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Review Article

A meta-analysis of extracorporeal membrane oxygenation for acute respiratory distress syndrome

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Abstract: Objective: Extracorporeal membrane oxygenation (ECMO) is an important rescue therapy for patients with severe lung failure. A meta-analysis was conducted to investigate the effect difference between ECMO and the conventional mechanical ventilation for acute respiratory distress syndrome (ARDS). Methods: Relevant studies on ECMO and ARDS were ascertained by retrieving PubMed, EMBASE, Web of Science and EBSCO databases until April, 2017. The odds ratio (OR) and corresponding 95% confidence interval (CI) were calculated to evaluate the mortality rate. Results: Thirteen studies with a total of 628 patients and 795 controls were included in this meta-analysis. The results demonstrated that there was no significant effect difference between ECMO and conventional mechanical ventilation in the treatment of ARDS, and the odds ratio was 1.12 (95% CI: 0.69 to 1.81, random effect model). However, we found that the mortality rate of ECMO group was lower than control group in the Chinese subgroup with OR at 0.39 (95% CI: 0.17 to 0.86, fixed effect model). No significant publication bias was found in current study. Conclusions: Except for mortality rates of certain Chinese patients, there was no significant effect difference between ECMO and conventional mechanical ventilation in the treatment of patients with ARDs. A more comprehensive assessment of major factors is needed to evaluate the mortality rate of ARDS after ECMO treatment.

Keywords: Extracorporeal membrane oxygenation, acute respiratory distress, mechanical ventilation, meta-analysis

Introduction

Acute respiratory distress syndrome (ARDS) was first described in the 1960s [1], which represented a syndrome of acute lung failure and resulted in severe hypoxemia [2]. Nowadays, substantial progress in treatment of ARDS and improved survival rates has been achieved, however, the mortality rate can still reach as high as 30% [3].

By pursuing a protective ventilation strategy, ventilation-associated lung damage could be reduced and could have an major impact on survival [4, 5]. Employing extracorporeal device to improve lung function had been investigated for past decades to serve as a tool to ensure gas exchange and to enable a lung protective ventilation strategy concomitantly. Since the first application of extracorporeal membrane oxygenation (ECMO) in an adult patient with severe lung failure after a motor vehicle accident in the early 1970s [6], the procedure was exerted in many aspects during the next few decades. In adults with ARDS, ECMO had only been considered a rescue therapy in selected patients, because early randomized trials failed to demonstrate a benefit in comparison with conventional therapy [7, 8]. Among ECMO-related complications, both clotting and bleeding contributed to the majority of unfavorable events in neonatal or pediatric cases [9] as well as in adult patients [10]. Transfusions of large amounts of blood products had been necessary in almost every patient on ECMO, limiting a safe prolonged continuation [11, 12]. The early reports of the use of ECMO in adult with severe respiratory failure were promising [6].

Although ECMO was effective with lower cost compared to conventional ventilation in new-

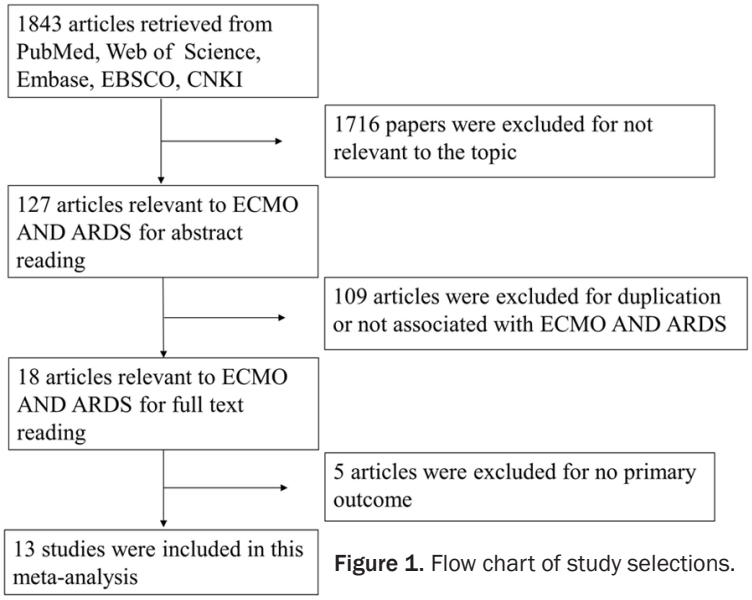

Figure 1. Flow chart of study selections.

borns [13], the evidence was much less convincing for the adult population. According to currently published studies, the benefit of ECMO for the treatment of ARDS is still controversial. Therefore, we performed this meta-analysis of published studies to investigate the integrated effect of ECMO for ARDS.

Methods

Study population, search criteria

The databases including PubMed, EMBASE, Web of Science and EBSCO were electronically searched for eligible studies to assess the association between ECMO and ARDS for all literature published until April 2017. The following search criteria were used as "extracorporeal membrane oxygenation" OR "ECMO" OR "extracorporeal life support" AND "acute respiratory distress syndrome" OR "ARDS" OR "acute respiratory failure", There were no restrictions on regions, sample size, or type of report so as to minimize potential publication bias. The reference lists of retrieved articles were analyzed to identify additional relevant studies. Newcastle-Ottawa scale (0-9) was used to assess the quality of cohort studies and Jadad Score (0-5) was used to evaluate the randomized controlled trials.

Inclusion and exclusion criteria

All studies reported mortality rates between ECMO and control group, and therefore the results were presented as pooled OR. Meta-analyses, letters, reviews, and editorial articles were excluded.

Data collection

Two reviewers independently searched and selected literature and collected relevant data. Disagreements were resolved by a third investigator. The data had covered the first author, year of publication, country of origin, research type, ECMO time, ECMO method, and evaluation indicators with sample size.

Survival outcomes

The primary clinical endpoint was mortality rate between ECMO and control group. Secondary outcomes were adverse drug reaction and hospital stay.

Statistical analysis

We used OR and their corresponding 95% CI to assess the pooled mortality rates between groups. Heterogeneity in these studies was examined by chi-square-based Q test and I^2 test. If the data showed no heterogeneity ($P>0.10$, $I^2<50\%$), the Mantel-Haenszel fix effect model was used, and otherwise the Der-Simonian-Laird random effect model was applied. Publication bias was quantitatively assessed by Egger's linear regression test and visual inspection of Begg's funnel plots. Data were analyzed using STATA 11.0 SE software (Stata Statistical Software, College Station, TX, USA, www.stata.com).

Results

Data collection

Electronic database searches identified 1843 studies with possible relevance to our study. Further investigation led to the exclusion of 1716 of these studies due to non-relevance. One hundred and nine articles were further excluded due to duplication or not being associated with ECMO AND ARDS. Two independent investigators read the full texts of the remaining 18 articles. From these 18 articles, 5 arti-

Table 1. Population characteristics of studies in the meta-analysis

Studies	Countries	Research Types	Age (T/C, year)	Gender (T/C) M:F	ECMO Time (day)	ECMO Methods	Evaluation Indicators	Sample Size (T/C)	Quality Score
Xu 2014	China	Cohort study	73 (46, 77) VS 34 (23, 46)	4:1 VS 4:2	/	V-V	Hospital mortality rates	5/6	4
Huang 2014	China	Cohort study	35-64 VS 35-64	13:11 VS 14:10	4-7	V-V	Hospital mortality rates, ADR	24/24	4
Qi 2016	China	Cohort study	34-76	40:18	/	V-V	Hospital mortality rates	28/30	4
Cianchi 2011	Italy	Cohort study	44.5 (36.8-48.8)	8:4	8 (6-16.5)	V-V	Hospital mortality rates, Hospital stay	7/5	4
Roch 2010	France	Cohort study	49 (26-57) VS 54 (43-60)	3:6 VS 4:5	10 (6-96) h	V-V	Hospital mortality rates	9/9	4
Davies 2009	Australia	Cohort study	36 (27-45) VS 44 (31-54)	29:32 VS 63:70	10 (7-15)	V-V	Hospital mortality rates	61/133	5
Beiderlinden 2006	Germany	Cohort study	42.2 ± 13 VS 41.9 ± 16	NA	/	V-V	Hospital mortality rates	32/118	5
Mols 2000	Germany	Cohort study	35 (11) VS 43 (17)	NA	15 (10)	V-V	Hospital mortality rates	62/183	5
Lewandowski 1997	Germany	Cohort study	31.5 ± 14.4 VS 33.3 ± 13.3	28:21 VS 46:27	22.6 (19.5)	V-V	Hospital mortality rates	49/73	4
Peek 2009	UK	RCT	39.9 (13.4) VS 40.4 (13.4)	51:39 VS 53:37	9 (6-16)	V-V	6 months mortality rates	90/90	3
Morris 1994	Germany	RCT	35 ± 2.3	17:23	8.7 (1.7)	V-V	3 months mortality rates	21/19	3
Zapol 1979	US	RCT	NA	NA	/	V-A	2 months mortality rates	48/42	3
Weingart 2015	Germany	Cohort study	48.5 (± 16.3) VS 49.9 (± 15.5)	133:59 VS 41:12	9 (6-15)	V-V	Hospital mortality rates	192/63	5

Note: RCT: randomized controlled trial; V-V: veno-venous; V-A: veno-arterial; T/C: ECMO treatment group/controls. M:F: Male: Female; NA: not applicable.

cles were excluded because of no primary outcome. The remaining 13 articles [7, 8, 14-24], which comprised 628 patients and 795 controls, met all inclusion criteria and were included in the meta-analysis. The screening process is illustrated in **Figure 1**.

Population characteristics

The characteristics of the included studies were given in **Table 1**. Among these studies, 3 were conducted in Germany, 3 in China, 1 in Italy, 1 in France, 1 in Australia, 1 in UK and 1 in US. The patients were from ICU, Respiratory Medicine, Critical Care Medicine, Department of Extracorporeal Membrane Oxygenation, Department of Anesthesia or Department of Internal Medicine. ECMO time and method details were given in **Table 1**.

Comparison between ECMO and conventional mechanical ventilation

Thirteen studies with a total of 628 patients and 795 controls were included in this meta-analysis. Meta-analysis demonstrated that there was no difference as mortality rates between the two groups (**Figure 2**). The OR was 1.12 (95% CI: 0.69 to 1.81, random effect model). However, we found that the mortality rate of ECMO group was lower than control group in the Chinese subgroup with OR at 0.39 (95% CI: 0.17 to 0.86, fixed effect model). The secondary outcomes are adverse events and hospital stay, but most papers have no relevant data, so we did not do the analysis.

Publication bias

No significant publication bias was observed. Visual inspection of Begg's funnel plot showed substantial asymmetry (**Figure 3**). The Begg's rank correlation test indicated no evidence of publication bias among studies (P=0.72).

Discussion

Current meta-analysis was performed to investigate the treatment effect of ECMO for ARDS. Data from 13 clinical studies was pooled and analyzed. Our analyses did not identify significant effect differences between ECMO and conventional method in the treatment of patients with ARDs, other than certain Chinese patients.

The typical clinical manifestations of ARDS are hypoxemia. Although remarkable progress had been made in mechanical ventilation, 12-15% patients with severe ARDS directly died of refractory hypoxemia [25]. Extracorporeal membrane oxygenation in adult patients with acute respiratory failure, especially veno-venous-ECMO (v-v ECMO), have gained flourishing evidence worldwide during the recent years. ECMO treatment could reduce or avoid ventilator associated lung injury for hypoxemia [26]. However, present studies showed that the outcomes in most of patients failed to support the advantages of ECMO treatment over conventional method in the treatment of ARDS. This is probably due to different population, environment, technology, time and other conditions.

Modern extracorporeal membrane oxygenation and conventional lung assist systems both allow a prolonged respiratory support without the major impairment in the coagulation system [21]. Furthermore, compared to conventional lung assist systems, thrombocytopenia was common in v-v ECMO group. However platelet transfusions were normally not required. A single study showed that the patients with ECMO treatment were more severe in baseline characteristics including lung injury score, sepsis-related organ failure assessment (SOFA) score, and positive end-expiratory pressure (PEEP) [17]. These patients were in a worse condition before treatment, thus probably leading to a higher mortality rate. Recent studies at home and abroad [27, 28] also found that ECMO could reduce the mortality rate induced by infectious influenza A (H1N1). This could remind us that ECMO may exert different influence on ARDS by various causes.

Current meta-analysis may have certain limitations. Since heterogeneity was high, a random effect model was used. The source of heterogeneity may come from the facts that studies were conducted in different countries, various ECMO time, and diverse departments. A more comprehensive assessment of major factors for clinical data is needed in order to evaluate the mortality rate of ARDS that can further reduce or even completely eliminate the treatment disparity in ECMO.

In conclusion, based on pooled analysis, our study suggests that the treatment effect

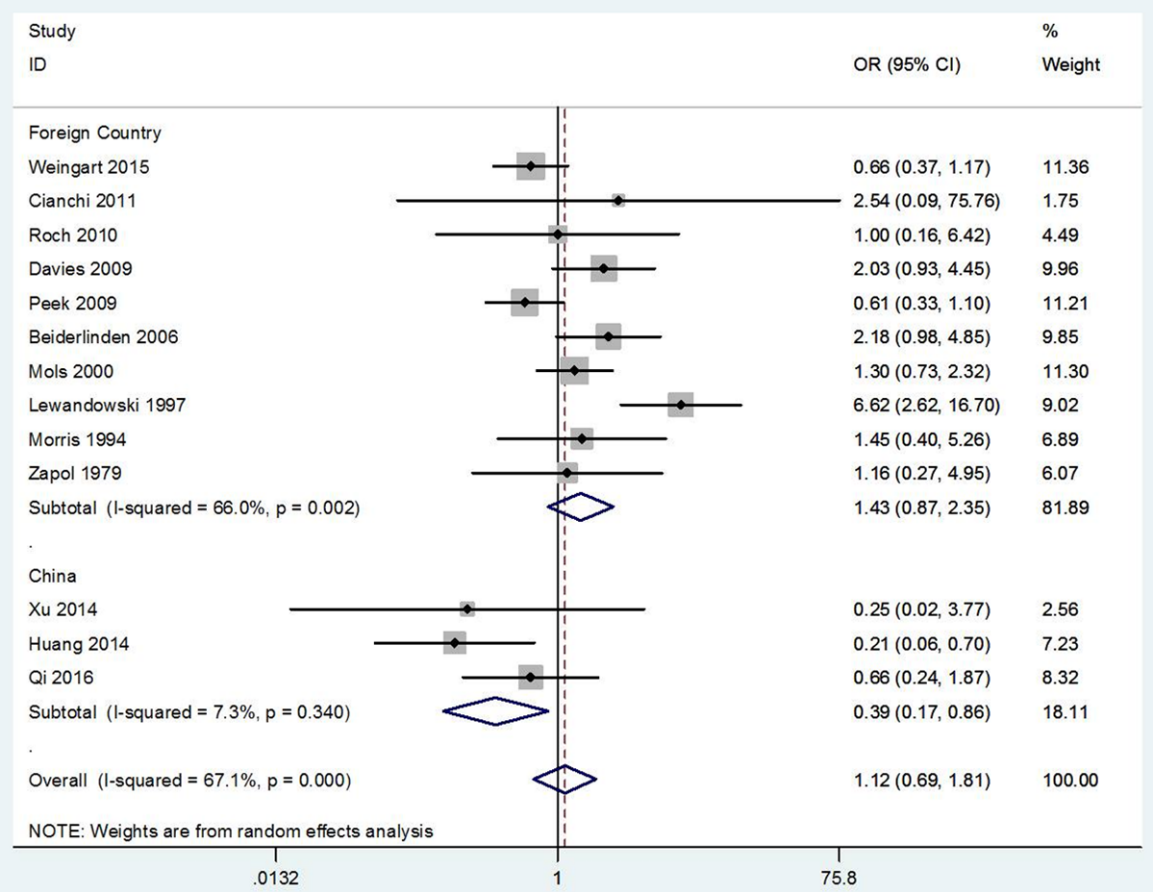

Figure 2. Forest plot of mortality rates between ECMO and conventional mechanical ventilation groups.

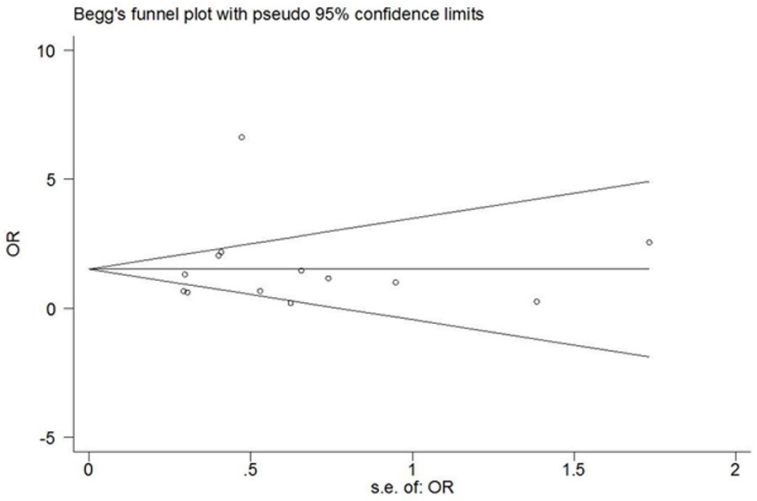

Figure 3. Begg's funnel plot of potential publication bias among studies.

between ECMO and conventional mechanical ventilation has no significantly difference for the mortality rate of ARDS. If further validated, our results may provide a cost-effective means to help physicians predict patient outcome and make decisions on treatment selection for ECMO.

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Disclosure of conflict of interest

None.

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