The Efficacy and Safety of Prone Positional Ventilation in Acute Respiratory Distress Syndrome: Updated Study-Level Meta-Analysis of 11 Randomized Controlled Trials

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Objective: The survival benefit of prone positioning during mechanical ventilation for acute respiratory distress syndrome has been a matter of debate. Recent multicenter randomized controlled trials have shown a significant reduction of 28-day and 90-day mortality associated with prone positioning during mechanical ventilation for severe acute respiratory distress syndrome. We performed an up-to-date meta-analysis on this topic and elucidated the effect of prone positioning on overall mortality and associated complications.

Data Sources: PubMed, EMBASE, BioMed Central, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and conference proceedings through May 2013.

Study Selection: Randomized controlled trial comparing overall mortality of prone-versus-supine positioning in patients with acute respiratory distress syndrome.

Data Extraction: Data were extracted for populations, interventions, outcomes, and risk of bias. The prespecified primary endpoint was overall mortality, using the longest available follow-up in each study. The odds ratio with 95% CI was the effect measure.

Data Synthesis: This analysis included 11 randomized controlled trial, 2,246 total adult patients, and 1,142 patients ventilated in the prone position. Prone positioning during ventilation significantly reduced overall mortality in the random-effect model (odds ratio, 0.77; 95% CI, 0.59–0.99; $p = 0.039$; $I^2 = 33.7\%$), and the effects were marked in the subgroup in which the duration of prone positioning was more than 10 hr/session, compared with the subgroup with a short-term duration of prone positioning (odds ratio, 0.62; 9% CI, 0.48–0.79; $p = 0.039$; $p_{interaction} = 0.015$). Prone positioning was significantly associated with pressure ulcers (odds ratio, 1.49; 95% CI, 1.18–1.89; $p = 0.001$; $I^2 = 0.0\%$) and major airway problems (odds ratio, 1.55; 95% CI, 1.10–2.17; $p = 0.012$; $I^2 = 32.7\%$).

Conclusions: Ventilation in the prone position significantly reduced overall mortality in patients with severe acute respiratory distress syndrome. Sufficient duration of prone positioning was significantly associated with a reduction in overall mortality. Prone ventilation was also significantly associated with pressure ulcers and major airway problems. (*Crit Care Med* 2014; XX:00–00)

Key Words: acute lung injury; acute respiratory distress syndrome; meta-analysis; prone position; randomized controlled trial

Prone positioning during mechanical ventilation for acute respiratory distress syndrome (ARDS) has a robust scientific background. Previous randomized controlled trials (RCTs) have demonstrated that prone positioning results in a significant improvement of oxygenation in patients with acute hypoxemic respiratory failure, as measured by the ratio of Pa_{O_2} to the F_{IO_2} (1–3). Despite these physiologic benefits, several RCTs reported no improvement of patient survival with prone positioning (1, 2, 4, 5). However, post hoc analysis of the first RCT carried out by Gattinoni et al (1), which compared prone and supine ventilation in patient with acute respiratory failure, demonstrated that prone positioning reduced mortality by 10 days in the subgroup of patients with the highest disease severity (Simplified Acute Physiology Score [SAPS II] ≥ 50). Furthermore, selected meta-analyses, which included the severest subgroup of patients (by SAPS II score or Pa_{O_2}/F_{IO_2} < 100 mm Hg), revealed similar findings (6–8). A recently published multicenter trial by Guérin et al (9) showed significant mortality reduction associated with prone positioning for patients with severe ARDS, as defined by Pa_{O_2}/F_{IO_2} less than or equal to 150 mm Hg with positive end-expiratory pressure (PEEP) more than or equal to 5 cm H_2O.

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We performed a systematic review and comprehensive meta-analysis of RCTs to compare the efficacy (reduction of overall mortality) and safety (adverse events) of prone versus supine positioning during mechanical ventilation for ARDS. We also evaluated a chronological trend of pooled estimates of prone positioning by cumulative meta-analysis and the effect of strength of the intervention (i.e., actual duration of prone positioning) to the pooled estimates by meta-regression.

METHODS

Data Sources and Searches

Pertinent published or unpublished studies were independently searched in PubMed, EMBASE, BioMed Central, Cochrane Central Register of Controlled Trials, and the United States National Institutes of Health registry of clinical trials (http://www.clinicaltrials.gov), using the following MeSH and key word terms: "acute respiratory distress syndrome" or "acute lung injury," and "prone position" or "prone positioning," and "randomized controlled trial" or "randomized trial" or "randomized clinical trial" (10, 11). Additional data sources included conference proceedings from the American Thoracic Society (1994–2013), the Society of Critical Care Medicine (1994–2013), the European Society of Intensive Care Medicine (1994–2013), the American College of Chest Physicians (1994–2013), and the International Symposium on Intensive Care and Emergency Medicine (1997–2013). There was no language restriction (12).

Study Selection

We included studies that met the following criteria: adult patients with acute hypoxemic respiratory failure ($Pa_{O_2}/F_{IO_2} \leq 300$ mm Hg), including acute lung injury (ALI) and ARDS, who were under mechanical ventilatory support; all studies that randomly assigned patients to two or more groups, including prone or supine positioning, during ventilation; and all-cause mortality was reported regardless of the timing of data collection. We excluded RCTs conducted on pediatric patients and randomized crossover trials that assigned patients to both prone and supine groups.

Data Extraction and Quality Assessment

Summary data as reported in the published articles were used in the analysis. A standardized form was used to extract trial characteristics, study design (including randomization sequence generation, allocation concealment, crossover between assigned groups, number of postrandomization withdrawals, or lost to follow-up), number of study patients, age, duration of prone positioning, mean Pa_{O_2}/F_{IO_2} ratio at enrollment, disease severity assessed by SAPS II or Sequential Organ Failure Assessment score, length of follow-up, and mortality/adverse events data reported on an intention-to-treat basis. Since all published meta-analyses confirmed improvement of oxygenation with prone positioning ventilation, we focused our analysis on the effect of prone positioning on both overall mortality and adverse events associated with the prone position during mechanical ventilation. The quality of eligible RCTs was assessed using the Cochrane Collaboration's tool for assessing the risk of bias for RCTs (**Supplementary Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A826) (13). Because most previous meta-analyses reported the methodological quality of each trial using the Jadad score, we also provided this score, as well as the Cochran Collaboration's tool, for each RCT (14). Two investigators independently evaluated the studies, abstracted data on methods and outcomes, and assessed the risk of bias. The last search was performed in May 2013.

Outcomes and Definitions

The primary outcome measure was overall mortality at the longest available follow-up. Secondary outcome measures included mortality stratified according to the duration of prone position (long duration group, ≥ 10 hr/session; short duration group, < 10 hr/session), whether there was lung protective ventilation ($V_T \leq 10$ mL/kg), and adverse events (ventilator-associated pneumonia, newly developed pressure ulceration after prone positioning, major airway problem including unplanned extubation, selective intubation into the main bronchus, endotracheal tube obstruction, loss of venous or arterial access line, dislodgement/kinking of the thoracostomy tube, pneumothorax, cardiac arrest after position change, or tachyarrhythmia or bradyarrhythmia).

Data Synthesis and Analysis

The primary outcome was analyzed by both random- and fixed-effect models. Odds ratios (ORs) with a 95% CI were presented as summary statistics. The pooled OR was calculated with the DerSimonian and Laird method for random effects and the Mantel–Haenszel method for fixed effects (15, 16). The number needed to treat to prevent overall mortality was calculated from an inverse of pooled risk difference in random-effect model. Because primary study designs, such as study population, planned duration of prone positioning, and clinical practice patterns, have progressively changed, we evaluated the impact of publication date on the overall effect of pooled ORs for prone ventilation by a cumulative meta-analysis. Exploratory meta-regressions were performed to assess the relationship between the effect size (log OR) and daily duration of prone positioning. Stratified subgroup analyses were done to assess treatment effects according to a short or long duration of prone positioning, lung protective ventilation, patient populations with ARDS only or mixed with ALI, severity of patient population by the means of Pa_{O_2}/F_{IO_2} ratio, concomitant use of high-frequency oscillatory ventilation (HFOV), and adequacy of concealment allocation; in addition, tests for interaction were derived from random-effects meta-regression. Statistical heterogeneity was assessed by Cochran's Q via a chi-square test and was quantified with the I^2 test (17). We considered statistical heterogeneity to be low for $I^2 = 0$–40%, moderate for $I^2 = 30$–60%, substantial for $I^2 = 50$–90%, and considerable for $I^2 = 75$–100%. Publication bias was assessed by funnel plot asymmetry, along with Egger and Begg test. The κ statistic was used to assess agreement between investigators for

study selection. Results were considered statistically significant at two-sided p value of less than 0.05. Statistical analysis was performed with the use of STATA/SE 10.1 (Stata Corp LP, College Station, TX). The study was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and the review protocol has not been registered (**Supplementary Table 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/A826) (18).

RESULTS

Search Results and Trial Characteristics

We identified 2,675 citations; 36 studies were retrieved for detailed evaluation; and 11 RCTs met inclusion criteria (**Fig. 1**) (1–5, 9, 19–23). These 11 RCTs included a total of 2,246 adult patients (prone, 1,142 [50.8%]; supine, 1,104 [49.2%]). The interobserver agreement for study selection was high ($\kappa = 0.88$).

The characteristics of the individual studies are summarized in **Table 1**. Assessment of risk of bias is summarized in Supplementary Table 1 (Supplemental Digital Content 1, http://links.lww.com/CCM/A826). All but one trial showed relatively high methodological quality (20). Among the 11 RCTs, none of trials were double-blinded. However, blinding of patients and caregivers was impossible in these trials to evaluate prone ventilation, and the authors judged that the outcome is not likely to be influenced by lack of blinding. All of the trials with one exception kept the concealed allocation (1–5, 9, 19, 21–23).

Earlier trials, published before 2005 (1, 2, 19), included patients with a wide spectrum of disease severity (n = 1,159; both ALI and ARDS), no use of lung protective ventilation, and a relatively short period of prone positioning (< 10 hr/session). Later trials, published after 2005 (3–5, 9, 20–23), enrolled more homogeneous patient populations with regard to disease severity (n = 1,087; only patients with ARDS); lung protective ventilation was used; and prone positioning duration was longer (11–20 hr/session). Patients in three RCTs had severe ARDS ($Pa_{O_2}/F_{IO_2} \leq 150$ mm Hg with PEEP ≥ 5 cm H_2O) (9, 21, 23). Two trials that used prone positioning with HFOV were included because there were comparative controls subjected to the same method of HFOV (21, 23).

Effect on Mortality

This meta-analysis included 11 RCTs (Fig. 1) (1–5, 9, 19–23). All provided mortality data. **Figure 2** presents the pooled OR along with the ORs of individual studies with regard to overall mortality. The overall mortality in the intention-to-treat population for prone and supine position was 474 of 1,142 (41.5%) and 510 of 1,104 (46.2%), respectively. In the

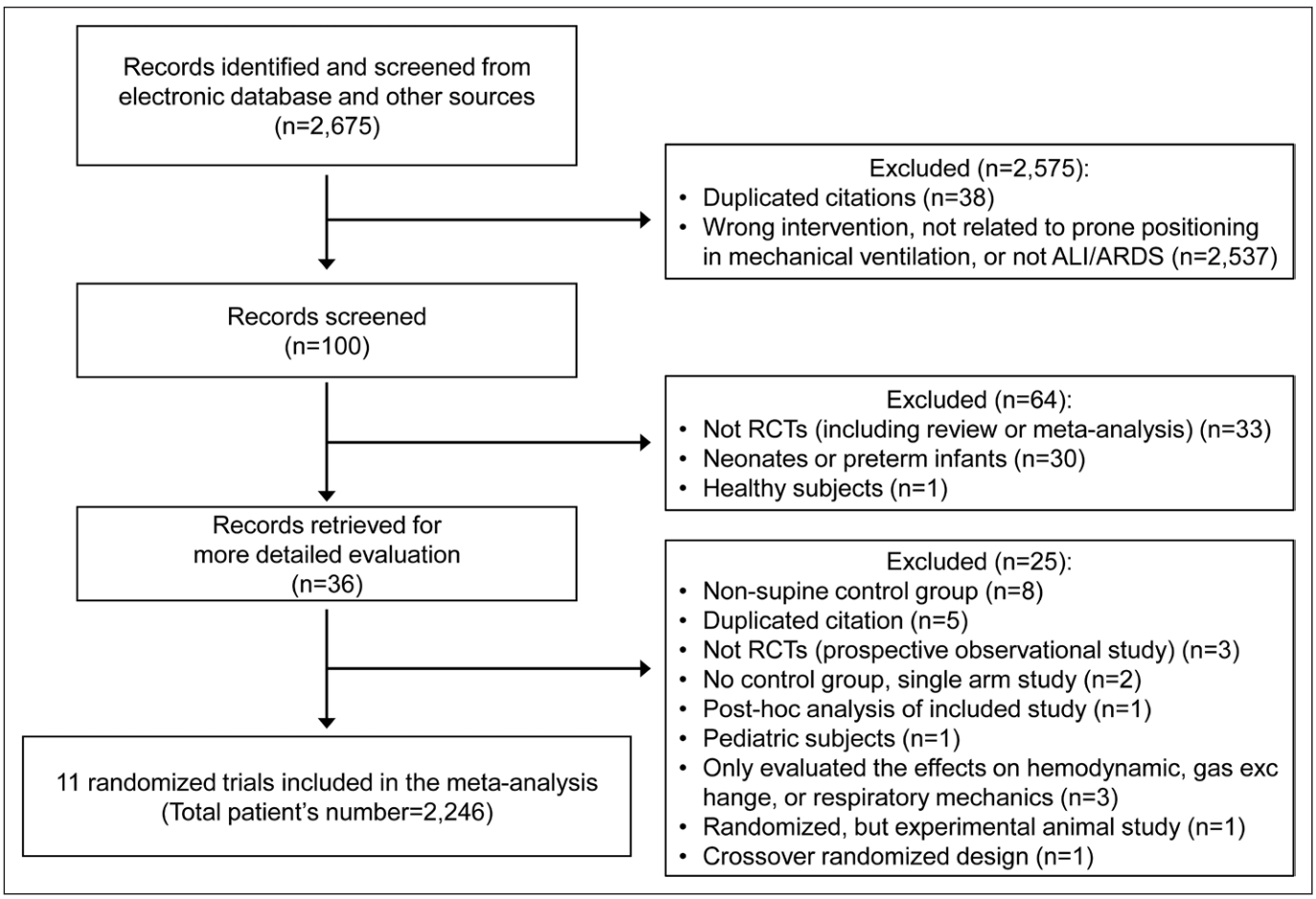

Figure 1. Flow diagram of trial selection. The study flow diagram was depicted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. ALI = acute lung injury, ARDS = acute respiratory distress syndrome, RCT = randomized controlled trial.

TABLE 1. Characteristics of the Randomized Controlled Trials Included in this Study

Variable	Gattinoni et al (1) (Prone-Supine I)	Beuret et al (19)	Guerin et al (2)	Voggenreiter et al (3)	Papazian et al (23)
Populations					
Total *n*	304	53	802	40	26
Enrollment period	1996–1999	1997–2000	1998–2002	1999–2001	Uncertain
Enrollment criteria and definition in the trials	ALI/ARDS with Pao_2/Fio_2 ≤ 200 with PEEP ≥ 5 cm H_2O or Pao_2/Fio_2 ≤ 300 with PEEP ≥ 10 cm H_2O, PAOP ≤ 18 mm Hg	Intubated coma, severe hypoxemia (Pao_2/Fio_2 ≤ 150) was excluded	ALI (Pao_2/Fio_2 ≤ 300) or ARDS (Pao_2/Fio_2 ≤ 200)	Traumatic ALI/ARDS with Pao_2/Fio_2 ≤ 200 with PEEP ≥ 5 cm H_2O or Pao_2/Fio_2 ≤ 300 with PEEP ≥ 5 cm H_2O, PAOP ≤ 18 mm Hg	ARDS only with Pao_2/Fio_2 ≤ 150 with PEEP 5 cm H_2O, PAOP ≤ 18 mm Hg
Disease	ALI/ARDS (6%/94%)	ALI/ARDS (7 patients, 13.2%)	ALI/ARDS (21%/31%)	ALI/ARDS (45%/55%)	ARDS (100%)
Mean age (yr)	58	55	62.2	41.4	53
Randomization					
Stratified by severity	No	No	No	No	No
Allocation concealment	Centrally by telephone	Sealed opaque envelopes	Sealed opaque envelopes	Centrally by telephone	Sealed opaque envelopes
Excluded patients after randomization	No	0/25 prone, 2/28 supine	4/417 prone, 7/385 supine	No	No
Intention-to-treat population, *n*	304	51	791	40	26
Crossover (prone to supine)	0/152	3/25	170/413	0/21	0/13
Crossover (supine to prone)	12/152	3/26	81/378	0/19	0/13
Severity at enrollment (mean)					
Pao_2/Fio_2 (mm Hg)	127.4	326.2	152.4	221.2	103.5
PEEP (cm H_2O)	10.0	NA	8.0	11.5	11.5
SAPS II score	40	50	45.6	NA	39.5
Sequential Organ Failure Assessment score	NA	NA	NA	11.5	7.6
Prone positioning					
Planned duration	6 hr/d for 10 d	4 hr/d until weaning	≥ 8 hr/d until weaning	8–23 hr/d until weaning	12 hr for 1 d
Actual duration	7 hr for 4.7 d	4 hr for 6.0 d	9 hr for 4.1 d	11 hr for 7 d	12 hr for 1 d

Mancebo et al (4)	Chan et al (20)	Demory et al (21)	Fernandez et al (22)	Taccone et al (5) (Prone-Supine II)	Guérin et al (9) (PROSEVA)
142	22	28	42	344	474
1998–2002	2002–2003	2003–2004	2003–2004	2004–2008	2008–2011
ARDS only with Pao_2/Fio_2 ≤ 200 with PEEP ≥ 5 cm H_2O, PAOP ≤ 18 mm Hg	ARDS due to pneumonia only with Pao_2/Fio_2 ≤ 200 with PEEP ≥ 5 cm H_2O, PAOP ≤ 18 mm Hg	ARDS only with Pao_2/Fio_2 < 150 with PEEP ≥ 5 cm H_2O, PAOP ≤ 18 mm Hg	ARDS only with Pao_2/Fio_2 ≤ 200 with PEEP ≥ 5 cm H_2O, PAOP ≤ 18 mm Hg	ARDS only with Pao_2/Fio_2 ≤ 200 with PEEP ≥ 5 cm H_2O, PAOP ≤ 18 mm Hg	Severe ARDS only with Pao_2/Fio_2 < 150 with Fio_2 ≥ 0.6, PEEP ≥ 5 cm H_2O, V_T 6 mL/kg (PBW)
ARDS (100%)	ARDS (100%)	ARDS (100%)	ARDS (100%)	ARDS (100%)	ARDS (100%)
54	62.3	50.9	54.6	60	59
No	No	No	Yes (SAPS II)	Yes (Pao_2/Fio_2)	No
Sealed opaque envelopes	No	Sealed opaque envelopes	Centrally by telephone	Centrally by telephone	Centrally by web-based system
4/80 prone, 2/62 supine	No	No	1/22 prone, 1/20 supine	1/169 prone, 1/175 supine	3/240 prone, 5/234 supine
136	22	28	40	342	466
0/76	0/11	0/13	0/21	0/168	0/237
5/60	0/11	0/15	2/19	12/174	0/229
144.8	109.3	122.0	117.8	113.0	100.0
7.0	13.0	11.0	11.0	10.0	10.0
40.8	22.7 (Acute Physiology and Chronic Health Evaluation II score)	40.1	38.4	41.0	46
NA	NA	NA	9.3	6.8	10
20 hr/d until weaning	24 hr/d, at least 3 d	12 hr for 1 d	20 hr/d until weaning	20 hr/d for 28 d	16 hr/d for 28 d
17 hr for 10.1 d	24 hr for 4.4 d	12 hr for 1 d	20 hr for 11.9 d	18 hr for 8.3 d	17 hr for 4 d

(*Continued*)

TABLE 1. (*Continued*). Characteristics of the Randomized Controlled Trials Included in this Study

Variable	Gattinoni et al (1) (Prone-Supine I)	Beuret et al (19)	Guerin et al (2)	Voggenreiter et al (3)	Papazian et al (23)
Discontinuation criteria	No	Able to sit in chair	Relative improvement of Pa_{O_2}/F_{IO_2} ≥ 30% with F_{IO_2} ≤ 0.6	Pa_{O_2}/F_{IO_2} > 300 for 48 hr	No
Last follow-up period	180 d	Hospital discharge (maximum 28 d)	90 d	Hospital discharge (maximum 90 d)	ICU discharge
Concomitant intervention					
Lung protective ventilation	Unclear	No	No	Yes (V_T 6–8 mL/kg of PBW)	Yes (V_T 6 mL/kg of IBW)
Weaning protocol	No	No	Yes	No	No
Sedation protocol	No	No	No	No	Yes
High-frequency oscillatory ventilation	No	No	No	No	Yes

ALI = acute lung injury, ARDS = acute respiratory distress syndrome, PEEP = positive end-expiratory pressure, PAOP = pulmonary artery occlusion pressure, V_T = tidal volume, PBW = predicted body weight, SAPS II = Simplified Acute Physiology Score II, NA = not available, IBW = ideal body weight.

random-effects model, overall mortality was significantly lower in the prone position patients (OR, 0.77; 95% CI, 0.59–0.99; $p = 0.039$). The number needed to treat for prone positioning to prevent overall mortality was 16. A fixed-effects model yielded a similar result (OR, 0.82; 95% CI, 0.69–0.97; $p = 0.019$) (**Supplementary Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A826). There was no statistical heterogeneity in either the random-effects or the fixed-effects model ($I^2 = 33.7\%$, $p = 0.129$ for both). Visual assessment by the funnel plot indicated no apparent publication bias (supported by Egger test [$p = 0.176$] and Begg test [$p = 0.586$]) (**Supplementary Fig. 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/A826). No study unduly influenced the pooled estimate of the prone position (**Supplementary Fig. 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/A826). Cumulative meta-analysis, which sorts trials chronologically, showed a progressive shift of pooled estimates of prone positioning from a negative to a positive effect, starting with the publication of Mancebo et al (4) (the first relatively large-scale RCT to include patients with ARDS only) (**Supplementary Fig. 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/A826). A study conducted by Papazian et al (23) enrolled only patients with ARDS; however, the sample size was insufficient to shift the pooled estimates. Since each included study reported mortality at a different time point, exploratory stratified analysis according to each time point (ICU mortality, at 28, 90, and 180 d) was performed. Although there were trends of reduced ICU mortality at 28 and 90 days for the prone positioning group, statistical significance was not achieved, possibly due to a limited sample size of each pooled analysis (**Supplementary Fig. 5**, Supplemental Digital Content 1, http://links.lww.com/CCM/A826).

Duration of Prone Positioning

All studies provided data regarding planned and actual duration of prone positioning. Exploratory meta-regressions that assessed the relationship between the actual duration of prone positioning and the effect size in the included trials are shown in **Figure 3**. Although a negative trend for overall mortality was observed when the actual duration of prone positioning was longer, the effect of the duration of prone positioning on mortality did not achieve statistical significance (regression coefficient –0.037; 95% CI, –0.089 to 0.013; $p = 0.130$).

Subgroup Analysis

The results of subgroup analysis are presented in **Figure 4**. The overall treatment effect of prone positioning was consistent for each event, regardless of whether a random- or fixed-effects model was used. Interestingly, there were significant interactions across the subgroup for lung protective ventilation ($p_{interaction} = 0.015$), less than 10 hr/session of prone positioning ($p_{interaction} = 0.015$), and the homogeneous patient population with ARDS only ($p_{interaction} = 0.021$). The effects of prone

Mancebo et al (4)	Chan et al (20)	Demory et al (21)	Fernandez et al (22)	Taccone et al (5) (Prone-Supine II)	Guérin et al (9) (PROSEVA)
F_{IO_2} ≤ 0.45 and PEEP ≤ 5 cm H_2O	Sp_{O_2} > 90%, F_{IO_2} < 0.6 for > 24 hr (after 72 hr)	No	Pa_{O_2}/F_{IO_2} > 250 and PEEP ≤ 8 cm H_2O for 12 hr	F_{IO_2} ≤ 0.4 and PEEP ≤ 10 cm H_2O	Pa_{O_2}/F_{IO_2} > 150, F_{IO_2} ≤ 0.6, and PEEP ≤ 10 cm H_2O for 4 hr or relative improvement of Pa_{O_2}/F_{IO_2} ≥ 20%
Hospital discharge (maximum 60 d)	Hospital discharge (maximum 28 d)	ICU discharge	Hospital discharge (maximum 60 d)	180 d	90 d
Yes (V_T ≤ 10 mL/kg of PBW)	Yes (V_T 6–8 mL/kg of IBW)	Yes (V_T 6–7 mL/kg of PBW)	Yes (V_T 6–8 mL/kg of PBW)	Yes (V_T ≤ 8 mL/kg of PBW)	Yes (V_T 6 mL/kg of PBW)
Yes	No	No	Yes	No	Yes
Yes	No	Yes	Yes	No	Yes
No		Yes	No	No	No

positioning were significantly different among these subgroups. Studies of short-term prone ventilation (< 10 hr/session) (1, 2, 19) did not show mortality reduction (OR, 1.04; 95% CI, 0.80–1.36; $p = 0.757$; $I^2 = 10.7\%$); however, studies with a duration of prone ventilation more than 10 hr/session (3–5, 9, 20–23) showed a significant reduction in overall mortality (OR, 0.62; 95% CI, 0.48–0.79; $p < 0.001$; $I^2 = 0.0\%$) (**Supplementary Fig. 6**, Supplemental Digital Content 1, http://links.lww.com/CCM/A826). As anticipated, subgroup analysis of lung protective ventilation showed the same results (Fig. 4 and **Supplementary Fig. 7**, Supplemental Digital Content 1, http://links.lww.com/CCM/A826). In addition, prone positioning had no significant effect in the studies that included patients with variable disease severity (all ALI or hypoxemic patients: OR, 1.02; 95% CI, 0.76–1.36; $p = 0.920$; $I^2 = 14.9\%$). However, prone positioning significantly reduced overall mortality in the studies that included populations that were homogenous and had severer disease (ARDS only: OR, 0.62; 95% CI, 0.48–0.80; $p < 0.001$; $I^2 = 0.0\%$) (Fig. 4 and **Supplementary Fig. 8**, Supplemental Digital Content 1, http://links.lww.com/CCM/A826). The effect of prone positioning was significant in the subgroup with a Pa_{O_2}/F_{IO_2} ratio less than 150 mm Hg (OR, 0.72; 95% CI, 0.55–0.95; $p = 0.021$; $I^2 = 21.5\%$), whereas the subgroup with a Pa_{O_2}/F_{IO_2} ratio more than 150 mm Hg did not show similar results. However, significant interaction was not observed ($p_{interaction} = 0.635$). There were no significant interactions among the other subgroups with regard to HFOV usage and adequacy of allocation concealment. The effect of prone positioning on mortality reduction was robust even after exclusion of the lower quality study (20) (Fig. 4).

Adverse Events

Table 2 summarizes adverse events. Prone positioning increased the risk of pressure ulcers (OR, 1.49; 95% CI, 1.18–1.89; $p = 0.001$; $I^2 = 0.0\%$). Major airway problems, including unplanned extubation, selective intubation into the main bronchus, and endotracheal tube obstruction, also significantly increased with prone positioning (OR, 1.55; 95% CI, 1.10–2.17; $p = 0.012$; $I^2 = 32.7\%$); this was primarily driven by an increased risk of endotracheal tube obstruction (OR, 2.16; 95% CI, 1.53–3.05; $p < 0.001$; $I^2 = 0.0\%$). Although major airway problems significantly increased with prone positioning, none of the included trials reported fatal consequences from a major airway problem. There was no significant association between prone positioning and the prevalence of ventilator-associated pneumonia, loss of venous or arterial access, thoracostomy tube problems, pneumothorax, cardiac arrests, or clinically significant arrhythmic events (Table 2).

DISCUSSION

The results of this meta-analysis indicate that prone positioning in mechanical ventilation for patients with acute hypoxemic respiratory failure reduced overall mortality. The effect of prone positioning was clearer in the ARDS population,

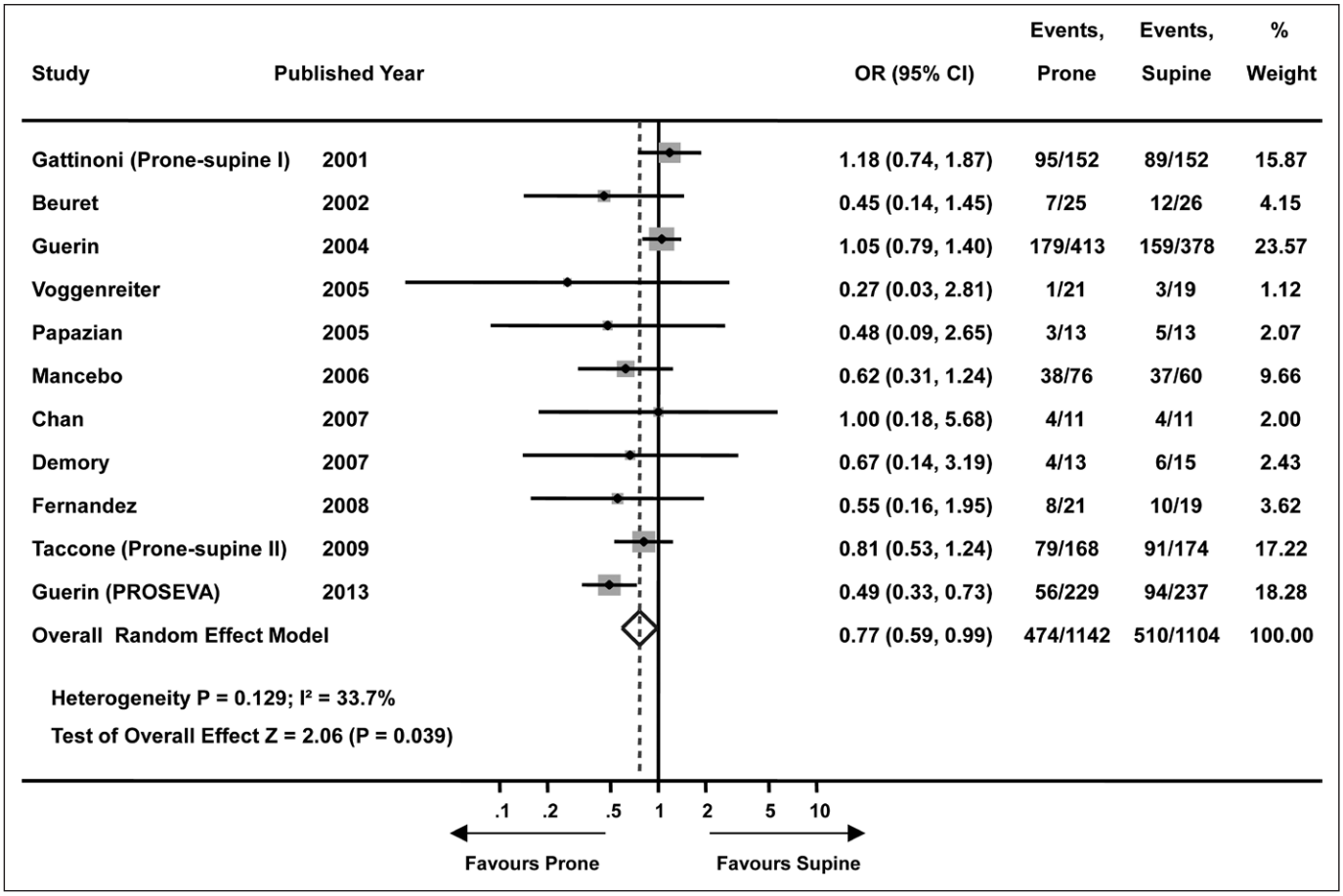

Figure 2. The effect of prone positioning on overall mortality by random-effects model. Forest plot with odds ratios (OR) for overall mortality associated with prone positioning (prone) versus supine positioning (supine) for individual trials and the pooled population. The *squares* and the *horizontal lines* indicate the ORs (by random-effects model) and the 95% CI for each trial included. The size of each square is proportional to the statistical weight of a trial in the meta-analysis. The *diamond* indicates the effect estimate derived from meta-analysis, with the center indicating the point estimate and the left and the right ends indicating the 95% CI.

compared with the wider spectrum of disease severity including both ALI and ARDS cases. The effect was also clearer in patients with a longer duration (≥ 10 hr/session) and in patients with concomitant usage of lung protective ventilation. Conversely, prone positioning showed significant associations with pressure ulcers and major airway problems.

This study included a larger number of RCTs than previous meta-analyses (8, 24, 25). Among those studies, seven were underpowered due to a sample size inadequate to detect potential differences in mortality ($n = 343$) (3, 4, 19–23). Four major trials (1, 2, 5, 9) ($n = 1{,}903$) were included in the analysis; however, two (1, 2) included patients with a wide range of disease severity (ALI and ARDS), no lung protective ventilation, and a relatively short duration of prone positioning (4–7 hr/session). Although the Prone-Supine II trial (5) included only patients with ARDS receiving lung protective ventilation and more than 18 hours of prone positioning, its results revealed a nonsignificant trend of mortality benefit of prone positioning up to 6 months (47.0% vs 52.3%; relative risk [RR], 0.90; 95% CI, 0.73–1.11; $p = 0.33$). It is noteworthy that patients were ventilated in the prone position for 51% of patient-days among those enrolled in the prone group of the Prone-Supine II trial. In addition, 12 patients (11.5%) in the supine group were ventilated in the prone position as a rescue maneuver. Both of these may account for the negative conclusions in the Prone-Supine II trial (5). Conversely, the recently published The Proning Severe ARDS Patients (PROSEVA) trial (9) enrolled patients with severe ARDS ($Pao_2/Fio_2 \leq 150$ mm Hg), and the intervention was more uniformly applied. They reported a significant reduction in 28-day and 90-day mortality from the prone position (hazard ratio [HR], 0.39; 95% CI, 0.25–0.63; $p < 0.001$ for 28-day mortality; HR, 0.44; 95% CI, 0.29–0.67; $p < 0.001$ for 90-day mortality). Possible explanations for the positive results of the PROSEVA trial are that it enrolled a more homogenous patient population with more severe ARDS and that it provided a longer duration of prone positioning with no crossover between the prone and supine groups. Previous meta-analyses showed a nonsignificant trend of mortality reduction in the overall pooled estimate; however, a significant reduction in mortality was observed in the subgroup of patients with the severest disease ($Pao_2/Fio_2 < 100$ mm Hg or patients with ARDS only) (8, 24). In addition, a recent meta-analysis by Abroug et al (24) explored a nonsignificant negative association between the duration of the prone position during ventilation and overall mortality in patients with acute respiratory failure. The current

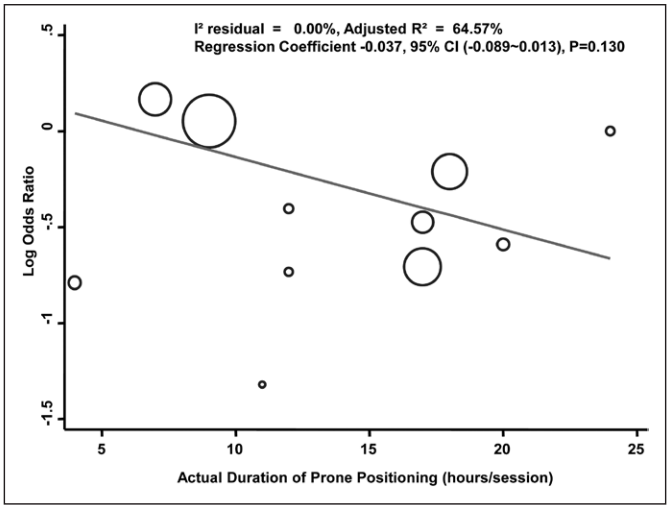

Figure 3. Meta-regression analysis of the effect of actual duration of prone positioning on overall mortality. Log odds ratio plotted according to actual duration of prone positioning (hr/session) with summary random-effects meta-regression. The strong but insignificant negative association between the actual duration of prone positioning and the overall mortality is observed (regression coefficient, −0.037; $p = 0.130$). Each trial included is represented by a *circle* proportional to its weight in the meta-analysis.

meta-analysis reinforces these results. The effects of the prone position were different according to the patient population (ALI/ARDS vs ARDS only) and duration of the prone position (short-term vs long-term) with significant interaction between the subgroups. These results might support the importance of judicious patient selection for prone positioning (Pao_2/Fio_2 ratio <150–200 mmHg) and the adequate application of prone positioning (≥ 10 hr/session). Alveolar recruitment during prone positioning, which is one of the potential beneficial mechanisms, is primarily dependent on the duration of this maneuver (24, 26). Our results of meta-regression did not reach statistical significance; however, we were able to observe a negative trend for overall mortality with a longer duration of prone positioning. The results of this study regarding the optimal duration of prone positioning remain theoretical; thus, further studies are warranted to determine the optimal duration.

Adverse Events

A significant increase in pressure ulcers and major airway problems occurred with prone positioning. Neither the prevalence of unplanned extubation nor selective intubation into the

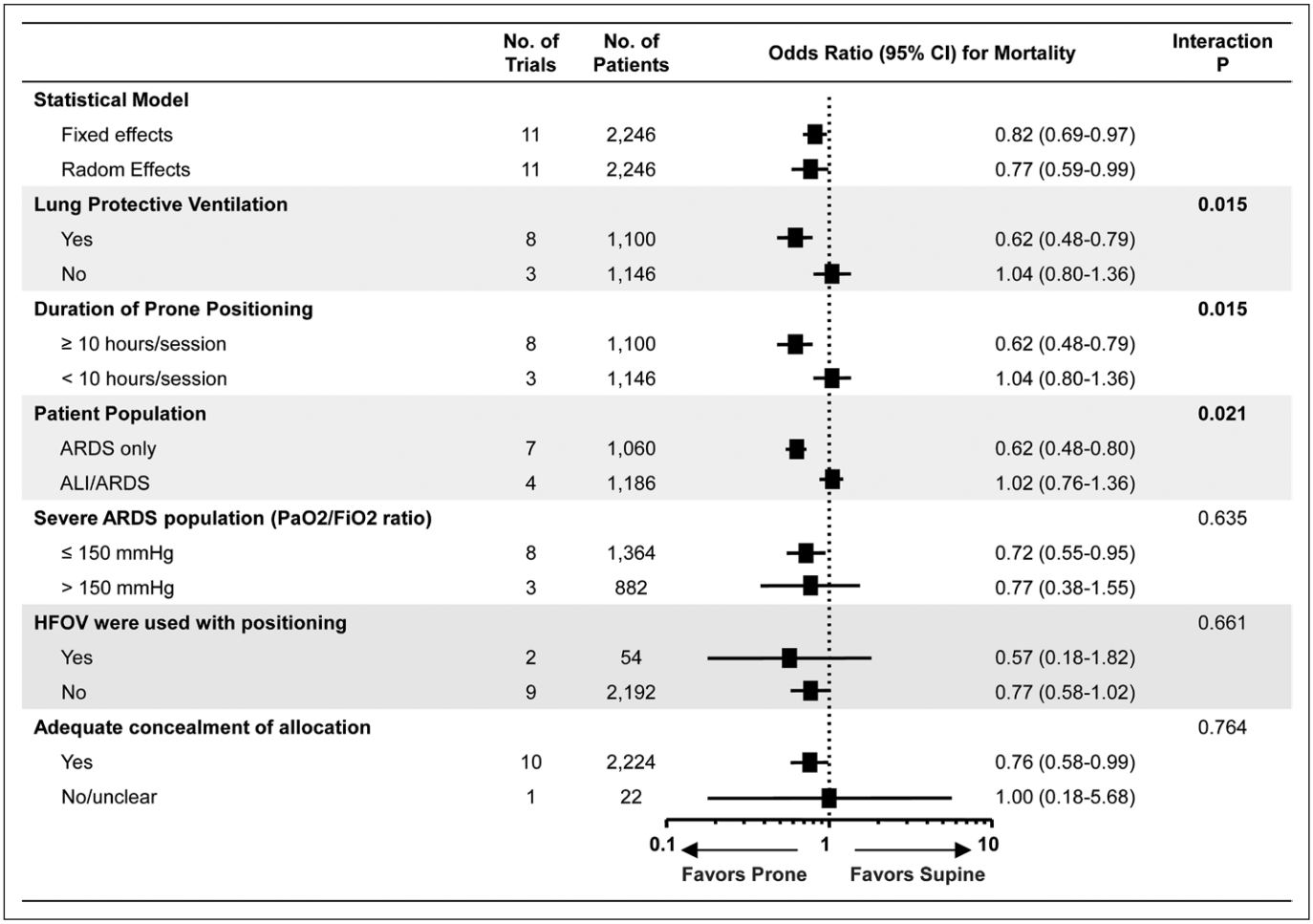

Figure 4. Stratified subgroup analyses according to the study protocols. The forest plot shows odds ratios (by random-effects model) for overall mortality associated with prone versus supine positioning with studies stratified according to 1) lung protective ventilation, 2) actual duration of prone positioning, 3) disease severity of patients, 4) Pao_2/Fio_2 ratio, 5) high-frequency oscillatory ventilation as a concomitant maneuver, and 6) adequacy of allocation concealment. The *squares* and the *horizontal lines* indicate the odd ratios (ORs) (by random-effects model) and the 95% CI for each trial included. The *dotted line* indicates the point of neutral effect for overall mortality (i.e., the point of random-effects model OR of 1.0). ARDS = acute respiratory distress syndrome, ALI = acute lung injury, HFOV = high-frequency oscillatory ventilation.

TABLE 2. Adverse Events Related to Prone Positioning

Adverse Events	No. of Trials Reporting the Outcome	Events/Prone	Events/Supine	Treatment Effect (Random-Effect Model)			Heterogeneity	
				OR (95% CI)	*p*	Number Needed to Treat/Number Needed to Harm	I^2 (%)	*p*
Ventilator-associated pneumonia	6	120/567	128/513	0.76 (0.44–1.33)	0.343	26	34.4	0.192
Pressure ulcers	6	294/698	218/646	1.49 (1.18–1.89)	0.001	12	0.0	0.617
Major airway problem[a]	9	255/1,104	180/1,063	1.55 (1.10–2.17)	0.012	16	32.7	0.167
Unplanned extubation	7	113/1,091	98/1,050	1.17 (0.80–1.73)	0.421	98	25.5	0.234
Selective intubation	2	12/642	5/615	2.73 (0.29–25.46)	0.378	95	55.9	0.132
Endotracheal tube obstruction	4	130/823	77/802	2.16 (1.53–3.05)	< 0.001	16	0.0	0.580
Loss of venous or arterial access	4	36/407	22/397	1.34 (0.29–6.26)	0.712	30	75.5	0.007
Thoracostomy tube dislodgement or kinking	4	14/407	14/397	1.14 (0.35–3.75)	0.827	1,154	42.6	0.175
Pneumothorax	4	29/513	33/462	0.77 (0.46–1.30)	0.333	67	0.0	0.528
Cardiac arrest	3	104/718	119/675	0.74 (0.47–1.17)	0.197	32	30.3	0.238
Tachyarrhythmia or bradyarrhythmia	3	115/663	102/634	1.08 (0.78–1.50)	0.643	80	8.8	0.334

OR = odds ratio.

[a]Unplanned extubation, selective intubation into the main bronchus, and endotracheal tube obstruction were included.

main bronchus differed between prone and supine positioning. However, the prevalence of endotracheal tube obstruction significantly increased with prone positioning; this result was similar to that of a study by Sud et al (8). Contrary to the findings of the Prone-Supine II trial, which reported a higher prevalence of adverse events in the prone position group (including increased sedation, transient desaturation or hypotension, and loss of venous access or thoracostomy tube), the more recent PROSEVA trial showed no significant difference between the two groups with regard to transient desaturation or hypotension. These discrepancies in adverse events might be due to different protocols for prone positioning among the various ICUs (8, 27). Together with the previous RCTs and meta-analyses, our findings suggest that prone positioning during ventilation can be harmful and is a complicated procedure that requires a coordinated, highly skilled team effort (28). Although our meta-analysis supports a significant reduction in overall mortality in patients with ARDS, the risk of adverse events should be carefully considered during the decision-making process, especially in ICUs with less experience in prone positioning.

Limitations

This meta-analysis included clinically and methodologically diverse studies. Although we included only RCTs for the final analysis and statistical heterogeneity was insignificant, there were some differences in the enrollment criteria and the target population of each study. Furthermore, different endpoint times were used for mortality evaluation (up to 180 d after admission). Because this study was a study-level meta-analysis, individual patient data were not included in the analysis; therefore, we could not adjust for patient-level confounders.

CONCLUSIONS

The use of prone positioning during mechanical ventilation for patients with acute hypoxemic respiratory failure resulted in a significant reduction of overall mortality. The effect of prone positioning was more obvious in patients with ARDS who underwent a longer duration of prone ventilation and lung protective ventilation strategy. The prevalence of pressure ulcers and major airway problems was significantly higher in the prone positioning group. Before using prone positioning, the risks and benefits for that particular patient with ARDS should be carefully weighed.

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