Review article

Impact of prone positioning duration on the outcome of patients receiving venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: A meta-analysis

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A B S T R A C T

Purpose: Research has shown that prone positioning (PP) improves the survival of patients receiving venovenous extracorporeal membrane oxygenation (V–V ECMO) for acute respiratory distress syndrome (ARDS). However, the reported impact of PP duration on the outcome of V–V ECMO patients with ARDS varies across studies.
Methods: A meta-analysis approach was used to identify studies that investigated the impact of PP duration on the outcome of ARDS patients who were treated with V–V ECMO; the following databases were used: MEDLINE, Embase, Wanfang, and the China National Knowledge Infrastructure. The primary outcome was cumulative survival. Secondary outcomes were length of stay in an intensive care unit, exchange of arterial blood gases, and adverse events.
Results: A total of 8 studies were included in the final meta-analysis. Patients with longer duration of PP ($\geq$12 h) had a longer survival period (risk ratio: 1.24; 95% confidence interval: 1.00, 1.54]) than those with PP < 12 h. There was no evidence of publication bias across the studies.
Conclusion: Our results imply that a longer duration of PP $\geq$ 12 h might improve the outcome of patients with ARDS who receive V–V ECMO therapy.

1. Introduction

Acute respiratory distress syndrome (ARDS) is a severe condition that can lead to refractory hypoxemia. The morbidity of ARDS is approximately 10% in intensive care units, whereas mortality has been estimated as 40% [1]. Venovenous extracorporeal membrane oxygenation (V–V ECMO) may be a therapeutic option for certain patients with severe ARDS, intractable hypoxemia, or uncontrolled airway pressure [2]. Despite the application of V–V ECMO, however, the survival rate of ARDS patients remains unsatisfactory. Fortunately, studies have shown that prone positioning (PP) not only improves oxygenation of patients with ARDS but also reduces the risk of ventilator-induced lung injury [3]. The positive effect on respiratory mechanics or mortality can be explained by a more uniform distribution of tidal volume, leading to a reduction of

ventilator-induced lung injury [4]. Moreover, PP can significantly reduce the mortality of patients with moderate to severe ARDS [5].

PP during ECMO may also promote alveolar recruitment and improve prognosis, and ECMO offers the lung a chance to rest and provides patients with an opportunity to recover from life-threatening hypoxemia [6]. Importantly, the combination of PP with ECMO has been considered to be safe [7] and can facilitate gas exchange [8]. According to a recent meta-analysis, the use of PP during V–V ECMO for patients with ARDS was associated with better survival [9], and the investigators recommended that PP be started early and continued for a relatively long period [10]. However, the optimal PP duration is inconsistent across studies. Therefore, we carried out a meta-analysis to investigate the impact of PP duration on the outcome of ARDS patients receiving V–V ECMO.

2. Methods

2.1. Search strategy and study selection

The meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses and guidelines from the Cochrane Diagnostic Test Accuracy Working Group [11]. Two investigators (J.H. and X.Y.) independently searched the databases MEDLINE, Embase, Wanfang, and China National Knowledge Infrastructure (commonly known as CNKI) to identify potentially relevant articles published up to April 30, 2022. The following keywords and their variants were included: "extracorporeal membrane oxygenation (ECMO, extracorporeal life support, ECLS, membrane oxygenation or extracorporeal oxygenation)" and "prone position (positioning therapy)" without language limitations. The bibliographies of these potentially relevant articles were also screened to identify other potentially relevant articles.

Two reviewers (J.H. and X.Y.) independently reviewed the relevant articles for eligibility and inclusion. Studies were included if they met the following inclusion criteria: (1) prospective or retrospective design published in a manuscript form; (2) patients ($\geq$18 years old) with ARDS undergoing V–V ECMO in which PP was explicitly described; (3) a definite duration of PP was provided; (4) the outcomes of V–V ECMO with or without PP were clearly indicated; (5) studies in which patients undergoing PP during V–V ECMO were compared with patients undergoing V–V ECMO without PP. Case reports, editorials, review articles, and clinical guidelines were excluded. Disagreements were resolved by consensus. Moreover, we contacted all authors for additional information on duration of PP that was not provided in the eligible articles.

2.2. Data extraction and quality assessment

Data were extracted using a custom-made standardized form. The following information was extracted: the surname of the first author, publication year, country, study design, sample size, age, V–V ECMO details, PP prior ECMO, the duration of PP, number of PP sessions, and survival.

The Newcastle Ottawa Scale was applied to assess the risk of bias for each eligible study [12]. This scale assigns a maximum of 9 points to each of three categories: (1) patient selection (three items); (2) comparability of the two study arms (two items); and (3) assessment of outcome (two items). Studies with 7–9 points were considered of high quality, studies with 5–6 points were considered of moderate quality, and studies with 0–4 points were considered of poor quality [13]. We used the Grading of Recommendations, Assessments, Developments and Evaluations approach to assess the certainty of evidence for each outcome [14]. Any conflicts were resolved by consensus.

The collected data were matched and stratified based on two defined groups, i.e., longer PP duration vs. shorter PP duration, before statistical analysis. Data for the included studies were dichotomized based on the mean or median duration of PP. As a result, the optimal cutoff for PP duration was determined to be 12 h. This model of comparison is indirect and should be considered weak when compared with a randomized controlled trial; nevertheless, the approach is comparable to a retrospective case-control study with matched groups.

2.3. Statistical analysis

The summary meta-analysis for each outcome variable is presented using forest plot graphs. We calculated the summary risk ratio (RR) with its corresponding 95% confidence interval (CI) using a random-effects model [15]. The heterogeneity of studies was measured using I^2 statistics (values <25% imply low heterogeneity; 25–75%, moderate heterogeneity; >75%, considerable heterogeneity) and P values using Cochran Q statistics [16]. Publication bias was evaluated using Begg's funnel plot and Egger's test [17]. All statistical analyses were performed using STATA software (version 14.0; College Station, TX, USA).

3. Results

3.1. Identification of studies for inclusion in a meta-analysis and study characteristics

Our initial literature search retrieved 414 citations, among which 379 were excluded after examining the titles or abstracts because they were reviews, experimental studies, meta-analyses, or other irrelevant articles. Ultimately, 8 studies [18, 19, 20, 21, 22, 23, 24, 25] were identified for inclusion in our meta-analysis (Figure 1). Table 1 lists the characteristics of the included studies. The 8 studies were published between 2019 and 2022 and were conducted in five countries: France
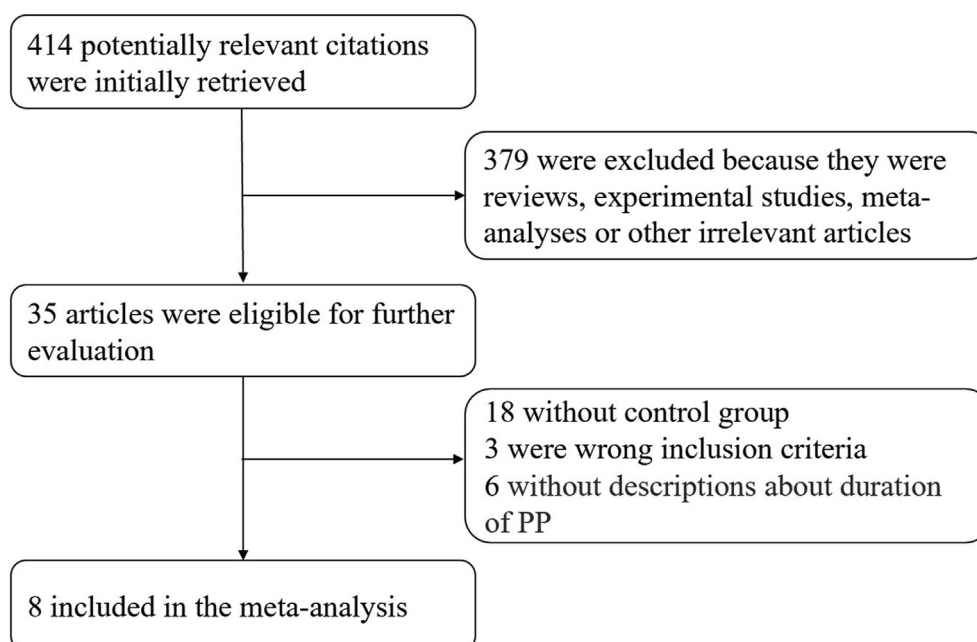

Figure 1. Flow chart of the study selection.

Table 1. Characteristics of studies included in the meta-analysis.

Study	Region	Study design	Overall ECMO, N	PP during ECMO, N	Pneumonia as main cause of ARDS, N (%)	Mean age (SD) or median (IQR), years		Male gender, N (%)		SOFA score Mean (SD) or median (IQR)		Patients who received PP prior ECMO, N (%)		Days of ECMO before PP; Mean (SD) or median (IQR)	Duration of PP, range or median (IQR)	Number of PP session, mean ± SD	Primary outcome
						ECMO only	ECMO + PP	ECMO only	ECMO + PP	ECMO only	ECMO + PP	ECMO only	ECMO + PP				
Guervilly et al. 2019 [18]	France	Observational	168	91	NA	53 (13)	49 (15)	52 (67)	66 (72)	11 (4)	10 (4)	39 (50)	69 (76)	5 (4)	12–16 h	3 ± 3	90-day survival
Garcia et al. 2020 [19]	France	Observational	25	14	25 (100)	57 (48–66)	59 (48–63)	10 (91)	12 (86)	NA	NA	11 (100)	14 (100)	1.5 (1–3)	16 (15–17) h	3.85 ± 2.93	28-day mortality
Rilinger et al. 2020 [20]	Germany	Observational	158	38	116 (73)	52 (39–64)	56 (44–64)	78 (65)	28 (74)	14 (11–17)	13 (11–15)	19 (16)	7 (18)	1.7 (0.5–5)	20 (17–21) h	2 ± 1.54	Hospital survival
Chaplin et al. 2021 [21]	New Zealand	Observational	72	13	62 (86)	46 (34–56)	45 (36–48)	39 (66)	7 (54)	NA	NA	NA	NA	8 (5–17.5)	11 (4–19) h	1.97 ± 1.45	6-month survival
Giani et al. 2021 [22]	Italy	Observational	240	107	221 (92)	49 (13)	48 (13)	83 (62)	73 (68)	10 (4)	9 (3)	38 (35)	34 (32)	4 (2–7)	15 (12–18) h	3.05	Hospital mortality
Yang et al. 2021 [23]	China	Observational	73	51	73 (100)	NA	NA	NA	NA	NA	NA	NA	NA	NA	6–12 h	NA	Hospital mortality
Petit et al. 2022 [24]	France	Observational	298	64	222 (74)	51 (39–60)	53 (45–61)	160 (68)	43 (67)	14 (10–17)	13 (9–16)	141 (60)	55 (86)	3 (2–6)	16 h	2	90-day mortality
Wang 2020 [25]	China	Observational	86	43	NA	51 (6)	49 (6)	25 (58)	28 (65)	NA	NA	NA	NA	NA	16 h	NA	28-day mortality

PP: Prone Positioning; ECMO: Extracorporeal Membrane Oxygenation; ARDS: acute respiratory distress syndrome; SD: Standard Deviation; N: Number; IQR: Inter Quartile Range; SOFA: Sequential Organ Failure Assessment; NA: Not Available.

(3 studies), Germany (1), New Zealand (1), Italy (1), and China (2). The number of participants in each study ranged from 25 to 298 and included 421 cases in which PP was done during V–V ECMO and 699 cases in which PP was not performed. One study did not report the number of male and female patients, and the main cause of ARDS was pneumonia. In 5 of the 8 studies [18, 19, 20, 24, 25], V–V ECMO patients without PP were similar at baseline to those with PP with respect to age and gender, and there was no significant difference in sequential organ failure assessment (SOFA) scores among patients [18, 20, 22, 24]. Duration of PP ranged from 6 h to 21 h, with a mean/median of 2–4 PP sessions per case per day. Of the 8 articles, 2 [19,25] reported 28-day survival, 2 [18,20] reported 30-day survival, 2 [18,23] reported 60-day survival, 2 [18,24] reported 90-day survival, 1 [20] reported survival in the intensive care unit, 2 [20,22] reported hospital survival, and 1 [21] reported 6-month survival. Table 2 presents data for the quality assessment of the included studies, all of which were of moderate to high quality.

3.2. Relationship between duration of PP and each of survival, ECMO duration, and arterial blood gas exchange

Of the 8 studies, 6 [18-20,22,24,25] reported a PP duration of $\geq$12 h, and 2 [21,23] reported a duration of <12 h. Each of the 8 studies reported different survival data, including 28-day, 60-day, and 90-day survival as well as hospital survival and discharged alive from an intensive care unit. The primary outcome of concern was pooled cumulative survival (reported survival at the longest time point). The cumulative survival of patients who underwent PP for $\geq$12 h was 0.56 (95% CI: 0.43, 0.70), and survival of patients who underwent PP for <12 h was 0.44 (95% CI: –0.03, 0.91, Figure 2A). Cumulative survival differed significantly between the PP $\geq$ 12 h patients (RR: 1.24, 95% CI: 1.00, 1.54) and PP < 12 h patients (RR: 1.05, 95% CI: 0.72, 1.53) (Figure 2B). In terms of being discharged alive from an intensive care unit, however, there was no statistically significant difference between PP $\geq$ 12 h (RR: 1.20, 95% CI: 0.91, 1.57) and PP < 12 h (RR: 1.00, 95% CI: 0.67, 1.49) (Figure 3).

If values reported in the various studies were obtained at the end of a fixed duration PP cycle or after a patient had been returned to the supine position, it was considered "after PP". Five studies reported data concerning PaO_2/FiO_2 for V–V ECMO patients both before and after PP. A higher PaO_2/FiO_2 after PP (an additional 65.59 mmHg) was associated with a greater yet non-significant chance of survival for the PP $\geq$ 12 h group (95% CI: –7.06, 138.24, Table 3). Patients had remarkably improved PaO_2 after a longer duration of PP, whereas $PaCO_2$ was not significantly affected by PP duration (Table 3).

3.3. Relationship between PP duration and complications

Four studies [18, 21, 23, 24] reported data on V–V ECMO–related complications, and one study [22] reported complications related to PP. The most common complications were hemorrhage, accidental decannulation, infection, and cardiovascular and mechanical complications. These complications tended to occur with approximate equal frequency in both the PP $\geq$ 12 h and <12 h groups. The main complications such as accidental decannulation and endotracheal tube displacement were reported in only one study [24]. Given the inconsistent reporting of these findings, the adverse events were not summarized.

3.4. Publication bias

There was no evidence for significant publication bias ($P = 0.138$ for the Begg's test, and $P = 0.103$ for the Egger's test) (Figure 4).

4. Discussion

To our knowledge, this meta-analysis represents the first attempt to summarize recent studies investigating the effects of PP duration on the outcomes of adult ARDS patients receiving V–V ECMO. Our main finding was that patients with longer-duration PP ($\geq$12 h) per day were associated with significantly longer cumulative survival than patients with shorter-duration PP (<12 h).

The mortality rate of patients with ARDS is high, ranging from 45% to 66% [25, 26]. Because the etiology of ARDS is multifactorial, treatment is usually supportive or palliative rather than targeted at the underlying cause. For patients with ARDS, maintaining oxygenation and preventing further lung injury has always been challenging. V–V ECMO is a therapy for patients with severe respiratory failure who do not improve with conventional mechanical ventilation or do not respond to other therapies [27]. PP is also a therapeutic option for patients whose organs are mechanically supported by extracorporeal circulation [28, 29]. Lung inflation in prone-positioned patients is significantly more uniform than in supine-positioned patients, resulting in more homogeneous distribution of the distending forces that can cause lung stress [30]. PP during ECMO is practical and safe, and it may improve oxygenation for patients with severe ARDS by reducing the damage of mechanical ventilation via alveolar recruitment and preventing hypoxemia-related complications [31].

Six studies included in our meta-analysis compared survival between ARDS patients receiving V–V ECMO with or without PP. Among these studies, 5 [17,18,21,23,24] reported patients who had undergone PP for $\geq$12 h during ECMO, and these patients had significantly prolonged

Table 2. Quality assessment of the studies included.

Study	Selection				Comparability		Assessment of outcome			NOS score
	Ia	Ib	Ic	Id	IIa	IIb	IIIa	IIIb	IIIc	
Guervilly et al. 2019 [18]	*	*	*	*	*	*	*	*	*	9
Garcia et al. 2020 [19]	*	*	*	*	*	*	*		*	8
Rilinger et al. 2020 [20]	*	*	*	*	*	*	*	*	*	9
Chaplin et al. 2021 [21]	*	*	*	*		*	*	*	*	8
Giani et al. 2021 [22]	*	*	*	*		*	*		*	7
Yang et al.2021 [23]	*	*	*	*			*		*	6
Petit et al. 2022 [24]	*	*	*	*	*	*	*	*	*	9
Wang. 2020 [25]	*	*	*	*	*		*		*	7

Ia: the exposed cohort was representative of the population; Ib: the non-exposed cohort was drawn from the same population; Ic: the exposure ascertainment was from secure records or a structured interview; Id: no outcome events before the start of the study; IIa: the cohorts were comparable for age and gender; IIb: the cohorts were comparable for all additional factor(s) reported; IIIa: cases were assessed from a secure record; IIIb: follow-up was long enough; and IIIc: follow-up was complete. NOS: Newcastle Ottawa score.
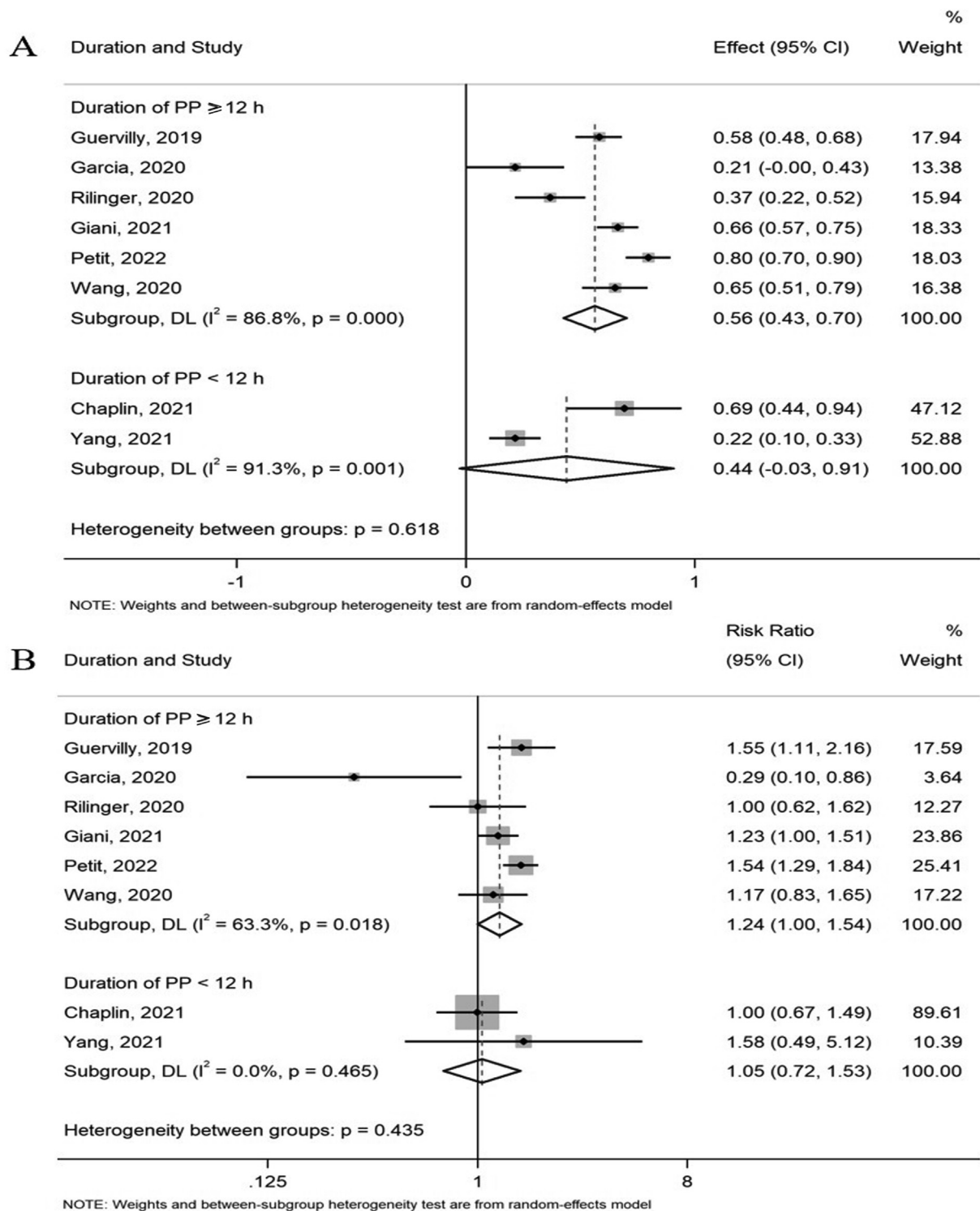
Figure 2. Forrest plots for cumulative survival rate of differences duration of PP (A) and comparison of cumulative survival in proned and control group patients (B).

survival compared with the PP < 12 patients. The benefit of PP in V–V ECMO has been described in previous studies, in which PP for >12 h considerably improved PaO$_2$/FiO$_2$ in ARDS patients during V–V ECMO [32]. Another study reported a significant reduction in mortality among patients with moderate to severe ARDS who underwent PP for 16 h per day and had protective lung ventilation [6]. When combined with V–V

ECMO, 24 h of PP can also improve oxygenation and respiratory compliance [7]. This is not surprising given that one of the mechanisms through which PP decreases mortality is by reducing ventilator-induced lung injury, with longer PP correlating with less injury [6]. In contrast, one study [19] found no advantage of long-duration PP (20 h) with respect to overall survival of patients with ARDS requiring V–V ECMO
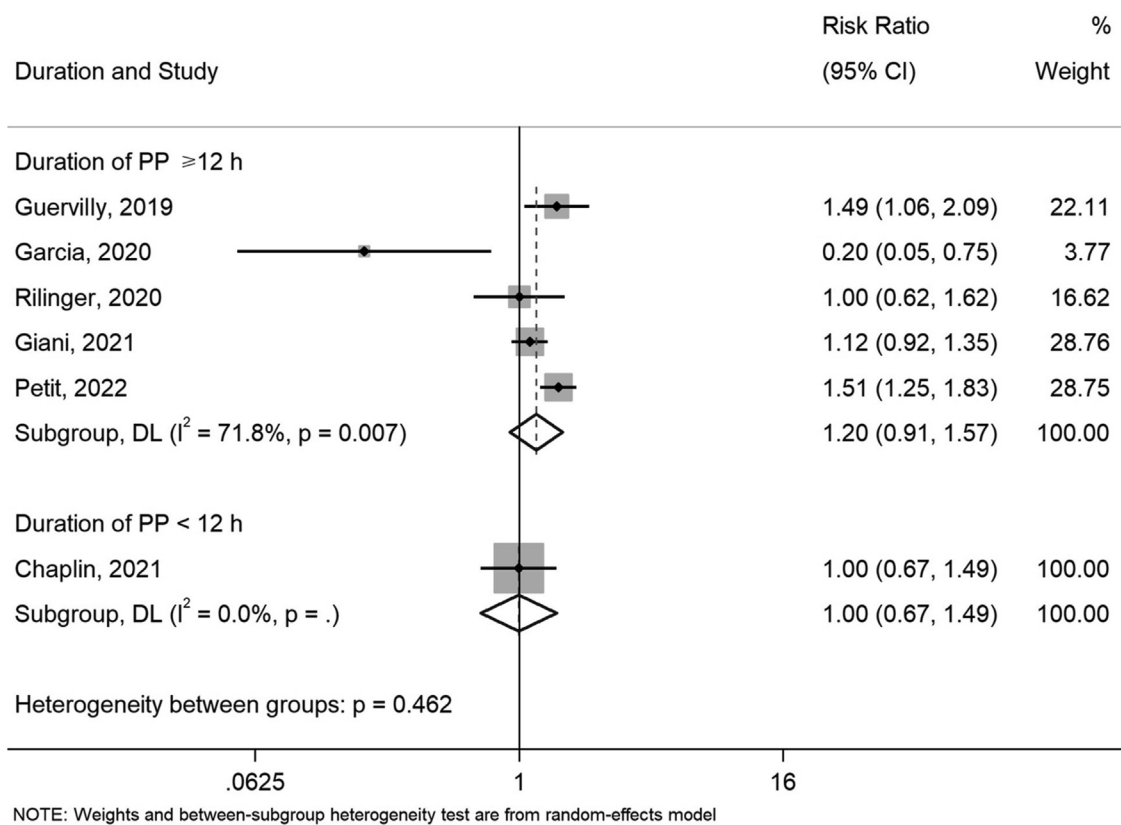
Figure 3. Forrest plots of differences duration of PP and ICU survival.

Table 3. Results of PaO_2/FiO_2, PaO_2 and $PaCO_2$ analysis between two groups.

	Group by PP duration	No. of studies	SMD (95% CI)	P value	I^2
PaO_2/FiO_2	>12 h	4	65.59 (−7.06, 138.24)	<0.001	97.9%
	<12 h	1	7.84 (−14.23, 29.91)		0.0%
$PaCO_2$	>12 h	4	0.05 (−1.21, 1.30)	0.273	23.0%
	<12 h	1	−0.37 (−4.20, 3.46)		0.0%
PaO_2	>12 h	4	18.24 (6.35, 30.12)	<0.001	91.7%
	<12 h	1	3.14 (−5.60, 11.97)		0.0%

PaO_2/FiO_2: Oxygenation Index; $PaCO_2$: Partial Pressure of Carbon Dioxide; PaO_2: Partial Pressure of Oxygen; SMD: Standard Mean Difference; CI: Confidence Interval.

support. The possible reason is that the patients in that particular study had more severe ARDS, and perhaps fewer patients underwent PP during ECMO. Furthermore, sedation for PP patients was titrated to maintain spontaneous breathing rather than deep sedation, and neuromuscular blockade was not used on a regular basis for this purpose. Moreover, that particular study [19] was a single-center report, and the sample size was small with only 38 patients who underwent PP and 76 control patients who did not undergo PP.

It has been reported that PP is particularly beneficial for patients with consolidation due to dependent lung atelectasis [33]. Our results show that PP did not significantly impact PaO_2/FiO_2 and $PaCO_2$ for patients with either longer (≥12 h) or shorter (<12 h) PP duration. However, the PP ≥ 12 h group had a significantly higher average PaO_2. These results can be explained in several ways. First, the management of PP, V–V ECMO, and ventilators depended on the discretion of clinicians and was not standardized. Second, the post-PP timing of arterial blood gas measurement varied between studies, and the benefit of PP may have been lessened after returning patients to the supine position for several hours. Finally, the power of the meta-analysis to control for multiple potentially confounding variables was limited by the relative paucity of data.

Our study has several limitations. All our results came from observational studies, perhaps lessening the certainty of our conclusions. The follow-up duration differed among the 8 studies included in our meta-analysis, which may have led to biased results. Moreover, although the visual examination of funnel plots did not reveal publication bias, definitive confidence to exclude bias was limited by the small number of studies—and hence data—included in the plot. We could not analyze the complications for patients with V–V ECMO, such as cannula-associated colonization or infection, bleeding, pressure sores, or accidental decannulation. Finally, although we found that a daily duration of PP of more than 12 h improved survival, the exact threshold required to confer benefit remains unknown.

Our results reveal that longer PP duration (≥12 h) is associated with improved survival in ARDS patients with ECMO. PP was beneficial to patients with ARDS receiving V–V ECMO when used for prolonged periods of more than 12 h each day. More prospective and randomized control trials are necessary to assess the long-term impact of PP duration on survival as well as complications in ARDS patients receiving V–V ECMO.
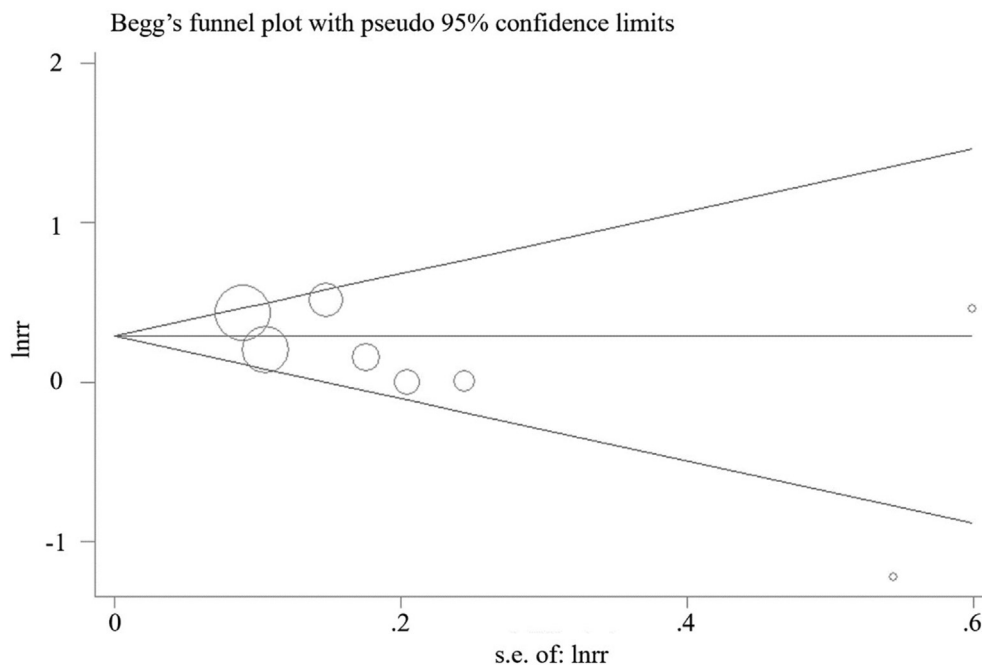
Begg's funnel plot with pseudo 95% confidence limits

Figure 4. Begg's funnel plot with pseudo 95% confidence limits showing the symmetrical distribution of the included studies.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no competing interests.

Additional information

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