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Low versus high positive end expiratory pressure in noninvasive ventilation for hypoxemic respiratory failure: a multicenter randomized controlled trial

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Abstract

Purpose: To assess whether high positive end expiratory pressure (PEEP) reduces the rate of noninvasive ventilation (NIV) failure in hypoxemic patients.

Methods: This multicenter, open-label, randomized controlled trial was conducted across seven ICUs in China. Hypoxemic patients who received NIV via oronasal or nasal mask were randomized 1:1 to either low PEEP (5 cmH_2O) or high PEEP (10–15 cmH_2O) groups, with inspiratory positive airway pressure (IPAP) set at 10–20 cmH_2O and 15–20 cmH_2O, respectively. The primary outcome was NIV failure, defined as intubation, death, or therapy withdrawal (refusal of intubation despite need).

Results: Between January 11, 2022, and August 31, 2024, 380 patients (190 per group) were enrolled in an intention-to-treat analysis. NIV failure occurred in 43% (82/190) of the low PEEP group and 32% (61/190) of the high PEEP group (absolute difference: 11.1%, 95% CI 1.3–20.5%, p = 0.034). Within 72 h post-randomization, the low PEEP group exhibited lower PaO_2/FiO_2 ratios (mean difference: − 31 mmHg, 95% CI − 38 to − 24) and higher tidal volume (0.8 mL/kg predicted body weight, 95% CI 0.5–1.1) than the high PEEP group. However, the low PEEP group required higher support pressure (mean difference: 2.9 cmH_2O, 95% CI 2.7–3.1). Adverse events did not differ between the groups.

Conclusions: High PEEP during NIV may reduce treatment failure in patients with acute hypoxemic respiratory failure, although this benefit may be partially confounded by higher tidal volume observed in the low PEEP group. However, the interpretation of this effect should be carried out with caution as the study has insufficient statistical power to detect a significant difference.

Keywords: Noninvasive ventilation, Positive end expiratory pressure, Hypoxemic respiratory failure

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Introduction

Noninvasive ventilation (NIV) is commonly used in patients with hypoxemic respiratory failure. In a previous study, NIV utilization rates were 14%, 26%, and 34% in patients with PaO_2/FiO_2 ratios of 200–300, 100–200, and < 100 mmHg, respectively [1]. In another study, it was used in patients with acute respiratory distress syndrome (ARDS) across all severity categories [2]. However, the rate of NIV failure remains high, particularly in ARDS patients (up to 61%) [3, 4]. Importantly, such failure is strongly associated with increased mortality [5, 6]. Consequently, reducing its rate is a critical clinical priority.

High positive end expiratory pressure (PEEP) is a standard therapy in invasively ventilated ARDS patients, improving oxygenation, reducing respiratory drive, and promoting alveolar recruitment. Clinically, PEEP > 10 cmH_2O is commonly titrated using various methods [7, 8]. In NIV, high PEEP is primarily applied via helmet interfaces and less frequently using oronasal/nasal masks [9–11]. A physiological study reported improved PaO_2/FiO_2 ratios with increases in PEEP from 5 to 10 cmH_2O during mask NIV [12]. Furthermore, a meta-analysis revealed significantly lower failure rates with PEEP > 6 cmH_2O (24.6%) versus ≤ 6 cmH_2O (43.2%) in mask NIV [13]. These findings suggest potential benefits of higher PEEP in hypoxemic respiratory failure managed via mask NIV. However, there is a lack of robust empirical comparisons, and evidence is limited. To address this gap, we conducted a multicenter randomized controlled trial (RCT) to evaluate the efficacy of the use of high PEEP in reducing NIV failure rates via oronasal/nasal masks.

Methods

Study design and participants

We conducted a multicenter, open-label, RCT across seven ICUs in China. The study protocol was approved for all centers by a central ethics committee (of The First Affiliated Hospital of Chongqing Medical University, No. 2021-282). Written informed consent was obtained from the patients or their next of kin before enrollment.

Patients admitted to participating ICUs with hypoxemic respiratory failure were screened. Inclusion criteria included: age 16–85 years, use of a dedicated noninvasive ventilator, $PaCO_2 \leq 50$ mmHg, $PaO_2/FiO_2 \leq 300$ mmHg, anticipated NIV duration > 12 h, and preserved consciousness (Kelly score ≤ 3 or Glasgow coma score [GCS] ≥ 13). The Kelly score was assessed as previously described (Supplementary Text 1) [14]. Exclusion criteria were: use of NIV > 24 h pre-randomization; NIV for heart failure, asthma, or acute exacerbation of chronic obstructive pulmonary disease; contraindications to NIV (e.g., anatomical malformations, recent pulmonary/esophageal surgery); end-stage disease; pneumothorax; NIV intolerance; refusal to participate; or need for emergency intubation. This trial is registered at ClinicalTrials.gov, NCT05193786.

Take-home message

This first randomized controlled trial investigates high versus low PEEP effects in hypoxemic respiratory failure patients receiving noninvasive ventilation via oronasal or nasal masks. High PEEP reduces ventilation failure risk without increasing adverse events, primarily by enhancing oxygenation.

Randomization

Patients were randomized at a 1:1 ratio to either a low or high PEEP group. Randomization was performed using a centralized system that produced random, computer-generated sequences of numbers. The allocation sequence was concealed using numbered, opaque, sealed envelopes. Site investigators enrolled patients, ensured protocol compliance, and completed case report forms. Upon confirming patient eligibility and obtaining informed consent, investigators contacted the coordinating center for randomization. As PEEP delivery via NIV cannot be masked, blinding of healthcare providers was not implemented.

Procedures

Following randomization, the strategy assigned to the patient was initiated immediately. In the low PEEP group, PEEP was maintained at 5 cmH_2O. Initial inspiratory positive airway pressure (IPAP) was set at 8 cmH_2O and titrated to maintain a respiratory rate < 25 bpm or the maximum tolerated level, with a target IPAP range of 10–20 cmH_2O. In the high PEEP group, PEEP was maintained at 10–15 cmH_2O. Initial IPAP was set at 10 cmH_2O and similarly titrated to achieve a respiratory rate < 25 bpm or the maximum tolerated level, with a target IPAP range of 15–20 cmH_2O.

Oronasal or nasal masks were selected by the attending physician based on the facial anatomy of the patient. Patients were encouraged to use NIV continuously, with brief interruptions permitted for eating, drinking, secretion clearance, and communication. If one felt any discomfort during the process, physicians, respiratory therapists, or nurses checked the parameters, circuit, humidification, air leak, and so forth to ensure maximum comfort. NIV intolerance was defined as discontinuation

due to patient refusal despite attempts at intermittent use [15].

NIV was administered intermittently until full liberation, provided that respiratory distress and oxygenation improved. However, invasive mechanical ventilation was initiated upon worsening respiratory failure and meeting intubation criteria [9, 16, 17]. Major criteria included respiratory or cardiac arrest, $PaO_2/FiO_2 < 100$ mmHg after NIV intervention, conditions requiring airway protection (e.g., coma, seizures) or management of excessive tracheal secretions, and hemodynamic instability unresponsive to fluids or vasoactive agents. Minor criteria were $PaO_2/FiO_2 < 150$ mmHg after NIV intervention, respiratory rate > 35 bpm, pH < 7.35, inability to correct dyspnea, unimproved respiratory muscle fatigue (e.g., accessory muscle use or paradoxical breathing), a new arrhythmia or tachycardia, $SpO_2 < 90\%$ for > 5 min without technical issues, or NIV intolerance. Intubation was recommended if one major or two or more minor criteria were met, with the final decision at the attending physician's discretion.

At randomization, baseline data, including vital signs and arterial blood gas results, were recorded. These variables were additionally assessed at 2 h, 12 h, 24 h, 48 h, and 72 h following NIV initiation. Ventilator parameters and discomfort scores were also collected from 2 to 72 h during NIV. ARDS diagnosis was established based on the Berlin definition [18].

Outcomes

The primary outcome was the rate of NIV failure, defined as intubation, death, or therapy withdrawal (refusal of intubation despite need). To evaluate NIV failure events, two independent experts retrospectively reviewed patient cases based on predefined intubation criteria and reclassified them as revised NIV failure when applicable. Secondary outcomes included 28-day mortality, duration of NIV, duration of invasive mechanical ventilation, ICU and hospital length of stay, PaO_2/FiO_2 changes, and adverse events. Adverse events included mask-related pressure ulcers, pneumothorax, vomiting, aspiration, and NIV intolerance. Pressure ulcer severity was graded as previously described (Supplementary Text 2) [19]. Oronasal dryness and abdominal distension were evaluated using a visual analog scale (VAS) [20].

Statistical analysis

Based on a previous study that demonstrated a 44% NIV failure rate [21], we hypothesized a 15% absolute reduction in NIV failure between the low and high PEEP groups. With $\alpha = 0.05$, $\beta = 0.20$, and accounting for 10% attrition, 348 participants were required. As calculation error, the final number of patients was increased to 380.

There were no missing data for the primary outcome. In other variables, data imputation was not performed due to minimal missing values (< 1%). A constrained linear mixed-effects model was used to analyze each outcome variable. Fixed effects included treatment group, a quadratic time effect (if applicable), and the treatment*time interaction. Random effects included time-varying intercept and slope. Within-subjects correlations were modeled using first-order autoregressive errors. In the mediation analysis, we hypothesized that the effect of PEEP on NIV failure was mediated by PaO_2/FiO_2 and tidal volume (V_T). This hypothesis was evaluated through process modeling.

Continuous variables are reported as means and standard deviations or medians and interquartile ranges when appropriate. Normally distributed continuous variables were analyzed using an unpaired Student's t test, and non-normally distributed continuous variables were analyzed using a Mann–Whitney U test. Categorical variables are presented as frequencies (percentages) and were compared using chi-square or Fisher's exact tests. Time-to-event outcomes were assessed using Kaplan–Meier analysis, with group comparisons performed by log-rank tests. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. A two-sided $p < 0.05$ was considered statistically significant. Analyses were performed using IBM SPSS version 25.0 and R version 4.4.0.

Results

From January 11, 2022, to August 31, 2024, 2376 patients were assessed for eligibility. Of them, 380 patients were randomly assigned to either the low PEEP (n = 190) or high PEEP group (n = 190, Fig. 1). All patients were enrolled in the intention-to-treat analysis. Baseline characteristics are presented in Table 1.

The NIV parameters are detailed in Supplementary Table 1. Within 72 h post-randomization, the median PEEP was 5 cmH_2O in the low PEEP group and 10 cmH_2O in the high PEEP group (mean difference −5.1 cmH_2O [95% CI −5.2 to −5.0]). The median IPAP values were 14–15 cmH_2O and 16 cmH_2O (mean difference -2.2 cmH_2O [95% CI −2.4 to −2.0]) and the median support pressures were 9–10 cmH_2O and 6 cmH_2O, respectively (mean difference 2.9 cmH_2O [95% CI 2.7–3.1]).

NIV failure occurred in 82 (43%) and 61 (32%) patients in the low and high PEEP groups, respectively (absolute difference 11.1% [95% CI 1.3–20.5], p = 0.034, Table 2). The cumulative incidence of NIV failure was also higher in the low PEEP group (HR = 1.44, 95% CI 1.03–1.99, Supplementary Fig. 1). The details of NIV failure are summarized in Supplementary Tables 2 and 3. The

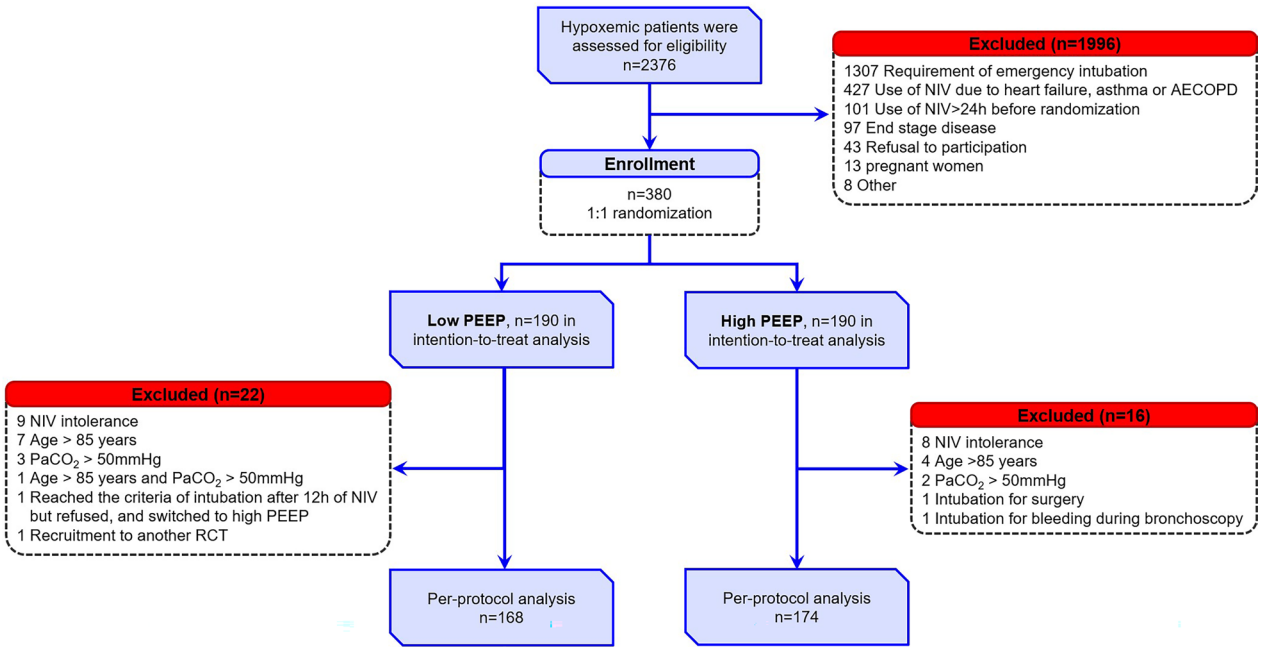

Fig. 1 Trial profile. *NIV* noninvasive ventilation, *AECOPD* acute exacerbation of chronic obstructive pulmonary disease, *PEEP* positive end expiratory pressure, *RCT* randomized controlled trial

revised NIV failure rates were 40.5% versus 28.9% in the low versus high PEEP groups (absolute difference 11.6% [95% CI 2.0–20.9], p = 0.023).

The duration of NIV, duration of invasive mechanical ventilation, ICU stay, and hospital stay did not differ between the groups. Mask-related pressure ulcers (mostly stage I) were the primary adverse event. Other adverse events included pneumothorax, vomiting, aspiration, and NIV intolerance. No differences were found between the groups for any adverse events.

At randomization, PaO_2/FiO_2 did not differ between the low and high PEEP groups. Within 72 h, the low PEEP group exhibited a lower PaO_2/FiO_2 (mean difference −31 mmHg, 95% CI −38 to −24, p < 0.01) and a reduced PaO_2/FiO_2 increment (p = 0.03 for time*group interaction; Fig. 2 and Supplementary Table 4). V_T was higher in the low PEEP group (mean difference 0.8 mL/kg predicted body weight, 95% CI 0.5 to 1.1, p < 0.01). Mediation analysis indicated that 77% of the total effect of PEEP on NIV failure was mediated through PaO_2/FiO_2, while 14% was mediated through V_T (Supplementary Fig. 2). No between-group differences were observed in VAS scores for abdominal distension or oronasal dryness (Supplementary Table 5). NIV failure rates across subgroups are detailed in Fig. 3 and Supplementary Table 6. It seems that high PEEP may benefit patients with pneumonia or ARDS.

In all, 22 and 16 patients were excluded from the low and high PEEP groups, leaving 168 and 174 patients, respectively, for per-protocol analysis. The baseline data were comparable (Supplementary Table 7). The low PEEP group had higher NIV failure rates (absolute difference 13.0%, 95% CI 2.8–22.9, p = 0.014) than the high PEEP group (Supplementary Table 8). There were no differences in NIV duration, invasive mechanical ventilation duration, length of ICU stay, or adverse events.

Discussion

This is the first RCT to explore the effects of high versus low PEEP in hypoxemic respiratory failure patients administered NIV via oronasal or nasal mask. High PEEP decreased NIV failure rates without increasing adverse events. This effect is mainly due to improved oxygenation.

We found that the primary factor contributing to NIV failure was the PaO_2/FiO_2 ratio. This effect was due to the physiological impact of high PEEP in patients with hypoxemic respiratory failure. High PEEP mitigates lung collapse, reduces intrapulmonary shunting, and decreases global and regional dynamic lung strain [22]. In a previous study on helmet NIV, the PaO_2/FiO_2 increased from 219 to 241 mmHg when the PEEP was increased from 0 to a median of 8 cmH_2O [23]. Similar findings have been observed in patients receiving NIV via face masks [12].

Table 1 Demographics and baseline characteristics

	Low PEEP N = 190	High PEEP N = 190
Age, mean (SD), years	66 (15)	65 (15)
Male, No. (%)	133 (70%)	135 (71%)
BMI, mean (SD)	22.9 (3.6)	22.9 (3.7)
APACHE II score, mean (SD)	17 (6)	17 (5)
Presence of ARDS, No. (%)	126 (66%)	139 (73%)
Diagnosis, No. (%)		
Pneumonia	132 (69%)	126 (66%)
Extra-pulmonary sepsis	24 (13%)	20 (11%)
Pancreatitis	18 (9%)	18 (9%)
Trauma	5 (3%)	9 (5%)
Other	11 (6%)	17 (9%)
Comorbidities, No. (%)		
Diabetes	54 (28%)	58 (31%)
Hypertension	85 (45%)	74 (39%)
Chronic cardiac disease	25 (13%)	24 (13%)
Chronic pulmonary disease	19 (10%)	22 (12%)
Chronic kidney disease	12 (6%)	17 (9%)
Chronic liver disease	10 (5%)	5 (3%)
Presence of immunosuppression	11 (6%)	19 (10%)
Use of HFNC before enrollment, No. (%)	7 (4%)	8 (4%)
Use of NIV before enrollment, No. (%)	69 (36%)	71 (37%)
Physiological measures at enrollment, mean (SD)		
Heart rate, bpm	101 (23)	103 (23)
Respiratory rate, bpm	28 (7)	28 (7)
Systolic blood pressure, mmHg	130 (22)	130 (21)
Diastolic blood pressure, mmHg	72 (13)	73 (13)
pH	7.44 (0.07)	7.43 (0.07)
$PaCO_2$, mmHg	34 (7)	34 (7)
PaO_2/FiO_2, mmHg	143 (50)	151 (54)
Interface for NIV, No. (%)		
Oronasal mask	151 (80%)	152 (80%)
Nasal mask	39 (20%)	38 (20%)

PEEP positive end expiratory pressure, *SD* standard deviation, *BMI* body mass index, *ARDS* acute respiratory distress syndrome, *APACHE* acute physiology and chronic health evaluation, *HFNC* high-flow nasal cannula, *NIV* noninvasive ventilation

Strong inspiratory effort is frequently observed in patients with hypoxemic respiratory failure, often manifesting as pronounced esophageal pressure swings and elevated V_T, which can lead to self-inflicted lung injury and NIV failure [24–27]. High PEEP can mitigate patient–ventilator asynchrony, reduce lung injury, and attenuate inspiratory effort [28, 29]. In a previous study on ARDS patients, those with a median PEEP of 5.1 cmH_2O required higher support pressure (approximately 3 cmH_2O) and FiO_2 but had a higher respiratory rate compared to those with a median PEEP of 8 cmH_2O [9]. Similarly, in our study, the low PEEP group required greater support pressure (mean difference of 2.9 cmH_2O). The V_T was also higher (mean difference of 0.8 mL/kg PBW). This suggests that low PEEP may worsen lung injury, partially contributing to NIV failure. However, elevated support pressure may also increase V_T, further raising the risk of lung injury. Consequently, the benefits of high PEEP may be overestimated.

High PEEP, typically ranging between 10 and 15 cmH_2O, is frequently employed in invasively ventilated ARDS patients [7, 8]. In NIV patients, it is predominantly administered at around 10 cmH_2O via a helmet [9, 11]. However, two COVID-19 studies have reported PEEP levels of 12–17 cmH_2O delivered through a face mask [30, 31], suggesting the feasibility of high PEEP via this interface. In our study, PEEP was delivered via an oronasal or nasal mask, with a median level of 10 cmH_2O in the high PEEP group. Adverse event rates were comparable between low and high PEEP groups, with low incidences of severe adverse events (e.g., pneumothorax). These results suggest that a median PEEP of 10 cmH_2O delivered via oronasal or nasal mask is safe. However, given the small sample size for adverse events, it may not be powered to detect significant differences in safety outcomes. High PEEP necessitated tighter mask fitting due to leakage, potentially increasing intolerance risk. Thus, higher PEEP levels should be used cautiously. Additionally, some patients received NIV via nasal mask, which warrants caution due to potential mouth opening, particularly at high respiratory rates and elevated PEEP levels.

Continuous positive airway pressure (CPAP) was utilized as an alternative therapy for hypoxemic respiratory failure. However, physiological studies indicate that NIV, whether delivered via face mask or helmet, significantly reduces respiratory effort compared to CPAP [12, 32]. Therefore, we did not evaluate the effects of CPAP. To the best of our knowledge, no RCTs have directly compared CPAP with face mask NIV, warranting further investigation. In addition, we included patients with $PaO_2/FiO_2 < 150$ mmHg. NIV in this population may increase ICU mortality due to delayed intubation [2, 33]. Given the high risk of NIV failure, timely intubation is crucial to prevent adverse clinical outcomes.

In a previous meta-analysis, low PEEP was noninferior to high PEEP in non-ARDS patients undergoing invasive mechanical ventilation [34]. In our study, subgroup analysis indicated that high PEEP was advantageous for ARDS patients, likely due to its role in alveolar recruitment and stabilization [29, 35], but not in those without ARDS. However, since these findings were derived from a subgroup analysis with small sample sizes, they are insufficient to conclusively establish the superiority of high PEEP in ARDS patients or its potential disadvantages in

Table 2 Primary and secondary outcomes and adverse events

	Low PEEP N = 190	High PEEP N = 190	Absolute or mean difference (95% CI)	*p*
Primary outcome				
NIV failure, No. (%)	82 (43%)	61 (32%)	11.1% (1.3 to 20.5)	0.034
Secondary outcomes				
28-day mortality, No. (%)	78 (41%)	57 (30%)	11.1% (1.4 to 20.4)	0.032
Duration of NIV, median (IQR), days	2.2 (1.1 to 5.0)	2.5 (1.1 to 4.9)	0 (−0.3 to 0.5)	0.78
Duration of invasive mechanical ventilation, median (IQR), days[$]	4.7 (2.1 to 7.4)	3.6 (1.0 to 6.3)	1.0 (−0.3 to 2.8)	0.17
Length of ICU stay, median (IQR), days	6.2 (3.9 to 11.1)	6.7 (3.7 to 9.8)	0.2 (−0.8 to 1.1)	0.72
Length of hospital stay, median (IQR), days	13.8 (8.0 to 20.3)	13.8 (8.2 to 22.8)	−0.5 (−2.4 to 1.3)	0.58
Post-hoc analysis				
Intubation or death within 28 days, No. (%)	90 (47%)	70 (37%)	10.5% (0.6 to 20.2)	0.048
Revised NIV failure[*], No. (%)	77 (40.5%)	55 (28.9%)	11.6% (2.0 to 20.9)	0.023
Use of sedative drugs, No. (%)	25 (13.2%)	22 (11.6%)	1.6% (−5.1 to 8.3)	0.76
Use of vasopressor, No. (%)	14 (7.4%)	19 (10%)	−2.6% (−8.5 to 3.2)	0.47
Adverse events				
Pressure ulcer caused by mask				
Stage I, No. (%)	34 (18%)	34 (18%)	0% (−7.7 to 7.7)	> 0.99
Stage II, No. (%)	4 (2%)	4 (2%)	0% (−3.4 to 3.4)	> 0.99
Pneumothorax, No. (%)	1 (0.5%)	3 (2%)	−1.1% (−4.0 to 1.6)	0.62
Vomiting, No. (%)	1 (0.5%)	0 (0%)	0.5% (−1.5 to 2.9)	> 0.99
Aspiration, No. (%)	1 (0.5%)	0 (0%)	0.5% (−1.5 to 2.9)	> 0.99
NIV intolerance, No. (%)	9 (5%)	8 (4%)	0.5% (−3.9 to 5.0)	> 0.99

PEEP positive end expiratory pressure, *NIV* noninvasive ventilation, *IQR* interquartile range, *ICU* intensive care unit

[$] Only for patients who received intubation

*NIV events were retrospectively assessed by two independent experts who were blinded to the intervention based on the intubation criteria

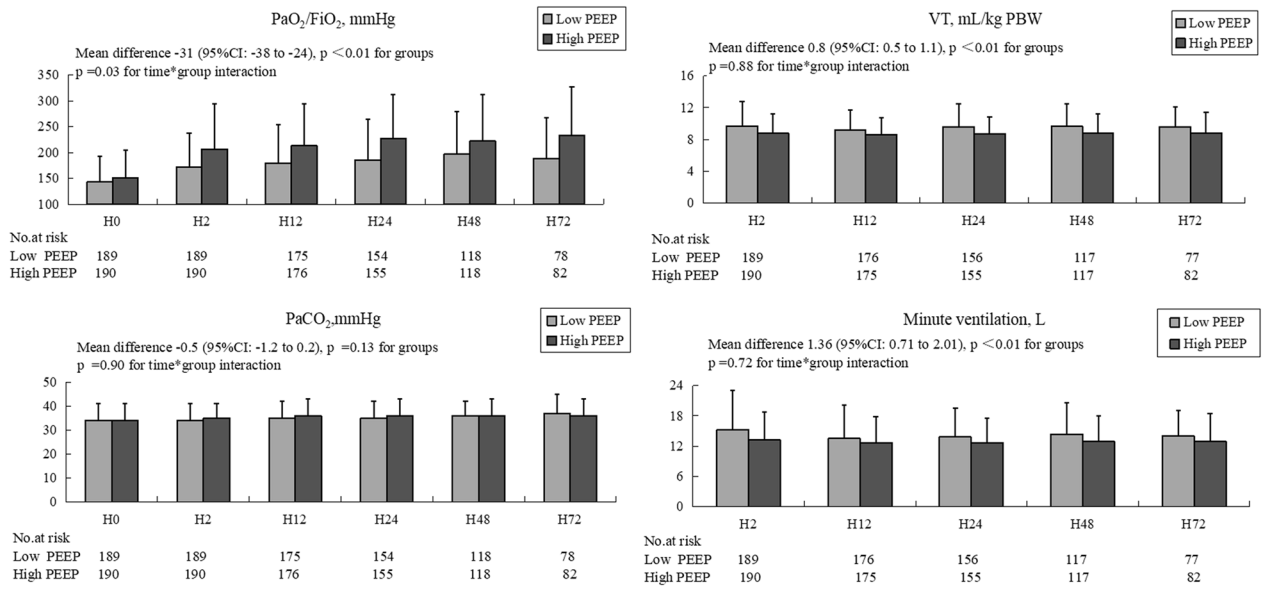

Fig. 2 PaO_2/FiO_2, $PaCO_2$, tidal volume (V_T), and minute ventilation measures within 72 h post-randomization. *PaO_2/FiO_2* ratio of PaO_2 to fraction of inspired oxygen, *PEEP* positive end expiratory pressure, *CI* confidence interval, *PBW* predicted body weight

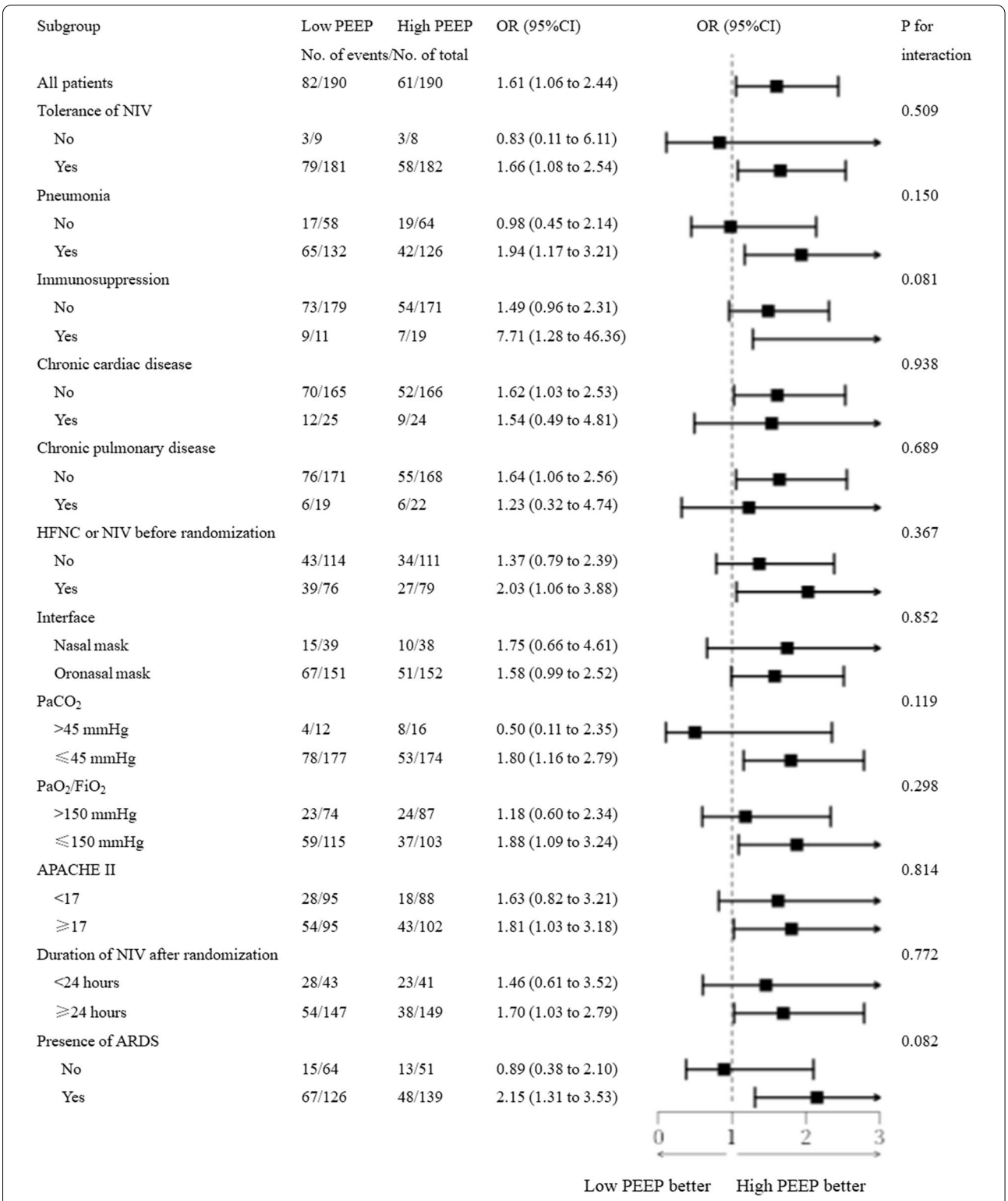

Fig. 3 Subgroup analyses for NIV failure. *PEEP* positive end expiratory pressure, *OR* odds ratio, *CI* confidence interval, *NIV* noninvasive ventilation, *HFNC* high-flow nasal cannula, *APACHE* acute physiology and chronic health evaluation, *ARDS* acute respiratory distress syndrome

non-ARDS patients. Further research is warranted to validate these observations.

This study has several limitations. First, treatment withdrawal is a major limitation in our research. One reason lies in the cultural factor in China for dying at home, where 71.5% of deaths occur [36]. Other reasons include unaffordable medical expenditures, patients being too severely ill to benefit from intubation, or the wishes of patients and their families. Notably, some cases involved overlapping reasons. Since these factors were neither documented during the study nor retrievable from medical records, we are unable to provide further details regarding the withdrawal of therapy. To address this confounding factor, two independent experts retrospectively reviewed NIV failure events based on intubation criteria, reclassifying them as revised NIV failure. The revised NIV failure rates were consistent with the original data, partially validating the observed effects of high PEEP.

Second, the observed correlation between PEEP and the PaO_2/FiO_2 ratio in relation to NIV failure may be subject to overestimation, as alternative physiological pathways could potentially influence this relationship. Third, the generalizability of our results is limited by our exclusive focus on Chinese patients with hypoxemic respiratory failure. The efficacy of high PEEP in populations with mixed respiratory failure or different ethnic backgrounds remains to be elucidated. Fourth, we did not collect data on post-intubation respiratory mechanics and alveolar gas exchange, as these were beyond the primary objectives of the study. However, such data could provide valuable insights into the mechanisms of NIV failure. Further research is needed to address this gap. Fifth, the sample size was calculated based on an anticipated 15% reduction in the NIV failure rate. However, because the observed acute NIV failure rate was 11.1%, the actual reduction may have been potentially underpowered to detect a statistically significant difference.

In conclusion, high PEEP delivered via an oronasal or nasal mask decreases the rate of NIV failure in patients with hypoxemic respiratory failure. This effect is mainly due to improved oxygenation. However, the effect of high PEEP may be overestimated considering the higher V_T observed in patients with low PEEP. Additionally, the interpretation of this effect should be carried out with caution as the study has insufficient statistical power to detect a significant difference.

Supplementary Information
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Author contributions
DJ and YMJ conceptualized the study and participated in its design. DJ took responsibility for the integrity of the study. LXY, SWW, TSJ, LQ, WK, YFX and MMY were involved in the management of participating centers, patient recruitment, and data collection. MMY and HWH conducted the literature search. HT, JL, HYL, HXL, AZ, BLF, MYW, HWH and HJ participated in study design, data collection, and patient recruitment. SAC contributed to study design and performed statistical analysis. DJ and MMY directly accessed and verified the raw data. All authors contributed to data interpretation, manuscript preparation and revision. All authors reviewed and approved the final manuscript.

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Data Availability
Research data will be made available upon reasonable request. All requests should be submitted to the corresponding author who will review with the other investigators for consideration. A data use agreement will be required before the release of participant data and institutional review board approval as appropriate.

Declarations

Conflicts of interest
We declare no competing interests.

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