Early neuromuscular blockade for acute respiratory distress syndrome: a systematic review with meta-analysis and trial sequential analysis

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Research

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Abstract

Background To assess the effect of neuromuscular blockade on outcomes in adults with acute respiratory distress syndrome who are receiving mechanical ventilation.Methods We searched from inception to 24 may 2019 in MEDLINE, EMBASE and CENTRAL. We included randomized clinical trials comparing early neuromuscular blockade to placebo or usual care in adults with moderate to severe ARDS (PaO2/FiO2≦150mmHg). The primary outcome was 90-day and 28-day mortality. Secondary outcomes included oxygenation, driving pressure, incidence of barotrauma and pneumothorax, ventilator-free days at 28 days and ICU-acquired weakness by 28 days. In addition, a trial sequential analysis was performed.Results Four trials were included with a total of 1437 patients. For the primary outcomes, there was no effect of neuromuscular blocking agent (NMBA) on 90-day mortality [relative risk (RR) 0.91, 95%CI 0.72-1.15, p=0.41] or 28-day mortality [RR 0.55, 95%CI 0.22-1.12, p=0.08], or ventilator-free days at 28 days [mean difference (MD) 0.86, 95%CI -0.61-2.33, p=0.25]. NMBA improved PaO2/FiO2 at 72h [MD 15.21, 95%CI 1.90-28.52, p=0.03]. NMBA reduced the incidence of barotrauma [RR 0.55, 95%CI 0.35-0.85, p=0.007] and pneumothorax [RR 0.46, 95%CI 0.28-0.76, p=0.002] and increased the driving pressure at 24 hours [MD 0.75, 95%CI 0.24-1.26, p=0.004] and 48 hours [MD 0.75, 95%CI 0.08-1.43, p=0.03]. There is no statistically significant difference in ICU-acquired weakness by 28 days [RR 1.20, 95%CI 0.72-1.98, p=0.49].Conclusions In adults with moderate to severe ARDS treated with early neuromuscular blockade, oxygenation increase, incidence of barotrauma and pneumothorax are reduced, ICU-acquired weakness are not increased, but 90-day and 28-day mortality are not decreased. Further large-scale, multicenter studies are needed to confirm our results.Trial Registry PROSPERO (ID: CRD42019137832)

Background

Acute respiratory distress syndrome (ARDS) is a type of acute diffuse, inflammatory lung injury characterized by hypoxemia, decreased lung compliance and bilateral radiographic opacities [1]. Despite decades of research, efficient approaches for the treatment of ARDS are still limited [2]. Numerous pharmacological interventions have been associated with disappointing results [3–6]. Other treatment strategies, such as nitric oxide and corticosteroids, are able to improve clinical parameters, but they are not definitely associated with survival benefit [7, 8]. Supportive care with mechanical ventilation to maintain gas exchange remains the mainstay of management [9].

Intriguingly, early continuous neuromuscular blockade in ARDS patients who are receiving mechanical ventilation was shown to be able to decrease mortality [10]. However, neuromuscular blockade hasn’t been widely adopted and was weakly recommended in clinical practice guideline [11]. The main reason is that the clinical guideline was based on three trials originated from the same group of investigators in France [10, 12, 13]. Recently in United States, a larger-scale randomized controlled trial have been carried out to re-evaluate the therapeutic effects of early neuromuscular blockade in the management of ARDS [14]. According to the results, early neuromuscular blockade failed to decrease the mortality of ARDS patients at 90 days compared with usual care. Therefore, the benefit of adjunctive therapy with neuromuscular blocking agent (NMBA) in ARDS patients remains debatable.

To provide an updated summary of the evidence, a systematic review and meta-analysis with trial sequential analysis was conducted to assess the benefit and risk of NMBA in the management of moderate to severe ARDS patients compared to placebo or usual care.

Methods

The protocol for this study was published in the online PROSPERO database (CRD42019137832) prior to the analysis. The protocol is available at: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=137832

Search and eligibility criteria

We performed a search of electronic databases, Medline, EMBASE and the Cochrane Central Registry of Controlled Trials. All searches were conducted from inception through to May 24, 2019. The search terms are “acute respiratory distress syndrome”, “ARDS” AND “neuromuscular blocking agents”, “neuromuscular blockade”, “atracurium”, “cisatracurium”, “pancuronium”, “rocuronium”[15]. We searched for randomized clinical trials (RCTs) of adult patients with acute respiratory distress syndrome intubated in the first 48 hours and use of any NMBA in one arm of the study compared with another arm without NMBA (placebo or usual care). And at least one of the outcomes outlined below were reported. We applied no language restriction. We also conducted a manual search of reference lists of relevant primary studies and previous review articles. Additional articles or abstracts were retrieved by manually scrutinising the reference list of relevant publications.

Study selection

Figure 1 summarized the study selection process. Two authors (XCZ, XPX) independently screened abstracts for potentially eligible studies. Full-text reports were then assessed for eligibility. Disagreement during the review process was resolved by discussion with a third reviewer (XWG) and by consensus.

Data extraction

Two investigators (DKL, FFG) independently extracted information from each included trial. We extracted all available data as outlined in the protocol, including characteristics of the included studies, details of the population enrolled, details of the intervention including dose and regimen of NMBA and whether the comparison group received placebo or usual care. Driving pressure in the protocol that were not available in trial reports were calculated according to formula as follow.

$PEEP_{tot}$ = external PEEP + intrinsic PEEP

Driving pressure = P_{plat}-$PEEP_{tot}$

Risk of bias assessment

Two investigators (XCZ, XPX) independently assessed risk of bias of the included trials according to the Cochrane risk of bias tool. Disagreements were resolved by discussion with a third reviewer (XWG) and by consensus. We adjudicated risk of bias across all predefined outcome measures, and overall risk of bias was adjudicated low only if all domains were assessed as low risk of bias.

Outcomes

Our primary efficacy outcome was mortality at day 90 and day 28. Secondary outcomes were PaO2/FiO2 ratio at 24,48,72 hours, driving pressure at 24, 48 hours, incidence of barotrauma and pneumothorax, the ventilator-free days at 28 days and ICU-acquired weakness by 28 day after randomization.

Trial sequential analysis

In the present study, we performed the trial sequential analysis (TSA) to decrease the risks of random errors due to sparse data and calculate the optimal information size. In this TSA model, we estimated the required information size using$\alpha = 0.05$ (two-sided), $\beta = 0.20$ (power of 80%) for primary and selected secondary outcomes. For primary outcome, a 20% relative risk reduction (RRR) and the control event proportions calculated according to trials included were used to calculate the optimal information size. TSA was performed using the trial sequential analysis v.0.9.5.10 beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark, available from www.ctu.dk/tsa).

Grading the quality of evidence

In the present study, we used the Grades of Recommendation, Assessment, Development, and Evaluation (GRADEpro GDT https://gradepro.org/) [16] to evaluate the quality of evidence. And evidences were categorized as high, moderate, low, and very low according to the quality of design, limitations, inconsistencies, indirectness, imprecision, and possible publication bias.

Statistical analysis

We used Review Manager 5.3 to calculate risk ratio (RR) with 95% confidence intervals (95% CI) for dichotomous variables and mean difference (MD) with CI for continuous outcomes. We assessed for heterogeneity between studies by using χ^2 statistic and the I^2 statistic (> 30% indicating substantial heterogeneity). In cases of significant heterogeneity ($I^2 > 30\%$), a random-effects model was used; otherwise, a fixed-effects model was applied. We had too few studies to assess for publication bias by using a funnel plot or conventional statistical methods. We assessed statistical significance at $p < 0.05$.

Results

Search Results and Trial Characteristics

Through electronic searches and from reading the references of potentially relevant articles, we identified 880 publications (Fig. 1). 25 studies were retrieved for detailed evaluation. We included 4 trials [10, 12–14] (Table 1), which randomized a total of 1437 participants (NMBA, 724 [50.4%]; Control, 713 [49.6%]).

Table 1
Characteristics of the included patients

Trial	Gainner 2004	Forel 2006	ACURASYS Trial 2010	ROSE Trial 2019
Populations				
(1) Study center	4 ICUs in France	3 ICUs in France	20 ICUs in France	48 ICUs in America
(2) Total number of included patients (NMBA vs control)	56 (28 vs. 28)	36 (18 vs. 18)	339 (177vs. 162)	1006 (501 vs. 505)
(3) ARDS definition	American-European consensus	American-European consensus	American-European consensus	Berlin definition
(4) Criteria for moderate-to-severe ARDS	PaO_2/FiO_2 < 150 mmHg with PEEP ≥ 5 cm H2O	PaO_2/FiO_2 ≤ 200 mmHg with PEEP ≥ 5 cm H2O	PaO_2/FiO_2 < 150 mmHg with PEEP ≥ 5 cm H2O	PaO_2/FiO_2 < 150 mmHg with PEEP ≥ 8 cm H2O
(5) Age	60.6	56.5	58	55.8
Severity of illness at enrollment (mean ± SD, NMBA vs control)				
(1) PH	7.33 ± 0.10 vs. 7.35 ± 0.09	7.32 ± 0.14 vs. 7.35 ± 0.11	7.31 ± 0.10 vs. 7.32 ± 0.10	7.32 ± 0.10 vs. 7.32 ± 0.10
(2) PaO_2/FiO_2 (mmHg)	130 ± 34 vs. 119 ± 31	105 ± 22 vs. 125 ± 20	106 ± 36 vs. 115 ± 41	116.1 ± 38.3 vs. 115.8 ± 40.1
(3) PaCO2 (mmHg)	48.3 ± 9.0 vs. 47.4 ± 11.3	51.1 ± 9.9 vs. 47.2 ± 9.8	47 ± 11 vs. 47 ± 11	44.1 ± 10.2 vs. 43.8 ± 12.0
(4) SAPS II	43.6	48	48.5	NA
(5) SOFA	NA	NA	NA	8.7
(6) APACHE III	NA	NA	NA	104.4
Intervention				

NMBA, neuromuscular blocking agent; ARDS, acute respiratory distress syndrome; NA, not available; SAPS II, simplified acute physiology score II; SOFA, Sequential Organ Failure Assessment; APACHE III, acute physiology, age, and chronic health evaluation III

Trial	Gainner 2004	Forel 2006	ACURASYS Trial 2010	ROSE Trial 2019
NMBA group	A bolus of 50 mg cisatracurium followed by 5 μg.kg^{-1}.min^{-1} infusion for 48 h	A bolus of 0.2 mg/kg cisatracurium followed by 5 μg.kg^{-1}.min^{-1} infusion for 48 h	A bolus of 15 mg cisatracurium followed 37.5 mg/h for 48 h	A bolus of 15 mg cisatracurium followed 37.5 mg/h for 48 h
Control group	An infusion of saline at a rate of 4 ml/h	An infusion of saline at a rate of 4 ml/h	A bolus of 15 mg placebo followed 37.5 mg/h for 48 h	Usual treatment for control group
Sedation strategies in control group	Deep sedation	Deep sedation	Deep sedation	Light sedation
Outcomes				
(1) 90-d mortality (NMBA vs. Control (n/N))	NA	NA	56/177 vs. 66/162	213/501 vs. 216/505
(2) 28-d mortality (NMBA vs. Control (n/N))	10/28, 17/28	5/18, 10/18	42/177, 54/162	184/501, 187/505
Oxygenation (mean ± SD with (no), NMBA vs control)				
(1) PaO2/FiO2 at 24 hours (mmHg)	159 ± 48 (28), 145 ± 56 (28)	183 ± 73 (18), 146 ± 47 (18)	164 ± 72 (172), 168 ± 72 (159)	198.4 ± 77.7 (436), 189.2 ± 76.8 (408)
(2) PaO2/FiO2 at 48 hours (mmHg)	183 ± 88 (28), 139 ± 42 (27)	205 ± 73 (18), 152 ± 49 (18)	NA	198.0 ± 73.4 (381), 193.2 ± 79 (348)
(3) PaO2/FiO2 at 72 hours (mmHg)	196 ± 78 (27), 170 ± 65 (27)	239 ± 91 (18), 175 ± 62 (18)	166 ± 70 (167), 157 ± 68 (152)	197.8 ± 74.6 (330), 186.6 ± 75.6 (272)
Driving pressure (mean ± SD with (no), NMBA vs control)				

NMBA, neuromuscular blocking agent; ARDS, acute respiratory distress syndrome; NA, not available; SAPS II, simplified acute physiology score II; SOFA, Sequential Organ Failure Assessment; APACHE III, acute physiology, age, and chronic health evaluation III

Trial	Gainner 2004	Forel 2006	ACURASYS Trial 2010	ROSE Trial 2019
(1) Driving Pressure Baseline (cmH2O)	14.8 ± 5.4 (28), 14.6 ± 3.5 (28)	14.3 ± 3.8 (18), 13.8 ± 4.9 (18)	15.8 ± 4.5 (177), 15.2 ± 4.2 (162)	12.7 ± 5.8 (274), 13.1 ± 5.9 (266)
(2) Driving Pressure At 24 h (cmH2O)	14.6 ± 5.5 (28), 15 ± 4.1 (28)	13.6 ± 3.5 (18), 14.1 ± 4.2 (18)	13.6 ± 4.3 (172), 12.4 ± 4.4 (157)	12.8 ± 4.1 (382), 12.1 ± 4.6 (331)
(3) Driving Pressure At 48 h (cmH2O)	14.7 ± 6.3 (28), 13.6 ± 4.2 (28)	13.8 ± 4.2 (18), 14 ± 4.0 (18)	NA	13.4 ± 4.2 (348), 12.6 ± 5.0 (297)
Others				
(1) Barotrauma (NMBA vs. Control (n/N))	0/28, 1/28	0/18, 0/18	9/177, 19/162	20/501, 32/505
(2) Pneumothorax (NMBA vs. Control (n/N))	0/28, 1/28	0/18, 0/18	7/177, 19/162	14/501, 25/505
(3) Days free of ventilation at day 28 (mean ± SD with (no), NMBA vs control)	3.7 ± 7.2 (28), 1.7 ± 5.3 (28)	6.0 ± 8.6 (18), 5.4 ± 6.4 (18)	10.6 ± 9.7 (177), 8.5 ± 9.4 (162)	9.6 ± 10.4 (501), 9.9 ± 10.9 (505)
Adverse reaction				
ICU-acquired weakness by day 28 (NMBA vs. Control (n/N))	0/28, 0/28	1/18, 1/18	28/96, 25/77	22/47, 14/51

NMBA, neuromuscular blocking agent; ARDS, acute respiratory distress syndrome; NA, not available; SAPS II, simplified acute physiology score II; SOFA, Sequential Organ Failure Assessment; APACHE III, acute physiology, age, and chronic health evaluation III

The details of the included studies are provided in Table 1. The years of publication ranged from 2004 to 2019. The sample size varied from 36 to 1006 participants. Of the four included trials, all were multi-center trial and were from same group in France except one, which is from United States [14].

Risk of bias in included studies

Three trials (75%) were assessed as high risk of bias concerning blinding of participants and personnel. All four trials (100%) had low-risk of bias regarding sequence generation, allocation concealment, blinding of outcomes assessment, incomplete outcome data and selecting reporting (Fig. 2). Accordingly, only one trial was assessed as low risk of bias [10].

NMBA did not decrease 90-day or 28-day mortality in ARDS patients

Table 1 shows that 90-day mortality were reported in two trials [10, 14] and 28-day mortality were reported in four trials [10, 12–14]. Combining all trials demonstrated no statistically significant effect of NMBA on 90-day mortality, with a risk ratio (RR) of 0.91 (95%CI 0.72–1.15, I^2 = 57%, p = 0.41), based on data from 1345 participants in two trials. Likewise, no significant differences in 28-day mortality were found between the NMBA and control groups (RR 0.55, 95%CI 0.22–1.12, I^2 = 58%, p = 0.08) (Fig. 3), based on data from 1437 participants in four trials. Results were analysed using a random-effect model because heterogeneity was high. We graded the overall strength of the evidence as moderate (Additional file 2).

The results of TSA indicated the optimal information size was 3771 patients for 90-day mortality based on 20% RRR (from a baseline event rate of 40%) and more high-quality randomized control trials (RCTs) are needed, since z curve did not cross the general boundary line or any adjusted boundary line favoring the NMBA group or control group (Fig. 4A). The optimal information size was 6458 patients for 28-day mortality based on 20% RRR (from a baseline event rate of 35%). Likewise, more high-quality randomized control trials (RCTs) are needed (Fig. 4B).

NMBA improved PaO2/FiO2 ratio at 72 hours in ARDS patients

For oxygenation, there were four trials [10, 12–14] that reported PaO2/FiO2 ratio at 24 hours and 72 hours, and three trials [12–14] that reported PaO2/FiO2 ratio at 48 hours. The pooled MD for PaO2/FiO2 at 72 hours compared to the control was 15.21 (95%CI 1.90-28.52, I^2 = 36%, p = 0.03). We graded strength of the evidence as high (Additional file 2). NMBA did not improve PaO2/FiO2 ratio at 24 hours (MD 7.76, 95%CI -3.74-19.27, I^2 = 33%, p = 0.19) or 48 hours (MD 29.77, 95%CI -4.68-64.27, I^2 = 76%, p = 0.09) (Fig. 5). The results of TSA indicated the optimal information size was 1583 patients for PaO2/FiO2 ratio at 72 hours and more high-quality RCTs are needed. (Additional file 1: Figure S1)

The control group showed lower driving pressure compared with NMBA group at 24 hours and 48 hours in ARDS patients

For driving pressure, there were four trials [10, 12–14] that reported driving pressure at 24 hours, and three trials [12–14] that reported driving pressure at 48 hours. Results were analysed using a fixed-effect model because there were no statistically significant heterogeneity ($I^2 = 0$). There are no significant difference in driving pressure at baseline between groups (MD 0.18, 95%CI -0.46-0.81, $p = 0.59$). Amazingly, the results showed lower driving pressure in the control group compared with NMBA group at 24 hours (MD 0.75, 95%CI 0.24–1.26, $p = 0.004$) and 48 hours (MD 0.75, 95%CI 0.08–1.43, $p = 0.03$) (Fig. 6). We graded the overall strength of the evidence as high (Additional file 2). The results of TSA indicated the cumulative z curve crossed both the conventional boundary for benefit and adjusted boundary line favoring the control group. Thus, further trials were not required and were unlikely to alter the conclusions (Additional file 1: Figure S2).

NMBA decrease the incidence of barotrauma and pneumothorax in patients with ARDS

The RR estimate for the incidence of barotrauma in patients treated with NMBA compared with control group was 0.55 (95%CI 0.35–0.85, $p = 0.007$). Moreover, the RR estimate for the incidence of pneumothorax in patients treated with NMBA compared with control group was 0.46 (95%CI 0.28–0.76, $p = 0.002$) (Fig. 7). We graded the overall strength of the evidence as high (Additional file 2). The results of TSA indicated the cumulative z curve crossed both the conventional boundary for benefit and adjusted boundary line favoring the NMBA group. Thus, further trials were not required and were unlikely to alter the conclusions (Additional file 1: Figure S3).

NMBA did not decrease the ventilator-free days at 28 days in ARDS patients

Four studies [10, 12–14] included 1437 patients provided data on ventilator-free days at 28 days. No significant differences in ventilator-free days were found between the NMBA and control groups (MD 0.86, 95%CI -0.61-2.33, $I^2 = 34\%$, $p = 0.25$) (Fig. 8). We graded the overall strength of the evidence as moderate (Additional file 2).

NMBA did not increase ICU-acquired weakness by 28 days in ARDS patients

When pooled together, the four studies [10, 12–14] included 363 patients and showed there are no statistically significant difference between NMBA and control groups (RR 1.20, 95%CI 0.72–1.98, $I^2 = 38\%$, $p = 0.49$) (Fig. 9). We graded the overall strength of the evidence as moderate (Additional file 2). The results of TSA indicated the optimal information size was 2083 patients for ICU-acquired weakness by 28 days based on 20% RRR (from a baseline event rate of 30%) and more high-quality randomized control

trials (RCTs) are needed, since z curve did not cross the general boundary line or any adjusted boundary line favoring the NMBA group or control group. (Additional file 1: Figure S4)

Discussion

The results of this systematic review and meta-analysis provide an evidence summary to inform clinicians regarding decisions to early use NMBA in moderate to severe ARDS patients. We found that assignment to treatment with NMBA did not decrease 90-day or 28-day mortality. Although improved oxygenation and lower incidence of barotrauma and pneumothorax in NMBA group, ventilator-free days at 28 days were not increased in patients assigned to NMBA. Significantly, NMBA exposure has no correlation with the increased incidence of ICU-acquired weakness in ARDS patients. Of note, the NMBA group exhibits higher driving pressure compared with control group, which might negate the potential benefits of NMBA.

The mechanisms underlying the therapeutic effects of NMBA in ARDS remain unclear. Previous systematic review demonstrate that early use of NMBA can improve oxygenation [17]. As shown in this meta-analysis, early use of NMBA indeed improve PaO2/FiO2 ratio at 72 hours in ARDS patients, which is consistent with the current evidence [17]. However, we did not find survival benefit of early NMBA for ARDS even if PaO2/FiO2 ratio was improved. It should be noted that the improved oxygenation is not necessarily correlated with improved survival. Furthermore, it is always important to remember to exercise caution with regarding oxygenation as a meaningful outcome variable in ARDS [18].

Another probable mechanism underlying the therapeutic effects of NMBA in ARDS is that early use of NMBA reduce ventilator dyssynchrony in ARDS patients [19, 20]. Since major concern in mechanically ventilated patients is the risk of ventilator-induced lung injury [21]. Especially, spontaneous ventilation superimposed on mechanical ventilation may result in a high respiratory drive and breathe with large tidal volumes, which may worsen lung injury including barotrauma [22, 23]. The results of this study also indicate that early use of NMBA in ARDS patients decrease the incidence of barotrauma and pneumothorax when compared with usual care. Notably, dyssynchrony and spontaneous respiratory efforts during the treatment of NMBA on ARDS were not monitored formally in our included trials. Consequently, we have also explored the association of prognosis with possible physiological “markers” that identify risk of injury, such as the driving pressure [24]. The most striking result to emerge from the data is that the control group shows lower driving pressure compared with NMBA group, which means the control group is associated with increased survival thereby confounding the impact of the intervention. Thus, in our view, the 90-day or 28-day mortality should be adjusted for driving pressure at 48 hour to exclude the effect of driving pressure on mortality. Nevertheless, Guervilly et al [25] reported that there was no change in driving pressure related to NMBA administration. The conflicting results might be due to the limited number of included patients in Guervilly’s study.

Intriguingly, experimental studies demonstrate that the beneficial effects of NMBA can largely be attributed to the result of modulation of inflammation and injury or even unexplored mechanisms instead

of its impact on respiratory muscle pump inactivation [26]. Besides, NMBA attenuate endothelial and epithelial injury merely in patients with a PaO2/FiO2 ratio ≤ 120 mmHg and ventilated with low tidal volumes [27]. Given the lack of effect on mortality of very potent anti-inflammatory agents in previous studies [4, 5, 28], this seems unlikely to be ultimate mechanism.

Benefits of NMBA use in ARDS patients must be weighed against potential harms [29]. The most concerning side-effect of neuromuscular blockade is the ICU acquired weakness [30]. Consistent with previous meta-analysis studies [31, 32], no evidence for ICU acquired weakness were found in the present study. Risk for ICU acquired weakness is increased with prolonged mechanical ventilation [33]. Here, our results showed that early use of NMBA did not lead to longer ventilation duration of ARDS patients, possibly due to short duration of blockade (48 hours). Although there is limited evidence of NMBA for efficacy beyond short-term physiologic improvement, web survey shows that clinicians are seeking to optimize the use of NMBA in ARDS, including types, dosing, duration [34]. It has been reported that paralysis can be continued beyond 48 hours without increasing the overall mortality [35], while whether longer or shorter infusions of NMBA would provide additional benefit or change the prevalence of ICU-acquired weakness is unknown. Moreover, when compared with vecuronium [36] or atracurium [37], cisatracurium, used in all of our included trials, was not associated with a difference in mortality, which suggest that those short-term positive outcomes were not cisatracurium-specific. Thus, a more economical selection of neuromuscular blocking agents in clinical settings should be considered in future.

Taken together, even though the evidences supporting NMBA use in ARDS patients remains relatively sparse, our meta-analysis are able to generate hypotheses that may be tested in future investigation. In the view of ventilator dyssynchrony, neuromuscular blockade should be titrated to ventilator synchrony instead of train of four monitoring, which is not correlate with gas exchange in patients with ARDS [38]. On the one hand, robust parameter are required to be sensitive to the occurrence of patient-ventilator dyssynchrony. On the other hand, maybe clinicians should use NMBA in ARDS patient according to the density or intensity of ventilator dyssynchrony especially those ARDS patients with high respiratory drive instead of severity of illness (PaO2/FiO2 ≤ 150 mmHg).

Several limitations of the present study should be concerned. Firstly, not all trials reported data on every outcome of interest. Secondly, the trials included a span of 15 years in which ICU practices have changed in the management of ARDS. For instance, the sedation targets used in the control group of ROSE trial [14] were lighter than those used in the ACURASYS trial [10]. Finally, as with all meta-analyses, the strength of conclusions that can be drawn are dependent on the strength of the included trials.

Conclusions

Based on the current available data, neuromuscular blockade in moderate to severe ARDS did not decrease 90-day or 28-day mortality. Although improved oxygenation and lower incidence of barotrauma and pneumothorax in NMBA group, ventilator-free days at 28 days were not increased in patients

assigned to NMBA. Fortunately, the use of NMBA was not associated with increased incidence of ICU-acquired weakness. Further large-scale, multicenter studies are needed to confirm our results.

Declarations

Ethics approval and consent to participate

Each enrolled trial was approved by the corresponding institutional ethical committee, and all participants provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

X.P.X and X.W.G had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. X.C.Z. contributed to study design; completed the literature search, data collection, data analysis, and data interpretation; and drafted the first version of the manuscript. D.K.L and F.F.G contributed substantially to the study design, data collection, data analysis and interpretation, and revised the manuscript.

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Abbreviations

NMBA

neuromuscular blocking agent; RR:relative risk; MD:mean difference; ARDS:acute respiratory distress syndrome; RCTs:randomized clinical trials; TSA:trial sequential analysis; RRR:relative risk reduction; CI:confidence intervals

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Figures

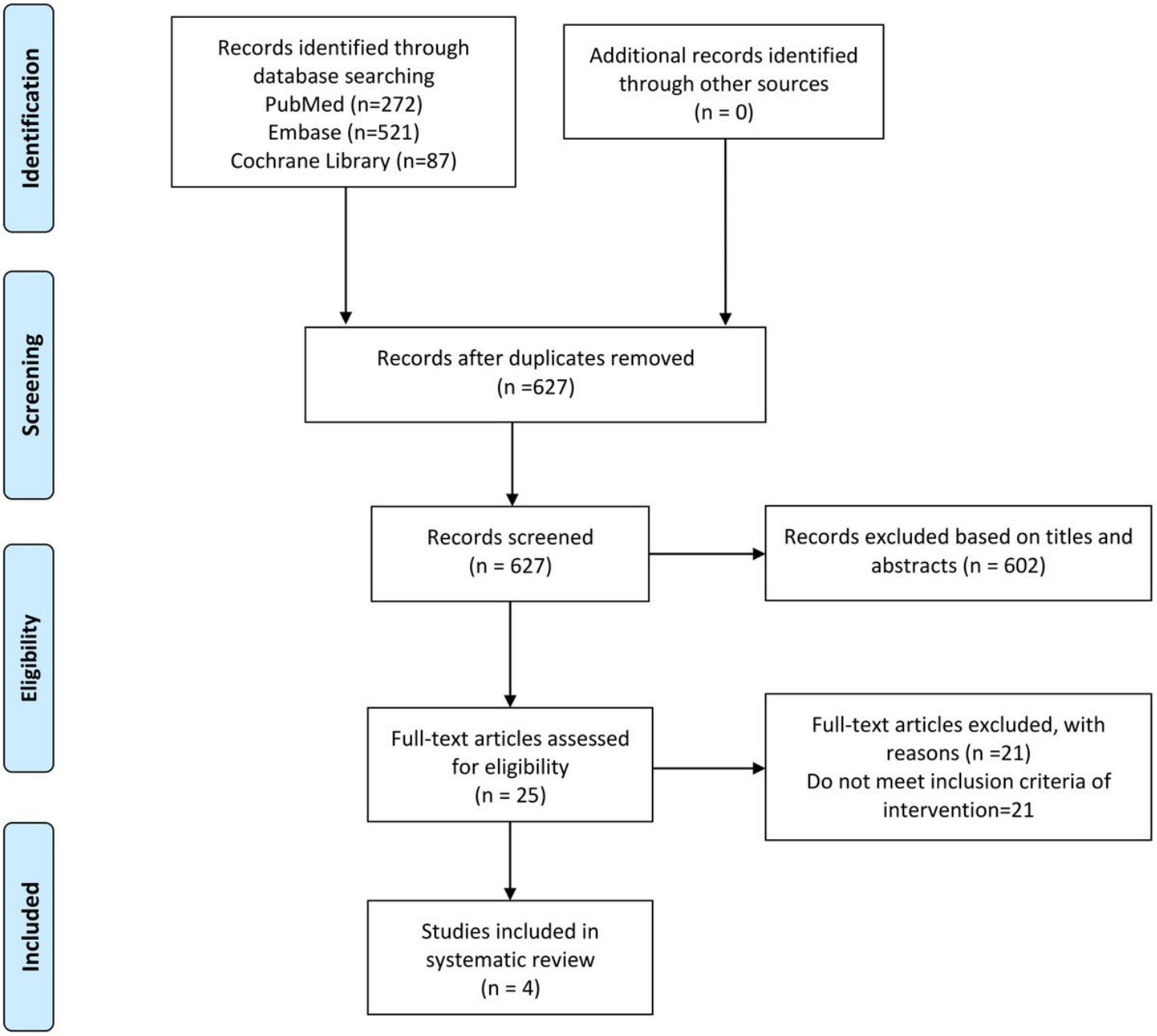

Figure 1

Flow diagram (PRISMA) of trial selection.

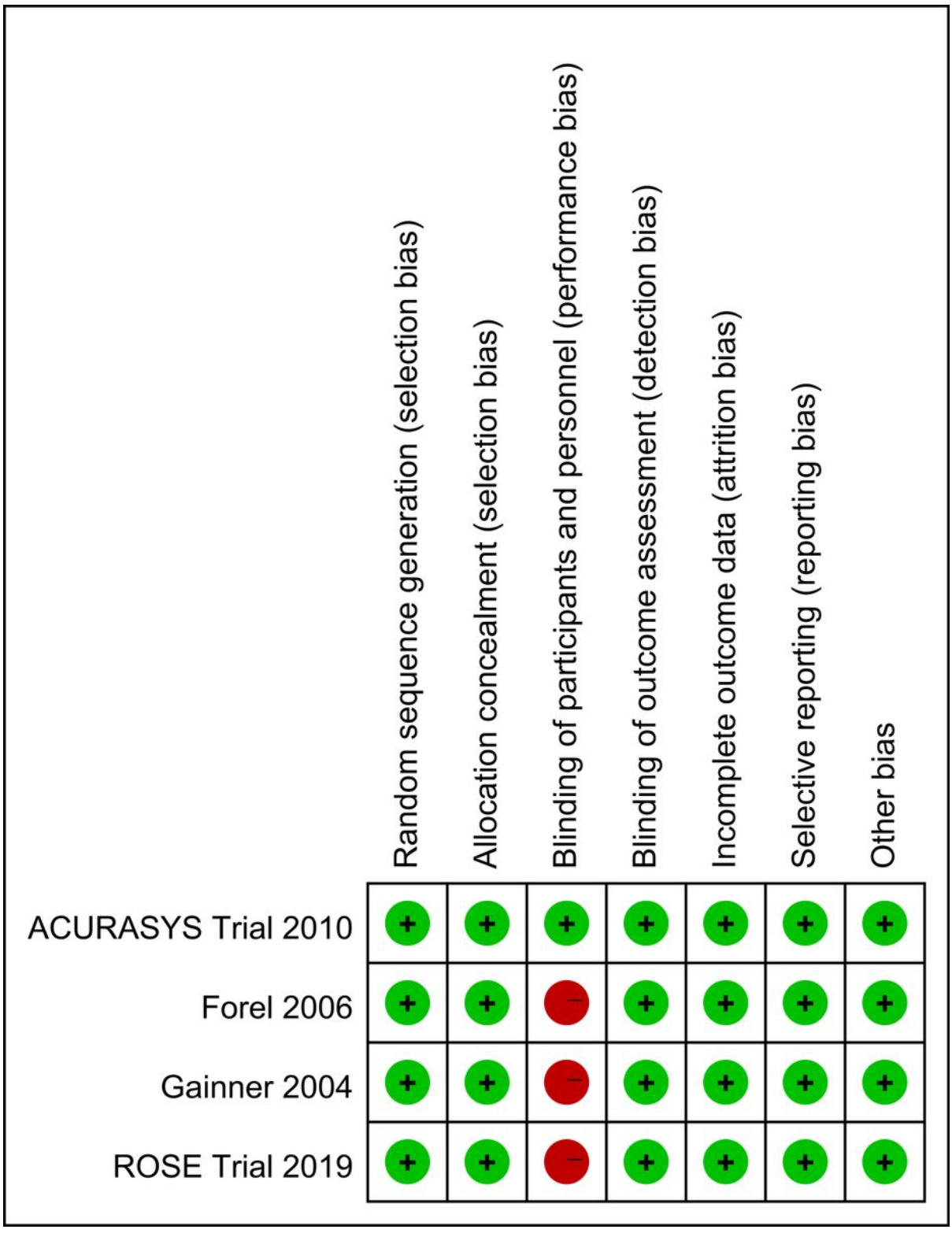

Figure 2

Risk of bias summary for each included study. Red (-): high risk of bias; Green (+): low risk of bias.

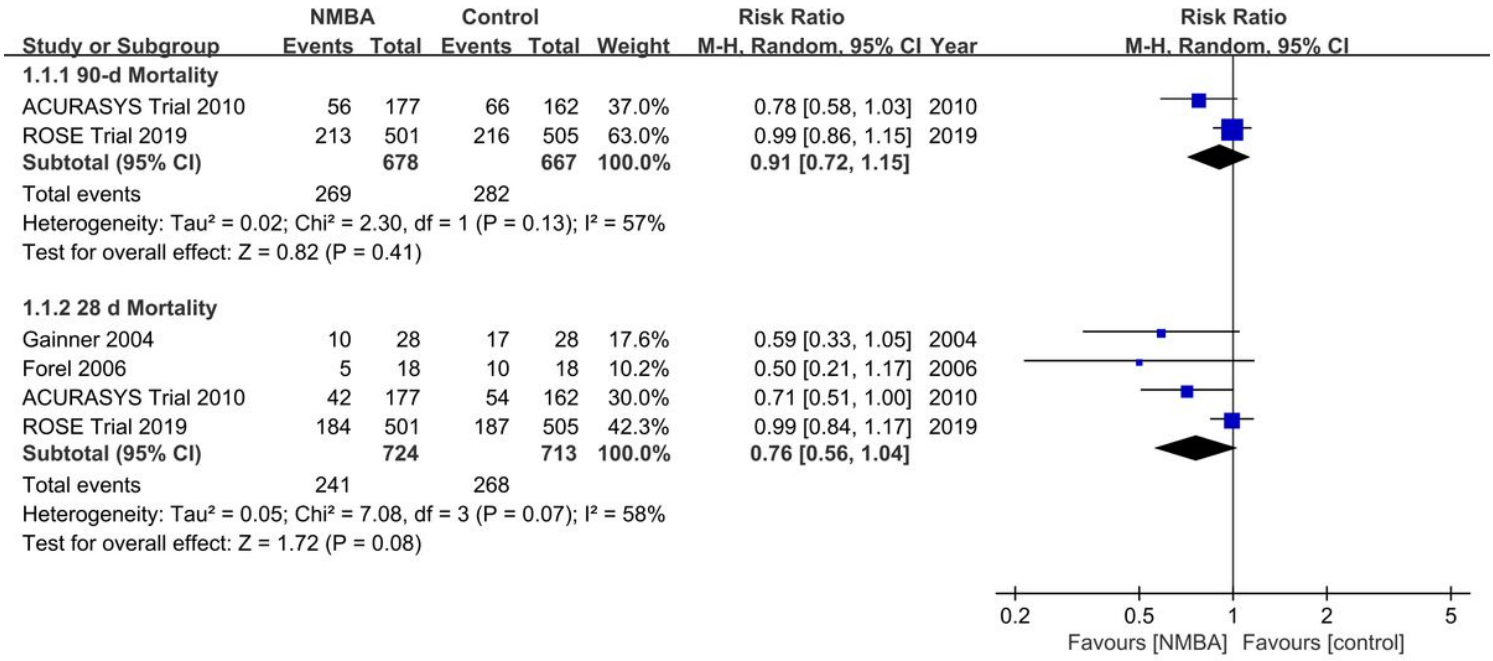

Figure 3

Meta-analysis of the effect of NMBA on mortality at day 90 and day 28 in ARDS patients. M-H = Mantel-Haenszel.

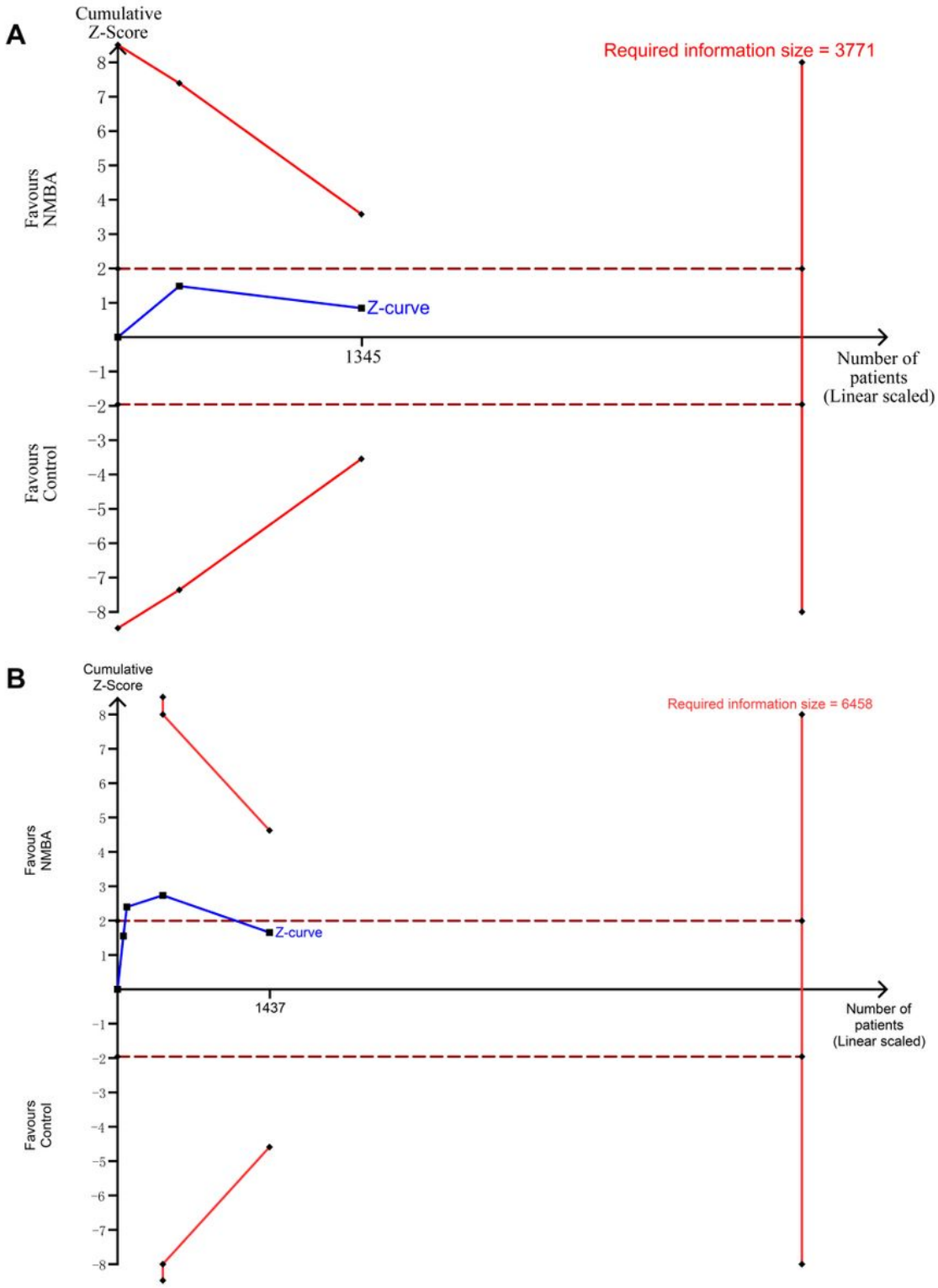

Figure 4

Trial sequential analysis for effects of NMBA on 90-day mortality (A) and 28-day mortality (B). A: The diversity-adjusted required information size (3771 participants) was based on a relative risk reduction of 20%, an alpha of 5%, a beta of 20%, and an event proportion of 40% in the control arm. The blue cumulative z curve was constructed using a random effects model. B: The diversity-adjusted required information size (6458 participants) was based on a relative risk reduction of 20%, an alpha of 5%, a beta

of 20%, and an event proportion of 35% in the control arm. The blue cumulative z curve was constructed using a random effects model.

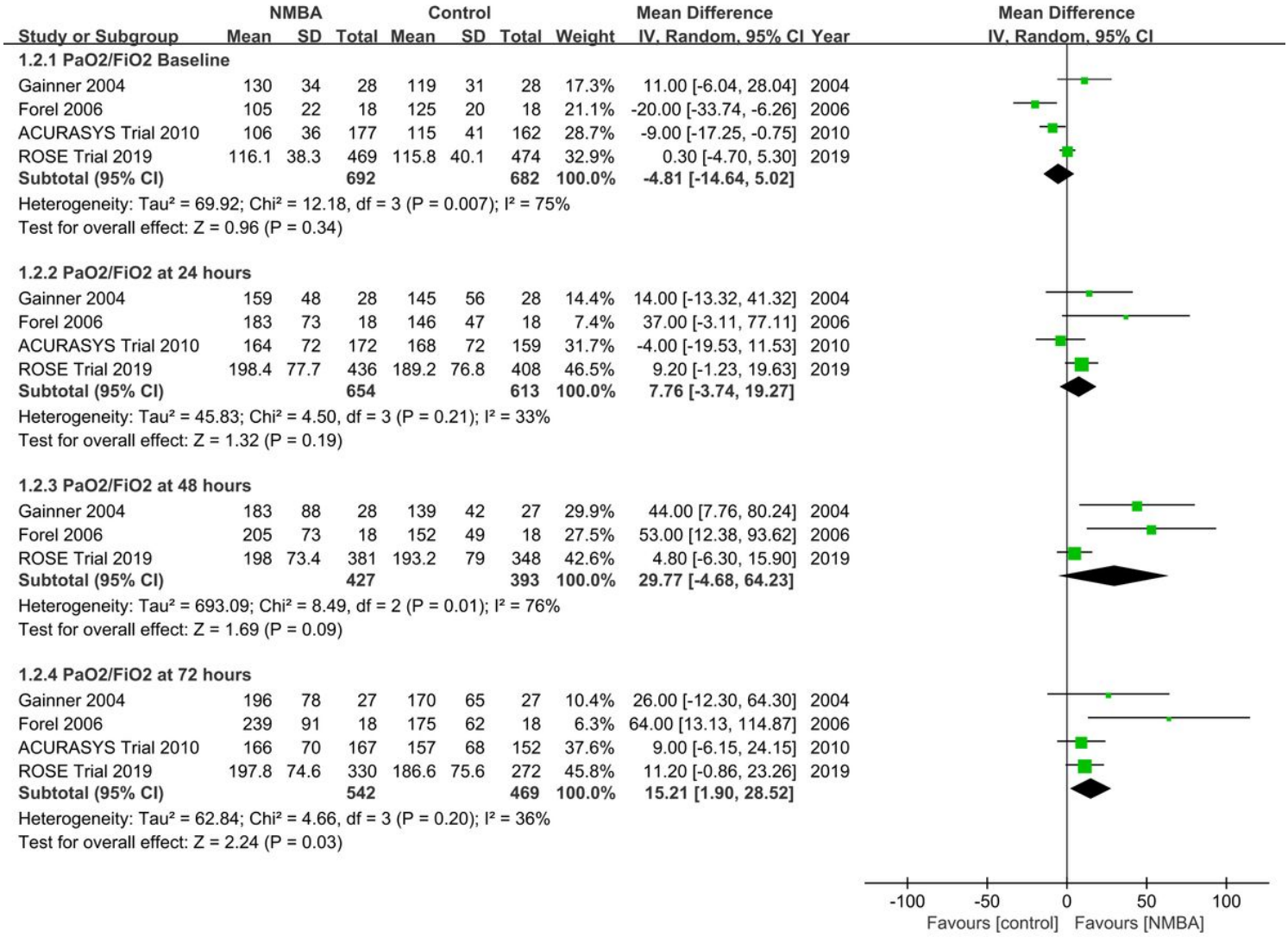

Figure 5

Meta-analysis of the effect of NMBA on PaO2/FiO2 at 24, 48 and 72 hours after randomization in ARDS patients. IV=Inverse Variance.

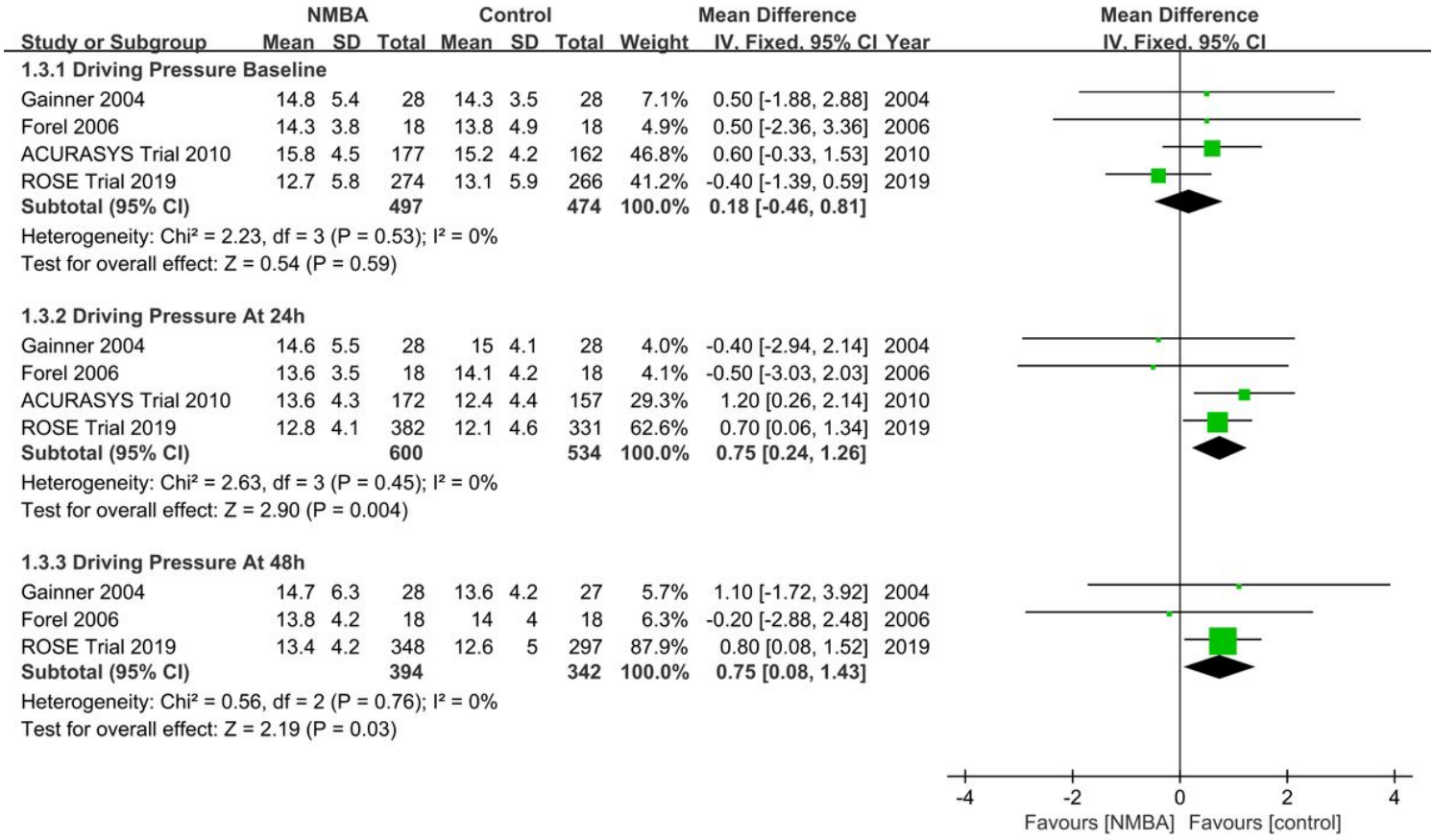

Figure 6

Meta-analysis of the effect of NMBA on driving pressure at 24 and 48 hours after randomization in ARDS patients. IV=Inverse Variance.

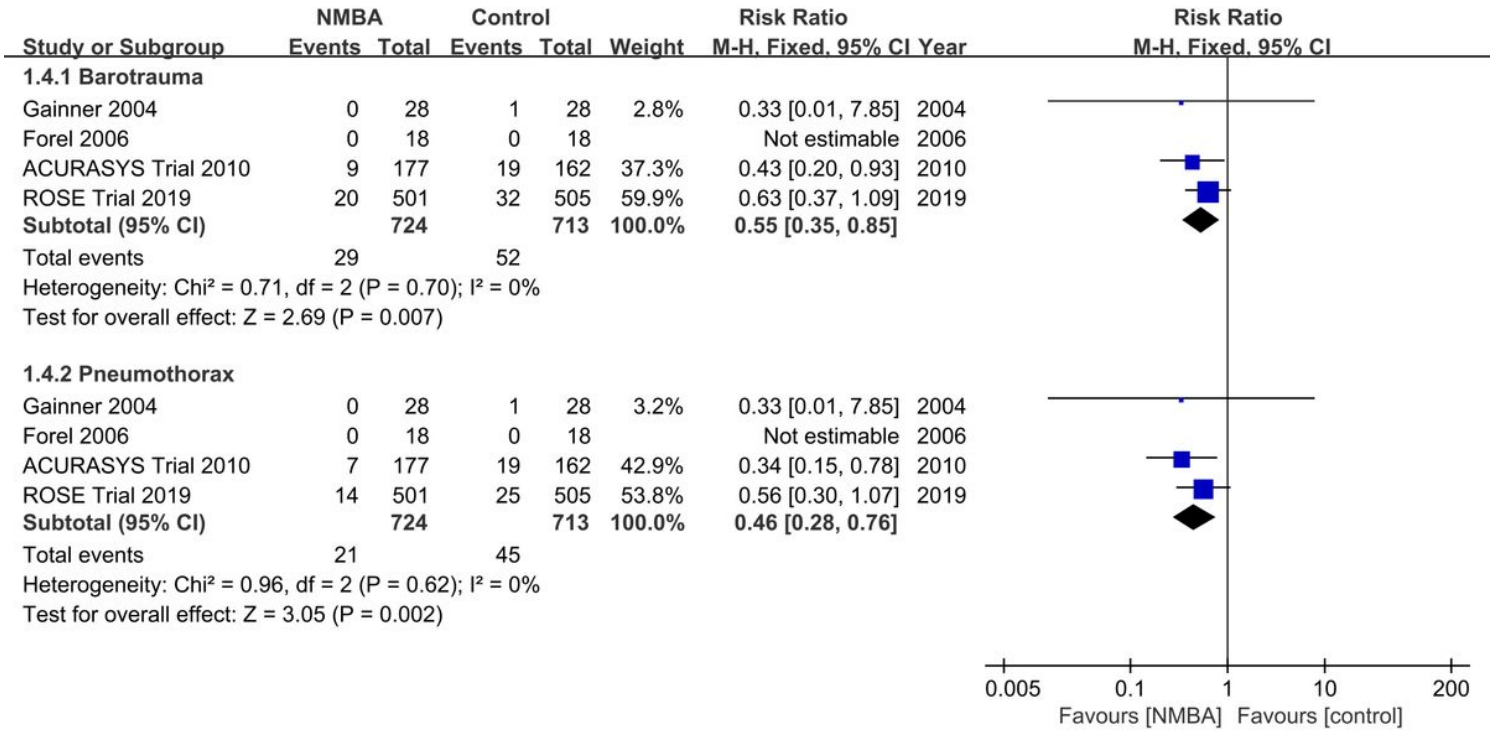

Figure 7

Meta-analysis of the effect of NMBA on the incidence of barotrauma and pneumothorax in ARDS patients. M-H = Mantel-Haenszel.

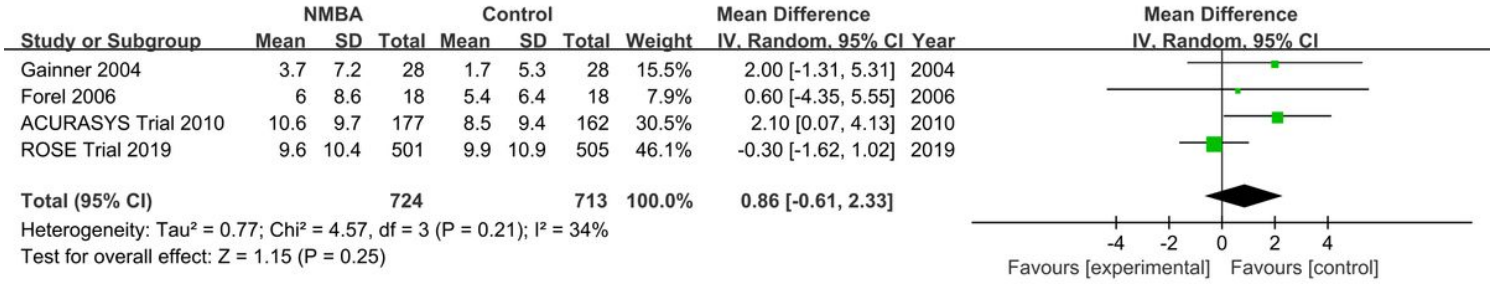

Figure 8

Meta-analysis of the effect of NMBA on the ventilator-free days at 28 days after randomization in ARDS patients. IV=Inverse Variance.

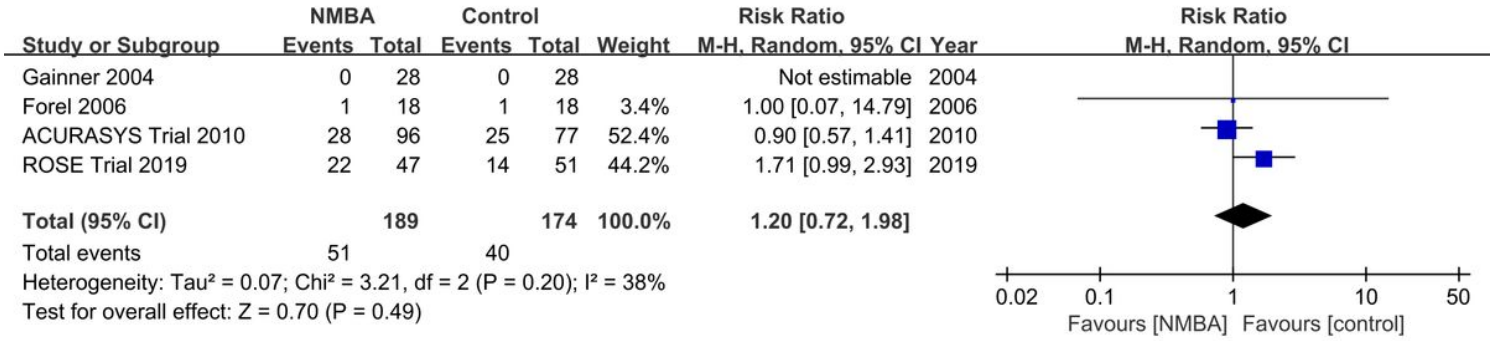

Figure 9

Meta-analysis of the effect of NMBA on ICU-acquired weakness in ARDS patients. M-H = Mantel-Haenszel.

Supplementary Files

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- Additionalfile2TableS1GRADEevidenceprofile.docx
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