24.1	11.8	<0.05
Jones 1995	SGRQ	The symptom score during NPSV-plus oxygen period was significantly better than oxygen-alone		<0.05
Clini 2002	ΔSGRQ	-5%	-4%	>0.05
	ΔMRF-28	The MRF-28 total score significantly improved in the NPPV group compared to the LTOT group		<0.05
Duiverman 2011	ΔCRQ	-3.6	-2.3	>0.05
	ΔMRF-28	3.8	17.2	<0.05
Funk 2010	SGRQ	57	53	>0.05
Struik 2014	ΔCRQ	0.7	0.7	>0.05
	ΔCCQ	-0.5	-0.5	>0.05
	ΔMRF-28	-7.3	-5.8	>0.05
	ΔSRI	7.0	2.2	>0.05
Köhnlein 2014	ΔSRI	Changes in the SRI summary scale score were in favour of the NPPV group (5.6 points, 95% CI 0.1-11.1)		<0.05
	ΔSF-36	SF-36 score did not differ significantly between treatment group		>0.05
	ΔSGRQ	SGRQ summary score improved more (6.2 points, 95% CI 0.7-11.8) in the NIV group		<0.05
McEvoy 2009	SGRQ	SGRQ was not different between the NIV + LTOT and LTOT alone groups		>0.05

Table 5. Dyspnea in NIV and control groups

Author (year)	Scales	NIV group	Control group	P
Strumpf 1991	ΔTDI	No improvements were observed in perform tasks or in functional activity		>0.05
Garrod 2000	ΔDyspnea	4.9	1.7	>0.05
Bhatt 2013	ΔTDI	0.9	-0.5	>0.05
Clini 2002	ΔMRC	Significantly improved in the NPPV group and better than in the LTOT group		<0.05
Casanova 2000	ΔBORG	-1.0	0.0	<0.05
	ΔMRC	-1.0	0.0	<0.05
Duiverman 2011	ΔMRC	0.2	0.6	<0.05
Struik 2014	ΔMRC	-0.4	-0.3	>0.05
Xiang 2007	MRC	2.4	3.9	<0.05

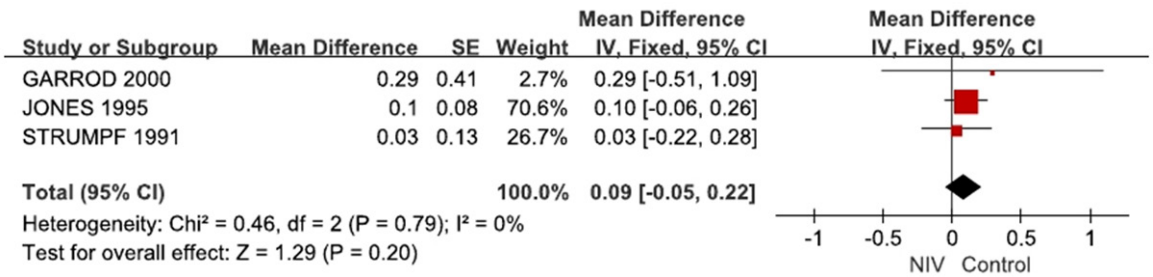

Figure 6. NIV versus control group on FVC in subgroup of short term.

significant (RD -0.02, 95% CI -0.08 to 0.05) and the heterogeneity were reduced by 44%.

Hospitalization

For short-term follow-up, one crossover study [35] demonstrated that one patient required two brief hospitalizations: one during the control phase and another during the NIV phase.

For long-term follow-up, four studies [20, 35, 37, 38] demonstrated that hospitalization rates were not different between the NIV and control groups. As shown in **Table 3**, three studies [19, 29, 36] demonstrated the beneficial effects of NIV.

Health status

As shown in **Table 4**, it was impossible to perform a meta-analysis for different scales. Two studies in the short-term subgroup and six studies in long-term subgroup measured HRQoL using seven different questionnaires.

Figure 7. NIV versus control group on FEV_1 in subgroup of short term.

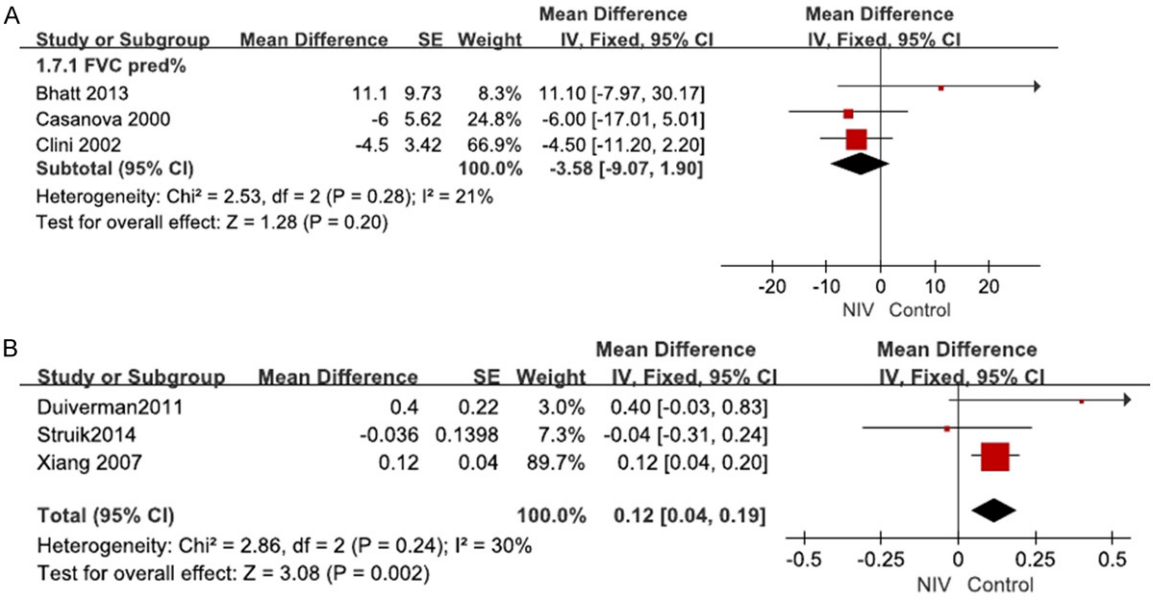

Figure 8. A. NIV versus control group on FVC in subgroup of long term (pred%). B. NIV versus control group on FVC in subgroup of long term (L).

There were trends toward a benefit noted in the NIV group, although three of the six long term studies demonstrated no significant differences. Three studies [19, 30, 37] demonstrated contradictory results using different scales. Two short term studies demonstrated that NIV significantly improve health state.

Dyspnea

Because different dyspnea scales were used in the RCTs, it was impossible to combine the outcome data (**Table 5**).

For short-term follow-up, one study [35], using the Transitional Dyspnea Index (TDI) to measure dyspnea, noted that no improvements were observed in the patients' abilities to perform tasks or to undertake functional activities after receiving NIV. Another study [31] demonstrated that there were no significant differences in dyspnea changes between the NPPV + ET and ET groups (MD 3.29, 95% CI -1.26 to 7.84).

For long-term follow-up, six studies provided data regarding dyspnea [18, 19, 28, 30, 36, 38]. Four studies demonstrated that significant improvements occurred in the NIV group compared with the control group, whereas two studies [28, 38] demonstrated no differences between the NIV and control groups.

Lung function

For short-term follow-up, three studies [31, 33, 35] reporting FVC values and four studies [31-

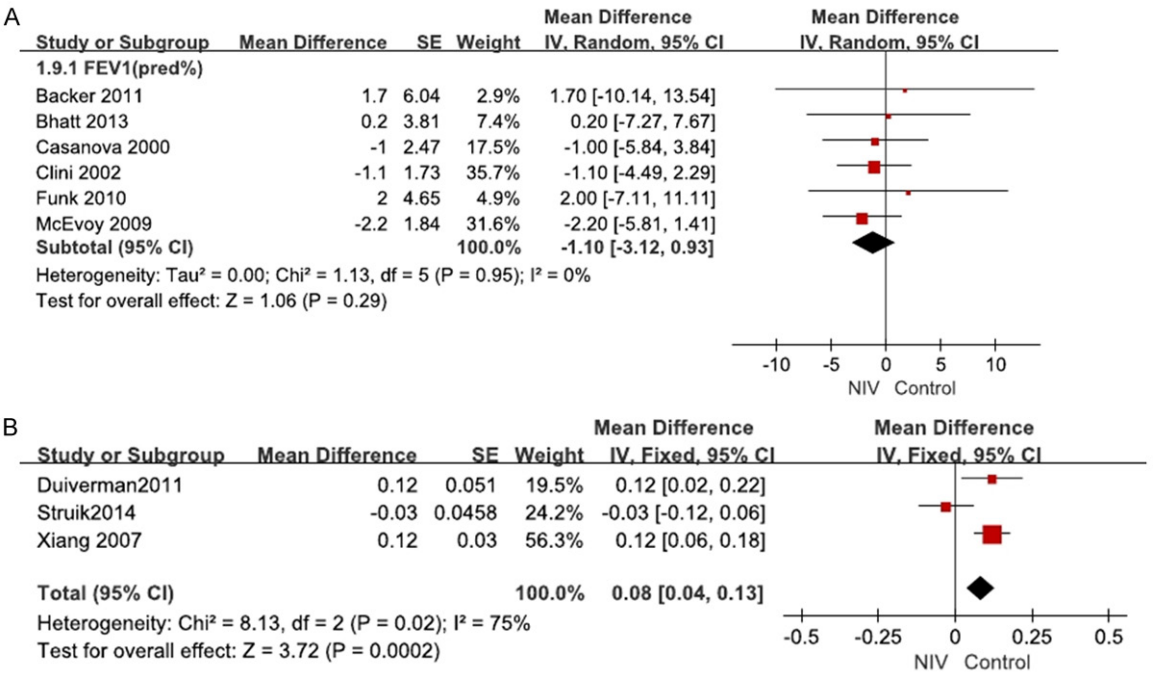

Figure 9. A. NIV versus control group on FEV_1 in subgroup of long term (pred%). B. NIV versus control group on FEV_1 in subgroup.

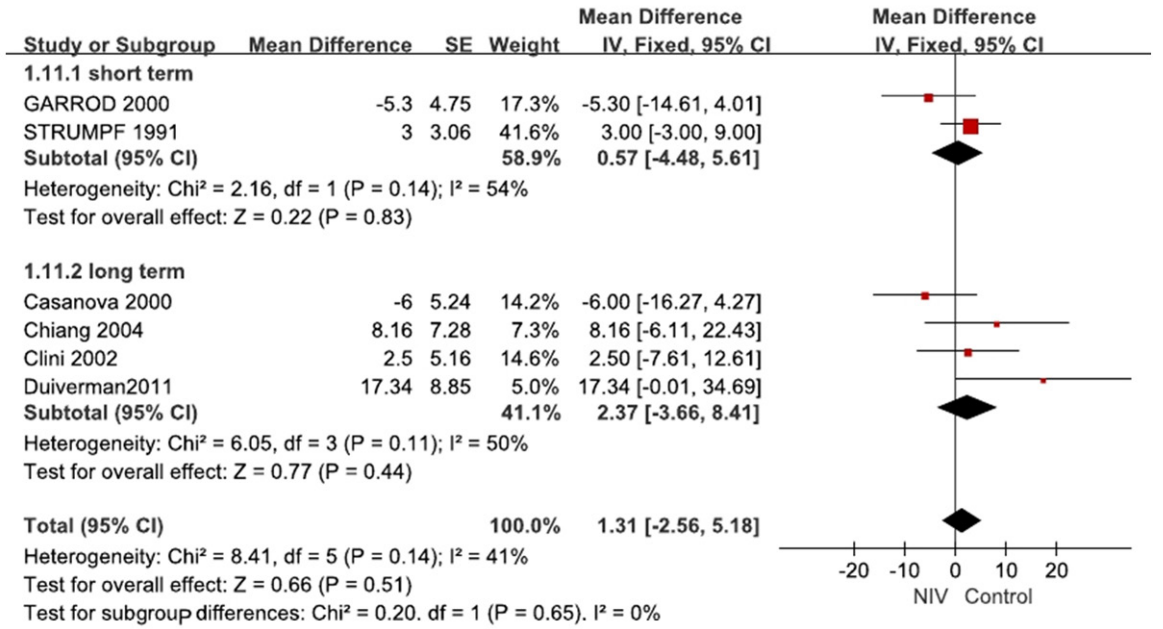

Figure 10. NIV versus control group on PImax.

33, 35] reporting FEV_1 values were included to perform meta-analyses, which demonstrated no significant differences in FVC or FEV_1 between the NIV and standard care groups (MD_{FVC} 0.09 L, 95% CI -0.05 to 0.22; MD_{FEV1} 0.01, 95% CI -0.04 to 0.07), as shown in **Figures 6** and **7**.

For long-term follow-up, three studies [18, 19, 28] involving 157 patients demonstrated no

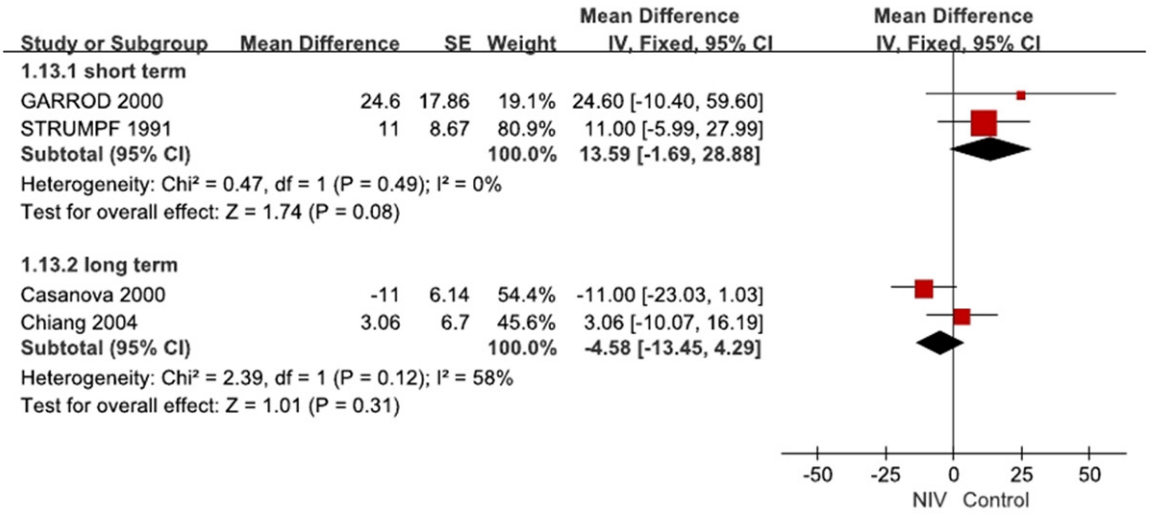

Figure 11. NIV versus control group on PEmax.

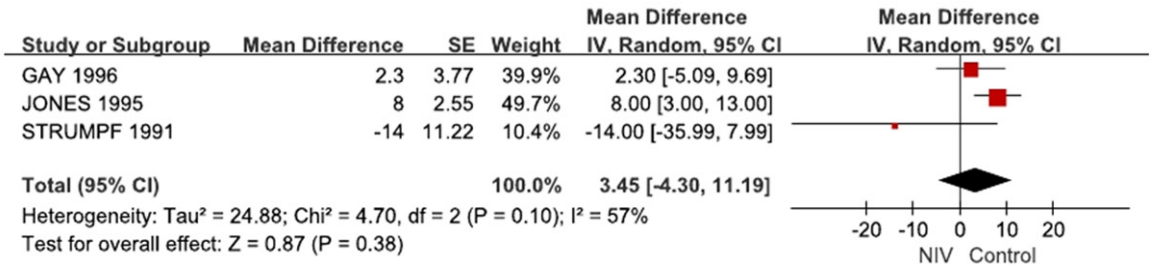

Figure 12. NIV versus control group on sleep efficiency in short term subgroup.

significant differences in predicted FVC (%) between the NIV and standard care groups (MD -3.58, 95% CI -9.07 to 1.90) (**Figure 8A**). Three studies [30, 36, 38] involving 190 patients demonstrated limited treatment effects on FVC and FEV_1 (MD_{FVC} 0.12 L, 95% CI 0.04 to 0.19; MD_{FEV1} 0.08 L, 95% CI 0.04 to 0.13) (**Figures 8B**, **9B**). Six studies [18-20, 22, 27, 28] involving 283 patients were included in the meta-analysis, which demonstrated no significant effects (MD -1.10, 95% CI -3.12 to 0.93) in predicted FEV_1 (%) values (**Figure 9A**).

Respiratory muscle function

For short-term follow up, two studies provided data regarding PImax and PEmax values [31, 35]. The improvements in PImax were not statistically significant (MD 0.57 cm H_2O, 95% CI -4.48 to 5.61). PEmax demonstrated small improvements following short-term NIV (MD 13.59 cm H_2O, 95% CI -1.69 to 28.88), as shown in **Figures 10** and **11**.

For long-term follow-up, four studies provided data regarding PImax [18, 19, 29, 30], and two studies provided data regarding PEmax [18, 29]. The differences in PImax and PEmax were not statistically significant (PImax MD 2.37 cm H_2O, 95% CI -3.66 to 8.41; PEmax MD -4.58 cm H_2O, 95% CI -13.45 to 4.29).

Sleep efficiency and sleep quality

For short-term follow-up, three studies provided data regarding sleep efficiency [32, 33, 35] that demonstrating small negative effects after three months (MD 3.45, 95% CI -4.30 to 11.19). These effects were characterized by substantial heterogeneity (I^2=57%) (**Figure 12**).

For long-term follow-up, a study evaluated sleep efficiency by measuring time sleep as a percentage of total time in bed [20], but it obtained follow-up measurements only in the NIV group. Another study [19] noted that sleep quality scores have not significantly change over time

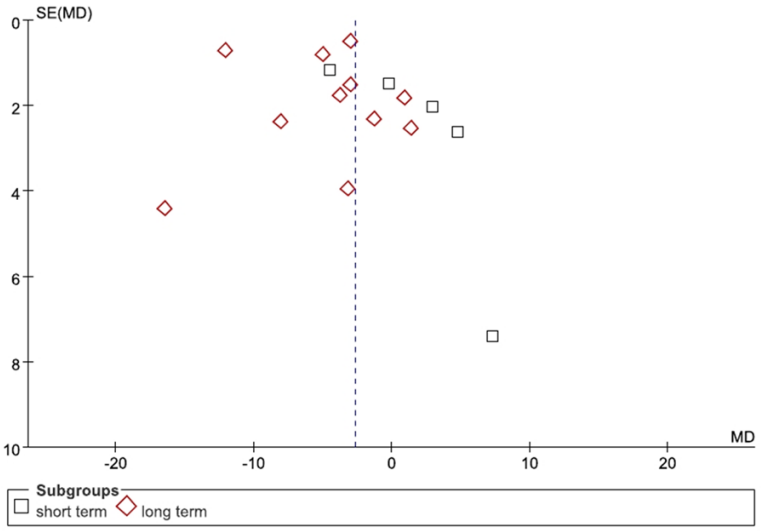

Figure 13. Funnel plot of $PaCO_2$.

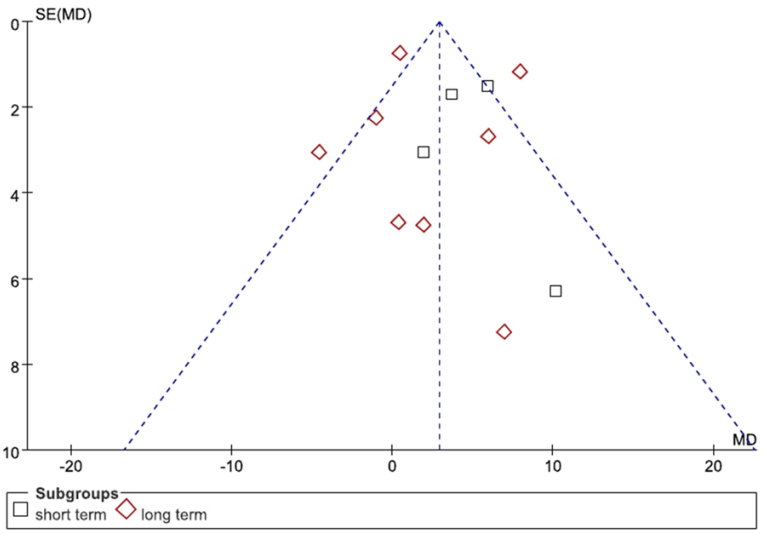

Figure 14. Funnel plot of PaO_2.

in either group, although sleep scores improved slightly for patients who received NIV. A third study [28] measured sleep quality that using the Pittsburgh Sleep Quality Index (PSQI) and found that there were no changes in the quality of sleep. No meta-analyses were performed.

Discussion

Main findings

In this meta-analysis, we found that NIV improved gas exchange significantly only in the long-term group. However, if we excluded the Chinese study [36], we determined that there was no significant improvement in PaO_2 in the long-term subgroup. Compared with the control group, there was a significant decrease in $PaCO_2$ in the long-term subgroup of the NIV group. However, the heterogeneity was high (Chi^2=142.94, P<0.00001; I^2=93%) which might have been the result of the varying treatment periods, inspiratory pressure levels and baseline of $PaCO_2$. If two of the Chinese studies [29, 36] were excluded, the heterogeneity was reduced by 36% in the long-term subgroup. The improvement in the 6MWD was not statistically significant, however, it was indicative of a positive trend in the meta-analysis. The pooled result of the meta-analysis reached the clinically minimal important difference of 26 m [39]. Compared with the short-term subgroup, the patients in the long-term group might have experienced greater improvements in the 6MWD among those patients who received NIV. We were unable to determine the standard errors for 6MWD changes in the studies by Backer and Bhatt because these values were uncertain. Additional high quality studies with larger sample sizes should clarify the role of this treatment.

The mortality due to COPD was low in the short-term group; however, it was high in the long-term follow-up group. The benefits of NIV were not demonstrated in the meta-analysis if a particular study [37] was excluded. Because COPD is a common disease which has a long natural history, a meta-analysis based on RCTs might not be sufficient to evaluate the benefits of survival and mortality; a cohort study or case-control study with a long follow-up period might be more appropriate. Köhnlein's study showed

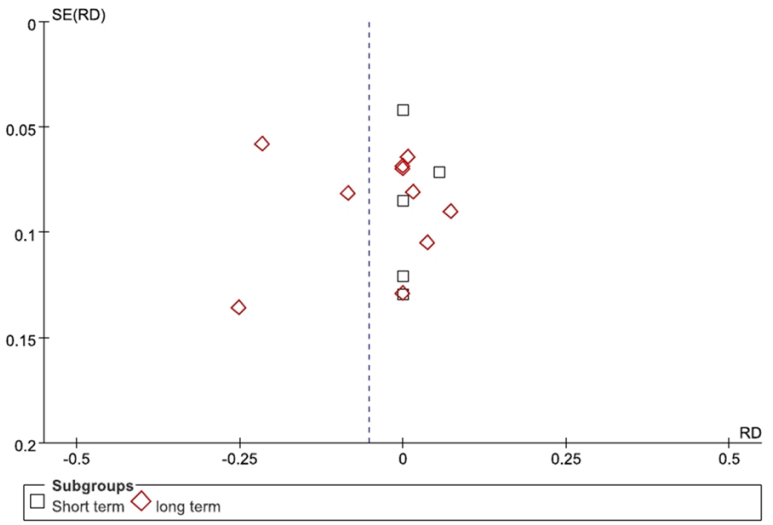

Figure 15. Funnel plot of death.

substantial improvement in survival (12% in the NIV and 33% in the control group) which was conflict to previous studies. Compared with previous studies, Köhnlein's study included more homogenous, higher concentration of hypercapnia, stable COPD cohort, and higher NIV doses than previous studies [40]. The study by Plant demonstrated that NIV could reduce COPD patients' treatment cost and mortality [41]. The benefit of NIV in $PaCO_2$ could be increased by ventilation strategy with higher inflation pressures and backup rate [42]. However, long term NIV efficacy for stable COPD remains uncertain in terms of hard outcomes [43]. Some cohort studies suggest that mortality or readmission rates of patients who were treated by NIV dependent upon the varieties of COPD patients [44, 45]. NIV is more effective in obese COPD patients, and unlikely to be beneficial if $PaCO_2$ is lower than 7 kPa [44, 46].

Outcomes such as HRQoL, dyspnea, and hospitalization were not combined due to differences in their measurements. Eight studies measured HRQoL with seven different scales, and seven studies measured dyspnea with four different scales. Different scales are characterized by different reliability and validity. In the assessment of COPD's HRQoL, the SRI performed slightly better than the CCQ, CRQ, and MRF-28 [47]. Hospitalization data were reported in seven studies, however, these data were measured as rates, numbers, visits or lengths of stay, depending upon the study in question.

Strengths and limitations

All of the included studies had low risk for bias of either randomization or allocation concealment, with the exception of three studies [27, 29, 36] which did not describe methods of allocation concealment. We determined that all of the studies were at low risk for blinding bias because their outcomes were not likely to have been influenced by a lack of blinding.

Two studies [32, 35] were judged as being at high risk for attrition bias due to their numbers of dropouts, which might have influenced their true outcomes. All of the outcomes that listed in the articles' methods sections were reported; however, the original protocols were not available, with the exception of the three studies [28, 30, 37]. We were not able to determine whether all of the pre-specified outcomes were reported, therefore, the risk of reporting bias was unclear. We excluded two studies due to their short treatment periods [48, 49]. We estimated standard deviations according to the *Cochrane Handbook* when we were unable to find the corresponding data within the published articles, which might have affected the precision of our evaluations of these studies' outcomes. The funnel plots were asymmetric, therefore, there were publication bias (**Figures 13**-**15**).

Comparison with other studies

Three systematic reviews have assessed the effectiveness of NIV for patients with stable COPD [23, 50, 51]. The systematic review by Kolodziej pooled six RCTs and nine non-RCTs, determined that bi-level NIPPV improved gas exchange and reduced both lung hyperinflation and the diaphragmatic work of breathing. However, the heterogeneity of the pooled results was high. Another systematic review by Chen included five RCTs and one crossover study, reported that NIPPV improved gas exchange, dyspnea and sleep quality. This systematic review might have missed some studies [22, 29, 34, 35].

Those reviews didn't perform subgroup analyses based on treatment periods. A recent Cochrane Systematic Review (CSR) included five RCTs and two crossover studies that involving 245 patients, and it found that home NIPPV, administered over a period of three months in patients with stable COPD, resulted in no significant improvements in gas exchange, exercise tolerance, HRQoL, lung function, respiratory muscle strength or sleep efficiency. Although the CSR represents the highest form evidence with which to make decisions, due to its rigorous methodology, this CSR did not include some of the studies [22, 29, 31]. Compared with these three systematic reviews, our study included studies missed by the other reviews and also included other five newly published articles [27, 28, 30, 37, 38] which could provide clinicians with additional important information with which to evaluate the usefulness of NIV in COPD. The outcomes of short-term subgroup were consistent with those of the CSR but they were different from those of two other reviews. At the same time, the outcomes of the long-term subgroup were different from those of the CSR and consistent with those of the two other reviews.

Although there were several reviews assessing the topic with the included studies in the past, they all had the same conclusions. However, recent data suggested that there are different results in the literature with regard to the underlying ventilator strategy. Previous studies using low inspiratory pressure levels gained no positive results, whereas studies using higher pressure levels got it, which has been shown in several papers [52-54]. The most recent study [37] significantly reducing $PaCO_2$ was a positive study with regard to survival using higher pressure levels. $PaCO_2$ reduction is a significant predictor of mortality, but it only makes a small contribution to the overall benefit of NPPV [40]. Whether this association has a causal effect needs discussion and long-term follow-up data of such patients to reconfirm the benefits of NPPV.

Conclusion

NIV administered to patients with stable COPD over periods of less than three months exerted no clinically or statistically significant effects on gas exchange, exercise tolerance, HRQoL, death, lung function or sleep efficiency. Blood gases, exercise tolerance and lung function were significantly improved following more than six months of NIV. However, long term NIV efficacy for stable COPD remains uncertain in terms of mortality and readmission. Long-term follow-up data of such patients is needed to reconfirm the benefits of NPPV.

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Disclosure of conflict of interest

None.

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