SYSTEMATIC REVIEW

Effect of prone positioning on survival in adult patients receiving venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis

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Abstract

Purpose: Previous studies support the potential efficacy of venovenous extracorporeal membrane oxygenation (vvECMO) for improving survival in severe acute respiratory distress syndrome (ARDS) cases. Prone positioning (PP) has been shown to improve the outcomes of moderate-to-severe ARDS patients. Few studies and no randomized controlled trials have evaluated the effect of PP performed in ECMO patients.

Methods: We performed a systematic review and meta-analysis examining the effect of prone positioning for ARDS patients receiving vvECMO on survival. All authors were contacted to obtain complementary information not mentioned in the original articles. The main objective was to compare 28-day survival in vvECMO patients with PP to vvECMO patients without PP (controls).

Results: Thirteen studies with a combined population of 1836 patients satisfied the inclusion criteria. PP was associated with a significant improvement in 28-day survival (503 survivors among 681 patients in the PP group [74%; 95% CI 71–77] vs. 450 survivors among 770 patients in the control group [58%, 95% CI 55–62]; RR 1.31 [95% CI 1.21–1.41]; I^2 22% [95% CI 0–62%]; $P < 0.0001$). Survival was also improved in terms of other endpoints (60-day survival, 90-day survival, ICU survival, and hospital survival). In contrast, the duration of mechanical ventilation was increased in vvECMO patients with PP (mean difference 11.4 days [95% CI 9.2–13.5]; 0.64 [95% CI 0.50–0.78]; I^2 8%; $P < 0.0001$).

Conclusion: According to this meta-analysis, survival was improved when prone positioning was used in ARDS patients receiving vvECMO. The impact of this combination on survival should be investigated in prospective randomized controlled trials.

Keywords: Mortality, ARDS, Meta-analysis, ECMO, Prone positioning

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Introduction

Acute respiratory distress syndrome (ARDS) is among the primary causes of intensive care unit (ICU) admission for adult patients. The current coronavirus disease 2019 (COVID-19) pandemic has further highlighted the importance of understanding the best approach to support respiratory function for patients with severe respiratory failure. Venovenous extracorporeal membrane oxygenation (ECMO) is used in patients with severe ARDS to facilitate gas exchange in the setting of profound hypoxemia and to reduce the intensity of mechanical ventilation. Two randomized controlled trials [1, 2] and a recent meta-analysis [3] support the potential efficacy of venovenous ECMO (vvECMO) for severe ARDS in improving survival. Since the results of the PROSEVA study [4], prone positioning (PP) has been considered a strategy to improve the outcomes of ARDS patients with a partial pressure of arterial oxygen to the fractional concentration of oxygen in inspired air (PaO_2/FiO_2) of less than 150 mmHg. Due to organizational issues and a lack of experience and appropriate medical literature, PP is generally not applied to ECMO patients. However, a rationale for the use of this adjunctive therapy in these patients has been proposed (derecruitment of the dependent part of the lungs related to a positive fluid balance, immobilization, a decreased tidal volume, and limited PEEP levels). A few years ago, some reports indicated that PP in patients receiving ECMO was safe and improved gas exchange [5–7]). More recently, PP has been suggested to be associated with an improved survival rate when applied to ARDS patients receiving ECMO [8–10]. In the absence of randomized controlled trials, we sought to perform a systematic review and meta-analysis examining the effect of prone positioning on survival in ARDS patients receiving ECMO.

Methods

Protocol and registration

The protocol of this study was preregistered on PROSPERO (CRD42021262598). This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines (Table S1).

Search strategy and selection criteria

The MEDLINE via PubMed (including In-Process and Epub ahead of print) and Embase databases and the Cochrane Central Register of Controlled Trials database were systematically searched without language restrictions or period limitations. Trial registries including ClinicalTrials.gov were also considered to identify completed and ongoing trials. The electronic search for relevant theoretical references was carried out in April 2021 (more

Take-home message

Thirteen studies with a combined population of 1836 patients were included in a meta-analysis. Use of prone positioning in acute respiratory distress syndrome (ARDS) patients receiving venovenous extracorporeal membrane oxygenation (ECMO) was associated with a significant improvement in 28-day survival (74 vs 58%, $P < 0.001$). Survival was also improved regarding other endpoints (60- and 90-day, ICU and hospital). Duration of mechanical ventilation was increased in venovenous ECMO patients who were proned.

recent publications were considered until September 2021). We searched for cohort studies and randomized controlled trials including adult ARDS patients receiving vvECMO, some of whom were positioned prone during vvECMO (only studies allowing comparisons of patients under ECMO submitted to PP and ECMO patients not turned prone during ECMO). Studies including patients receiving vvECMO without PP during the ECMO period, studies including patients receiving vvECMO with PP prior to the ECMO period but not during ECMO, and studies including patients submitted only to PP and not receiving ECMO were not considered. We searched for studies referring to adults and the following subject terms: ["ECMO (extracorporeal membrane oxygenation)" OR "extracorporeal oxygenation"] AND "prone position" In Abstract AND/OR Title AND/OR keywords.

We included randomized controlled trials and observational studies in which patients undergoing invasive mechanical ventilation plus prone positioning during vvECMO were compared with patients submitted to invasive mechanical ventilation plus vvECMO without prone positioning following cannulation. We excluded studies focusing on venoarterial ECMO and those in which the use of extracorporeal CO_2 removal was assessed. All authors were contacted to obtain complementary information not mentioned in the original articles regarding mortality at different time points, the duration of mechanical ventilation, and ventilator-free days (VFD) to day 28.

Data extraction

Article selection was first performed by two independent reviewers based on titles and abstracts. They then independently reviewed the full texts of studies that appeared potentially relevant to determine their eligibility for inclusion. Data extraction was also performed by the two independent reviewers with the use of a data collection form. Disagreements were resolved by a third reviewer who had the deciding vote. General and specific characteristics were obtained, including the year of publication, country, study design, the number of patients, age, disease severity, the duration of mechanical ventilation,

ventilator-free days, and mortality. If needed, the researchers were contacted to obtain additional results (survival at different timepoints, the duration of mechanical ventilation, VFD to day 28).

Quality assessment

A quality assessment was performed by two independent reviewers at both the individual study level and outcome level. The Newcastle–Ottawa Scale (NOS) was used to assess the risk of bias in each included study [11]. The NOS explores the following domains: selection of the cohort, comparability of exposed and non-exposed participants and the methods for the assessment of outcomes. Studies are then rated as good-, fair-, and poor-quality research. The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) tool was used to assess the overall quality of evidence for each outcome [12]. This tool specifies four levels of certainty (high, moderate, low, and very low) depending on the design of the included studies, the risk of bias, inconsistencies in the results, the indirectness of the evidence, imprecise results, publication bias, large effects, dose–response relationships, and all plausible confounding factors and biases. Disagreements regarding the Newcastle–Ottawa Scale and GRADE assessments were resolved by discussion.

Data analysis

The primary outcome was 28-day survival. Other outcomes included hospital survival, 60-day survival, 90-day survival, ICU survival, ventilator-free days to day 28, the duration of mechanical ventilation, and in-ICU adverse events related to PP. Only exact information was used for each evaluation. As an example, no extrapolation from 90-day survival was implemented to include a study in the hospital survival assessment. Information not provided in the original articles was obtained from the authors (Fig. S1).

Outcomes were pooled using a random-effects model with the inverse variance method [13] to account for statistical heterogeneity among studies, and were summarized as risk ratio (RR) and mean differences (MDs) with their respective 95% confidence intervals (95% CIs). Between-study heterogeneity was measured using I^2 statistics (values < 25% indicate low heterogeneity; 25–75%, moderate heterogeneity; and > 75%, considerable heterogeneity), the τ^2 with the restricted maximum-likelihood estimator, and P values using the Cochran Q statistic [14, 15].

Sensitivity analyses were performed by serially excluding each study to determine the implications of individual studies for the pooled estimates [16].

We considered several a priori subgroup analyses for survival regarding ARDS aetiology (COVID-19 ARDS vs. non-COVID-19 ARDS) and study design (prospective vs. retrospective; monocentre vs. multicentre). An additional analysis was conducted including studies using a matching procedure to compare proned and non-proned patients [17, 18]. Subgroup analyses were performed using a mixed-effects model [19].

Potential publication bias was assessed by visual inspection of funnel plots, and plot asymmetry was considered suggestive of a reporting bias [20]. Plot asymmetry was tested using Egger's test based on a weighted linear regression of the treatment effect on its standard error [21].

All analyses were performed using R statistical software version 4.1.1 [22] with the 'meta' package [23]. All significance tests were two-tailed, with $P < 0.05$ considered statistically significant.

Role of the funding source

This study had no funding source. The corresponding author had full access to all study data and had the final responsibility for the decision to submit this article for publication.

Results

Study characteristics

The electronic search recovered 377 citations, 34 of which were selected for full-text assessment (Fig. 1). Thirteen studies with a combined population of 1836 patients satisfied the inclusion criteria, including one randomized controlled trial [1] and 12 observational studies [8–10, 24–32], four of which were observational studies [8–10, 26] with matched controls. All these studies have been published since 2018. ECMO was initiated at a median of 1–7 days following mechanical ventilation initiation, while PP was generally initiated after a few days on ECMO (Table 1). The predominant cause of ARDS was pneumonia, and 7 of the 13 studies involved only COVID patients. In contrast, none of the four studies with matching included COVID patients. The PaO_2/FiO_2 ratio evaluated prior to PP showed a broad distribution (Table 1). The criteria for using PP were specified in three [9, 10, 25] of the 13 studies. In the four observational studies with matching procedures [8–10, 26], ECMO patients without PP were similar at baseline to those with PP with respect to age, the severity of illness scores, and several other clinical variables (Table 2). At least four of the same five variables (age, sex, SOFA score, and mechanical ventilation duration before ECMO and PP use before ECMO) were always used for matching (Table S2). Duration of prone positioning was generally longer than 12 h and a mean/median of 2 to 3 sessions of proning have been performed (Table S3).

Fig. 1 Flow diagram of study selection
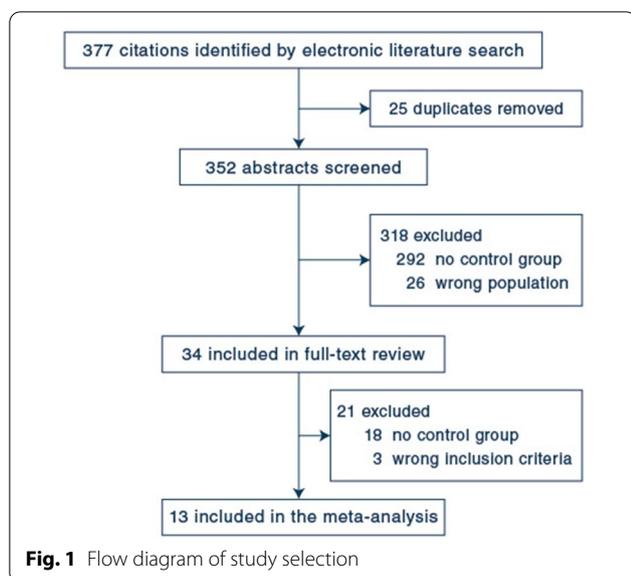
Association of PP with survival, ventilator-free days, and mechanical ventilation duration

PP was associated with a significant improvement in 28-day survival (503 survivors among 681 patients in the PP group [74%; 95% CI 71–77] vs. 450 survivors among 770 patients in the control group [58%, 95% CI 55–62]; RR 1.31 [95% CI 1.21–1.41]; I^2 22% [95% CI 0–62%]; $P < 0.0001$; Fig. 2A). This difference was observed in both COVID-19 and non-COVID-19 ECMO patients (Fig. 2B), and no significant between-group difference was detected. Additional analyses according to the designs of the studies (single centre or multicentre; prospective or retrospective; Figs. S2, S3) showed that the differences in survival between the prone group and the control group persisted (test for subgroup differences, not significant). Hospital survival was also improved when PP was applied to ECMO patients (438 survivors among 814 patients in the PP group [54%, 95% CI 50–57] vs. 464 survivors among 977 patients in the control group [47%, 95% CI 44–51]; RR 1.30 [95% CI 1.18–1.43]; I^2 9% [95% CI 0–47%]; $P < 0.0001$; Fig. 3). The results were similar when survival was assessed at other timepoints (i.e., 60-, 90-day and ICU survival) (Table S4; Figs. S4, S5, S6). When data from the four observational studies with matching were considered, hospital survival was significantly higher in ECMO patients with PP (134 survivors among 213 patients [63%, 95% CI 56–69]) than in ECMO patients without PP among 213 patients (104 survivors [49%, 95% CI 42–56]; RR 1.29 [95% CI 1.09–1.53]; I^2 0% [95% CI 0–85%]; $P < 0.0026$; Fig. 4).

In contrast, the duration of mechanical ventilation was increased when PP was applied to ECMO patients

(mean difference 11.38 days [95% CI 9.24–13.53]; I^2 8% [95% CI 0–65%]; $P < 0.0001$; Fig. S7), whereas the number of ventilator-free days to day 28 slightly decreased (mean difference −1.29 day [95% CI −2.39 to −0.19]; I^2 67% [95% CI 30–84%]; $P = 0.02$; Fig. S8).

The GRADE assessment of the certainty of the evidence supporting the association of PP with better outcomes was low or very low (Table S5), mainly due to the observational study design described in the quality assessment analysis (Table S6).

The associated funnel plots were globally symmetrical for the different outcomes, although the limited number of studies does not allow the exclusion of publication bias (Fig. S9). The P values of Egger's regression intercept were all > 0.05, suggesting that the asymmetry can be considered statistically nonsignificant. Sensitivity analyses based on a serially exclusion process for each study did not change the effect on survival endpoints, confirming the robustness of our findings (Table S7; Fig. S10).

Association between PP and adverse events

Four studies [9, 10, 24, 30] included data for ECMO-related complications comparing the patients according to the use of PP. In six other studies [1, 26–28, 31, 32], these ECMO-related complications were presented without comparisons according to PP use. Specific complications due to the positioning procedure were assessed in only two studies [8, 24]. In the Chaplin et al. study [24], complications were evaluated in only 40 of the 72 included patients. No major complications (tracheal tube displacement, chest tube displacement, and intravenous catheter displacement) occurred, and six (21%) reversible pressure injuries were observed. In the Giani et al. study [8], no major complications due to PP were reported. A few minor complications assessed only in the prone group were also described in this latter study [11]. Given the inconsistent reporting of these outcomes across the studies, the adverse events were not pooled.

Discussion

This systematic review and meta-analysis of 13 studies (total $N = 1836$) showed that PP of ARDS patients receiving venovenous ECMO was associated with a significant improvement in 28-day survival compared with supine positioning of ECMO patients. All other timepoints, including hospital survival, showed a beneficial effect of PP on patients receiving ECMO.

Lung inflation is significantly more homogeneous in the prone position than in the supine position, inducing a more homogeneous distribution of the distending forces causing lung stress [33]. In contrast, the distribution of pulmonary blood flow is only minimally altered by

Table 1 Baseline characteristics of included studies

	Combes et al. [ ], 2018	Guervilly et al. [ ], 2019	COVID-ICU [29], 2020	Garcia et al. [25], 2020	Jozwiak et al. [28], 2020	Le Breton et al. [30], 2020	Rilinger et al. [26], 2020
Study type	RCT[b]	Observational	Observational	Observational	Observational	Observational	Observational
Country	France, USA, Australia, Canada	France	France, Belgium, Switzerland	France	France	France	Germany
N participating ICUs	42	1	138	1	1	1	1
N							
Overall	124	168	269	25	11	13	158
PP during ECMO	17	91	184	14	6	7	38
Pneumonia as main cause of ARDS, N (%)	80 (65)	NA	269 (100)	25 (100)	11 (100)	13 (100)	116 (73)
Only COVID patients	No	No	Yes	Yes	Yes	Yes	No
Mean (SD) or median (IQR) duration of invasive mechanical ventilation before ECMO initiation	1.4 (0.6–3.7)	5 (6)	NA	7 (4–10)	6 (3–11)	6 (3.5–6.5)	1.3 (0.3–5)
Mean age (SD), years							
ECMO only	NA	53 (13)	NA	57 (48–66)	NA	52 (9)	52 (39–64)
ECMO + PP		49 (15)		59 (48–63)		47 (6)	56 (44–64)
Male gender, N (%)							
ECMO only	NA	52 (67)	NA	10 (91)	NA	5 (83)	78 (65)
ECMO + PP		66 (72)		12 (86)		5 (71)	28 (74)
Mean (SD) SOFA score at cannulation							
ECMO only	NA	11 (4)	NA	NA	NA	11 (2)	14 (11–17)
ECMO + PP		10 (4)				9 (2)	13 (11–15)
Indication for PP	Not specified	specified	Not specified	specified	Not specified	Not specified	Not specified
Mean (SD) or median (IQR) days of ECMO before PP	NA	5 (4)	NA	1.5 (1–3)	NA	NA	1.7 (0.5–5)
Duration of PP	NA	12 to 16 h	NA	16 (15–17) h	NA	NA	20 (17–21) h
Mechanical ventilation protocol	specified	specified	Not specified	specified	Not specified	Not specified	specified
Patients who received PP prior ECMO, N (%)							
ECMO only	NA	39 (50)	NA	11 (100)	5 (100)	NA	19 (16)
ECMO + PP		69 (76)		14 (100)	6 (100)		7 (18)
Mean (SD) or median (IQR) PaO$_2$/FiO$_2$ under ECMO before PP	NA	135 (57)	NA	84 (73–108)	NA	NA	77 (63–107)
Corticosteroids on ECMO, N (%)	80 (65)	NA	NA	4 (16)	NA	NA	NA
Primary outcome	60-day mortality	90-day survival	90-day mortality	28-day mortality	ICU mortality	ICU mortality	Hospital survival

Table 1 (continued)

	Schmidt et al. [31], 2020	Chaplin et al. [24], 2021	Giani et al. [8], 2021	Lebreton et al. [32], 2021	Petit et al. [10], 2021	Yang et al. [27], 2021
Study type	Observational	Observational	Observational	Observational	Observational	Observational
Country	France	New Zealand	Italy	France	France	China
N participating ICUs	5	1	6	17	1	21
N						
Overall	83	72	240	302	298	73
PP during ECMO	67	13	107	193	64	51
Pneumonia as main cause of ARDS, N (%)	83 (100)	62 (86)	221 (92)	302 (100)	222 (74)	73 (100)
Only COVID patients	Yes	No	No	Yes	No	Yes
Mean (SD) or median (IQR) duration of invasive mechanical ventilation before ECMO initiation	4 (3–6)	NA	2 (1–6)	5 (3–7)	4 (1–10)	4 (1-7) [n = 59] 1.5 (0–6) [n = 14]
Mean (SD) or median (IQR) age, years						
ECMO only	NA	46 (34–56)	49 (13)	NA	51 (39–60)	NA
ECMO + PP		45 (36–48)	48 (13)	NA	53 (45–61)	
Male gender, N (%)						
ECMO only	NA	39 (66)	83 (62)	NA	160 (68)	NA
ECMO + PP		7 (54)	73 (68)	NA	43 (67)	
Mean (SD) or median (IQR) SOFA score at cannulation						
ECMO only	NA	NA	10 (4)	NA	14 (10–17)	NA
ECMO + PP			9 (3)	NA	13 (9–16)	
Indication for PP	Not specified	Not specified	Not specified	Not specified	Specified	Not specified
Mean (SD) or median (IQR) days of ECMO before PP	NA	8 (5–17.5)	4 (2–7)	NA	3 (2–6)	NA
Duration of PP	NA	11 (7–16)	15 (12–18) h[a]	NA	16 h	NA
Mechanical ventilation protocol	Specified	Not specified	Specified	Specified	Specified	Not specified
Patients who received PP prior ECMO, N (%)						
ECMO only	NA	NA	38 (35)	NA	141 (60)	NA
ECMO + PP			34 (32)	NA	55 (86)	
Mean (SD) or median (IQR) PaO$_2$/FiO$_2$ under ECMO before PP	NA	145 (127–158)	135 (61)	NA	NA	NA
Corticosteroids on ECMO, N (%)	17 (20)	NA	NA	84 (28)	NA	45 (62)
Primary outcome	60-day survival	6-month survival	Hospital mortality	90-day survival	90-day mortality	Hospital mortality

[a] Median (IQR)

[b] RCT, randomized controlled trial comparing ECMO and controls with ECMO as a late rescue strategy

gravity whn turning patients prone, and the remaining blood flow predominantly perfuses (nondependent) dorsal regions, resulting in a better ventilation-to-perfusion relationship [33]. However, the improved outcome associated with PP (and documented in the PROSEVA trial) [4] is probably not related only to increased oxygenation [34] but rather to decreased levels of lung stress and strain and corresponding ventilator-induced lung injuries (VILIs). During ECMO, the supine position, the positive fluid balance, and the use of sedatives and myorelaxants may cause an increase in collapsed lung units in the dependent parts of the lungs. However, the rationale for using PP in ECMO patients must be counterbalanced by the risk of complications, especially in unexperienced centres.

Table 2 Main characteristics of the four studies using a propensity-matched analysis

Author	Guervilly et al. [3]		Rilinger et al. [26]		Giani et al. [8]		Petit et al. [10]	
Year of publication	2019		2020		2021		2021	
Prone positioning	Yes	No	Yes	No	Yes	No	Yes	No
No. patients	50	50	38	38	66	66	59	59
Only COVID patients	No		No		No		No	
Age	50 ± 14	50 ± 14	51.5 (38.5–64)	55.5 (44–62.5)	47 ± 12	47 ± 14	53 (46–61)	51 (45–59)
Male gender, no. (%)	31 (62)	34 (68)	28 (74)	32 (84)	43 (65)	44 (67)	40 (68)	42 (71)
SOFA score	10 ± 4	11 ± 4	13 (11–15)	12.0 (8.8–16)	10 ± 3	10 ± 3	12 (8–16)	13 (9–17)
Pneumonia as main cause of ARDS, no. (%)	32 (64)	42 (84)	33 (87)	32 (84)	60 (91)	60 (91)	47 (80)	45 (76)
Prone positioning prior ECMO, no	34 (68)	29 (58)	7 (18)	9 (24)	16 (31)[a]	26 (39)	50 (85)	48 (81)
Duration invasive mechanical ventilation—ECMO initiation	4 ± 5	4 ± 5	2.2 (0.2–7.6)	1.7 (0.1–6.5)	2 (1–4)	2 (0–4)	4 (1–9)	4 (2–10)

[a] Information available for 51 patients

The design, execution, and completion of randomized controlled trials regarding ECMO are difficult and require a long time [1, 2]. Difficulties include the need to very rapidly randomize patients with a high risk of imminent death, the inclusion of many centres in different countries, the establishment of a management protocol regarding other measures (such as mechanical ventilation settings, the use of neuromuscular blocking agents, and weaning strategies) and an ethical aspect (lack of equipoise). Indeed, PP has demonstrated a clear beneficial effect regarding outcomes [4], but many intensivists in Europe or elsewhere are reluctant to implement this technique for severe ARDS patients even if receiving ECMO. As a result, a large study evaluating the effect of PP on survival among ECMO patients with severe ARDS in the near future is unlikely. Thus, our meta-analysis provides clinicians with the most comprehensive synthesis of available evidence for the efficacy of PP in adult patients with severe ARDS placed under venovenous ECMO. Two studies aiming to evaluate the time to successful ECMO weaning are in progress (ClinicalTrials.gov Identifiers: NCT04607551 and NCT04139733) and may reinforce our conclusions.

A recent systematic review related to PP in ECMO patients has been published [35]. The cumulative survival (pooling survival proportions from the longest postdischarge timepoint reported) in patients with PP was 57% [35]. The cumulative survival among patients who were submitted to PP compared to those without PP was nonsignificant [35]. However, this latter meta-analysis [35] included only 7 studies, whereas 13 were included in the present study. Another major difference from the present study is that the primary outcome of interest was pooled cumulative survival based on studies reporting varying survival interval data, as well as survival to ICU discharge, hospital discharge, and 30-, 60- and 90-day survival [35]. In the present study, the timepoints considered were based on the exact rates obtained from the authors when not reported in the original studies.

Our study has several important limitations. Our primary results mainly result from observational studies responsible for the low or very low certainty of our findings. Due to the design of these studies, the criteria regarding the use of PP were provided in less than 25% of them. Despite having obtained from the authors many additional numbers not mentioned in their original manuscript, few missing data remained. As stated above, obtaining the results of a large interventional trial regarding the survival effect of PP in ECMO patients is very unlikely in the next 5 years. To minimize clinical heterogeneity, we performed a prespecified analysis including only the four studies using a matching process [8–10, 26]. This additional analysis confirmed the beneficial effect of proning on the survival of ECMO patients. Second, although visual inspection of funnel plots did not suggest publication bias, definitive confidence in excluding bias was limited by the small number of studies included in our plot. Finally, we could not analyse the risks of proning ECMO patients, such as cannula-associated colonization or infection, skin lesions, catheter accidental removal or ECMO circuit dysfunctions.

The use of prone positioning in adult patients with severe ARDS for venovenous ECMO was associated with improved survival across our meta-analysis. Awaiting prospective randomized controlled trials, prone positioning may be considered in adults with severe ARDS at expert, high-volume centres.
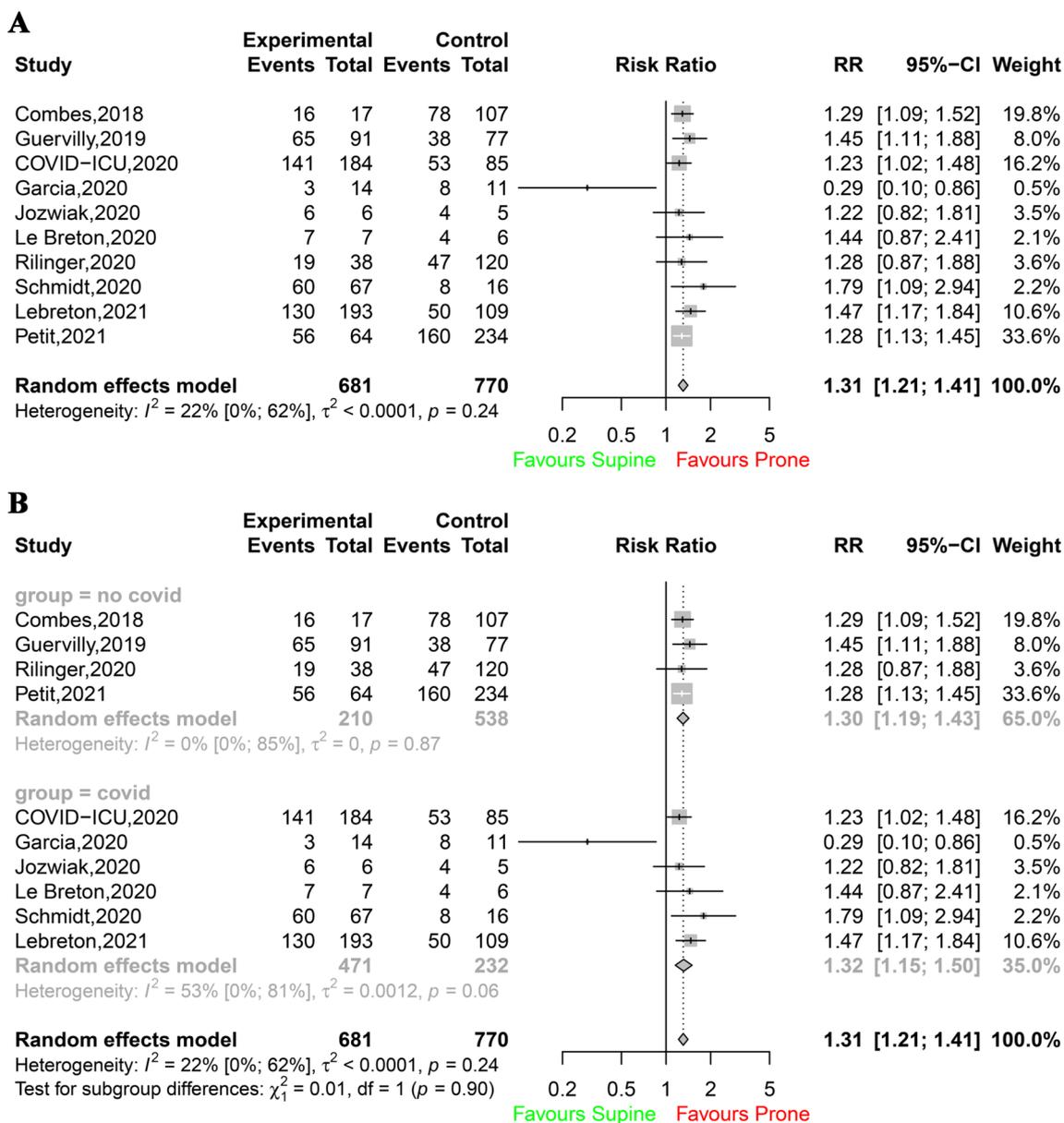
Fig. 2 A Survival at day 28. **B** Survival at day 28 according to the ARDS aetiology
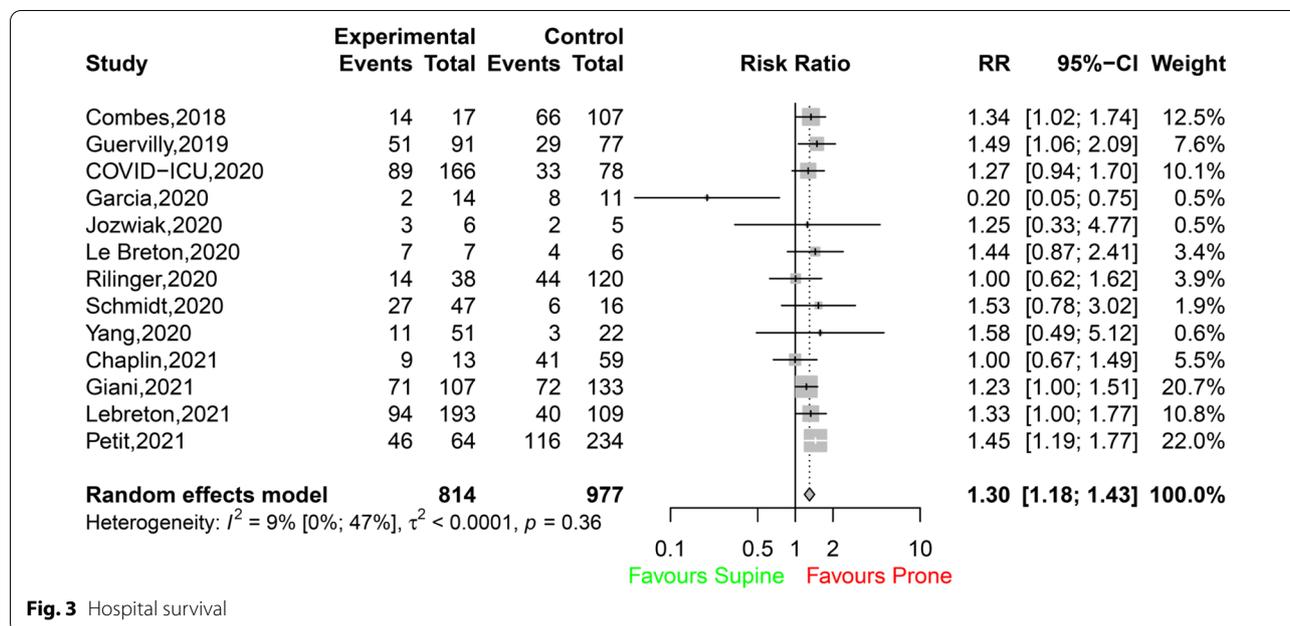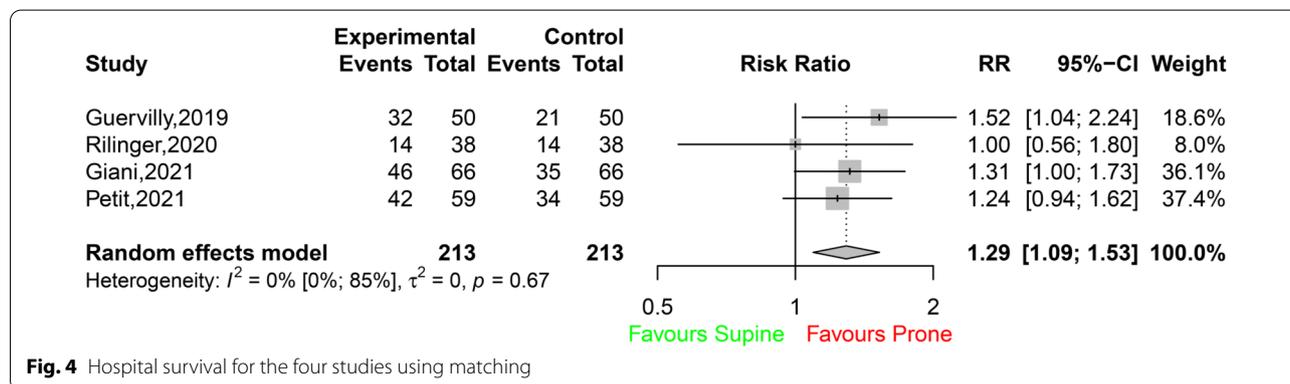
Fig. 3 Hospital survival

Fig. 4 Hospital survival for the four studies using matching

Author details

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Author contributions

LP and LB conceived and coordinated the study; LP wrote the manuscript. LB and CG critically reviewed the manuscript; MS, DH, MP, AC, GL, JR, MG, CB, TD, MJ, TW, DR, RP, and CG collected the additional required information; LB and

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