Is Extracorporeal Membrane Oxygenation the Standard Care for Acute Respiratory Distress Syndrome: A Systematic Review and Meta-Analysis

Jing Wang, MM [a], Yanling Wang, MM [b], Tao Wang, MM [a], Xiaokang Xing, MM [a], Ge Zhang, MM [a],*

[a]Department of Critical Care Medicine, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China
[b]Department of Medical Oncology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

Background	Acute respiratory distress syndrome (ARDS) is a type of acute respiratory failure syndrome characterised by severe respiratory distress and stubborn hypoxaemia. Patients with ARDS have a prolonged hospital stay and high mortality rate. Over long-term follow-up, ARDS is found to be associated with a high incidence of long-term complications and decreased quality of life. Venovenous extracorporeal membrane oxygenation (vv-ECMO) has been widely used for the treatment of refractory ARDS. However, it is not the standard treatment as recommended by ARDS guidelines.
Aim	The aim of this study was to compare the effects of ECMO (vv-ECMO) and conventional mechanical ventilation (CMV) on the clinical outcomes in patients with ARDS.
Method	We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, Medline, EMBASE, Web of Science, and PubMed databases up to November 2019. We selected appropriate studies according to our inclusion and exclusion criteria, and extracted and analysed the data using RevMan 5.0 software to evaluate the effectiveness of ECMO systematically.
Results	A total of 18 articles and 2,399 patients were included in this meta-analysis: 898 patients in the ECMO group and 1,501 patients in the CMV group. Treatment with ECMO may be associated with reduced 1-year mortality (95% confidence interval [CI], 0.27–0.83; p=0.009) and 60-day mortality (95% CI, 0.37–0.86; p=0.008), but increased Intensive Care Unit mortality (95% CI, 1.26–2.36; p=0.0007) of patients with ARDS. Extracorporeal membrane oxygenation may not be related to 30-day mortality or complications such as nosocomial pneumonia, haemorrhagic stroke, or continuous renal replacement therapy in patients with ARDS. However, some results showed heterogeneity, such as bleeding complications and in-hospital mortality. Subgroup analysis showed that ECMO treatment might increase ICU mortality (p=0.002) and nosocomial pneumonia complications (p=0.03) in patients with H1N1 ARDS.
Conclusions	Compared with CMV, ECMO contributed to lower 60-day and 1-year mortality, and increased ICU mortality in patients with ARDS. However, H1N1 ARDS was independently associated with higher ICU mortality and nosocomial pneumonia. The results were not affected by removing retrospective control studies or articles published >20 years ago from the sensitivity analysis. This meta-analysis demonstrates the effectiveness of ECMO and its importance in standard treatment of patients with ARDS.
Keywords	ECMO • ARDS • H1N1 • Mortality • Complications

*Corresponding author at: Department of Critical Care Medicine, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China; Email: 3204091@zju.edu.cn

Introduction

Acute Respiratory Distress Syndrome

First discovered in 1967 [1], acute respiratory distress syndrome (ARDS) is a unique type of hypoxaemic respiratory failure characterised by the acute onset of hypoxaemia and diffuse alveolar damage caused by non-cardiogenic pulmonary oedema. Without timely intervention, ARDS can evolve into to multi-organ failure. Therefore, it should not be underestimated.

Acute respiratory distress syndrome is a multifactorial lung injury. At present, there is no clear understanding of its epidemiology and outcome. Several studies have indicated that the most common risk factors for ARDS include pneumonia and non-pulmonary sepsis [2–4]. Other susceptibility factors include smoking, alcohol, drugs, heavy blood transfusions, obesity, and genetic factors.

A prospective, multicentre study found that the morbidity and mortality of ARDS increased with age, and that the in-hospital mortality rate was 41.1% [5]. In the USA, there are an estimated 190,000 cases, 74,000 deaths, and 3.6 million hospital days annually. Another large observational study, Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE (LUNG SAFE) [6], included 29,144 patients from 459 intensive care units (ICUs) in 50 countries; 3,022 (10.4%) of whom met the ARDS criteria over 4 weeks. Mortality increased with the severity of ARDS. For patients with mild, moderate, and severe ARDS, hospital mortality rates were 34.9%, 40.3%, and 46.1%, respectively.

A small number of patients with ARDS die from respiratory failure, while most die from their primary illness or secondary complications, such as sepsis and multiple organ dysfunction syndrome. Muscle weakness after ICU discharge is a frequent complication of ARDS and usually recovers within 12 months [7]. Any serious physical injury and decreased quality of life associated with muscle weakness lasts for >24 months.

Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome

At present, there are several treatment options for ARDS. Lung protective ventilation with low tidal volume, limited plateau pressure, and prone positioning are strongly recommended treatment options for ARDS, as per 2018 guidelines [8]. High-frequency oscillatory ventilation has no advantages over conventional mechanical ventilation (CMV), and may result in higher mortality [9]. For many years, extracorporeal membrane oxygenation (ECMO) remained a weak recommendation for ARDS owing to its significant complications and the lack of high-quality clinical research data.

Extracorporeal membrane oxygenation can improve oxygenation and remove carbon dioxide, and then reduce ventilator support (low tidal volume and low airway pressure, etc.), to rest the lungs and maintain a protective ventilation strategy of open lungs in order to buy time for treatment of the original disease [10].

In recent years, with the continuous progress in technology, ECMO has progressively achieved better clinical results in ARDS. The Conventional ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) study [11], a UK-based multicentre trial, recommend that patients with serious and recoverable ARDS should be sent to hospitals with ECMO availability. Extracorporeal membrane oxygenation did not only increase the survival rate, but also the quality-adjusted life-years in ARDS without disability. However, the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) study [12], a recent international randomised controlled trial (RCT), found that 60-day mortality in the ECMO group was not significantly lower compared with the CMV group.

This meta-analysis combined previously published high-quality clinical research, with an evaluation of whether ECMO should be the standard care in ARDS.

Methods

Study Selection Criteria

The inclusion criteria were based on the PICOS acronym (participant, intervention, comparison, outcomes of interest, and study design). Included patients with ARDS were identified according to ARDS criteria [1,13–15], which were defined when the articles were published. Meaningful outcomes for patients with ARDS treated with venovenous (vv)-ECMO included mortality and the associated incidence of complications, such as 30-day mortality, 60-day mortality, 1-year mortality, ICU mortality, in-hospital mortality, and nosocomial pneumonia, haemorrhagic stroke, bleeding, and the need for continuous renal replacement therapy (CRRT).

The exclusion criteria were clear: patients without ARDS, those <18 years of age, pregnancy, treatment with veno-arterial ECMO, had none of the abovementioned outcomes, animal studies, and non-control studies.

Search Methods

We searched RCTs and retrospective control studies (RCS) for the use of ECMO in ARDS in the following databases, up to 24 November 2019: the Cochrane Library, EMBASE, PubMed, Medline, Web of Science, and CNKI (China National Knowledge Infrastructure). The medical subject heading terms and EMTREE keywords included "extracorporeal membrane oxygenation", "Oxygenation, Extracorporeal Membrane", "Membrane Oxygenation, Extracorporeal", "Extracorporeal Life Support", "Life Support, Extracorporeal", "Support, Extracorporeal Life", "ECLS", "ECMO", "Acute respiratory failure", "Adult Respiratory Distress Syndrome", "Acute Respiratory Distress Syndrome", and "ARDS".

The scope of this screening article was huge, and the process of article inclusion and exclusion is shown in Figure 1.

Figure 1 Study flowchart.
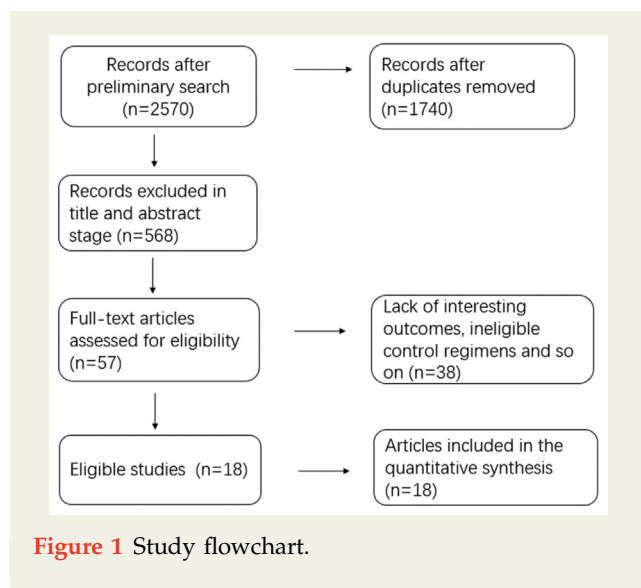
Data Collection

Two independent investigators were responsible for extracting articles and related data based on the inclusion/exclusion criteria. The disagreements were solved by consultation with the corresponding author (G.Z.). In addition, we tried to contact the original authors by email for incomplete data but received no response.

Quality Assessment and Data Analysis

The risk of bias of the screened RCTs was evaluated by RevMan version 5.3 (Cochrane Collaboration, Copenhagen, Denmark). The quality of non-RCTs was assessed with the Newcastle–Ottawa Scale. Data processing of the meta-analysis of was done with RevMan 5.3.

Results

A total of 2,570 articles that described the effects of ECMO in ARDS were retrieved. After screening, four RCTs and 14 RCSs were included in the meta-analysis. However, two of the RCTs were published >20 years ago. The study group included 898 patients with ARDS treated with ECMO and 1,501 patients with ARDS treated with CMV (control group).

The baseline characteristics of the included studies are given in Table 1 [11,12,16–31]. Next, we extracted data from the 18 studies and analysed the correlation between ECMO therapy and outcomes in patients with ARDS.

Thirty-Day Mortality

Three (3) articles (80 patients) reported 30-day mortality. As can be seen in Figure 2, ECMO may not be related to 30-day mortality in ARDS (odds ratio [OR], 1.37; 95% confidence interval [CI], –0.62 to 3.00 [z=0.79; p=0.43; χ^2=8.39; p for heterogeneity=0.47; I^2=0%]).

Sixty-Day Mortality

As can be seen in Figure 3, ECMO may be associated with decreased 60-day mortality in ARDS (OR, 0.57; 95% CI, 0.37–0.86 [z=2.65; p=0.008; χ^2=2.39; p for heterogeneity=0.3; I^2=16%]). Subgroup analyses showed that even if the article from 1979 was excluded, the result remained the same (p=0.007).

Intensive Care Unit Mortality

As is shown in Figure 4, ECMO in ARDS may be associated with higher ICU mortality (OR, 1.72; 95% CI, 1.26–2.36 [z=3.37; p=0.0007; χ^2=26.46; p for heterogeneity <0.0001; I^2=81%]).

Next, the therapeutic effect of ECMO in ARDS caused by H1N1 (H1N1-ARDS) in the pneumonia subgroup was analysed. Subgroup analyses found that ECMO treatment might worsen ICU mortality in the H1N1-ARDS subgroup (p=0.002; I^2=80%). However, the I^2 suggested significant heterogeneity among the studies. Sensitivity analyses was carried out, and the results showed that, after removing the study by Pham et al. [26], the I^2 of the ECMO study group with H1NI ARDS was 0. The I^2 of the whole ECMO study group was 0 after the removal of the studies by Munoz et al. [30] and Pham et al. [26]. Moreover, the results did not change, suggesting they were reliable.

In-Hospital Mortality

Figure 5 shows that the effect of ECMO in ARDS might not be associated with in-hospital mortality (OR, 1.06; 95% CI, 0.81–1.38 [z=0.42; p=0.67; χ^2=49.90; p for heterogeneity <0.00001; I^2=84%]). Subgroup analysis showed that ECMO was not associated with in-hospital mortality of the H1N1-ARDS subgroup (p=0.90; I^2=91%).

The I^2 value suggested significant heterogeneity among the studies. We did not find a suitable solution to the heterogeneity. Therefore, this result might not be reliable.

One-Year Mortality

Figure 6 shows that ECMO in ARDS might be associated with 1-year mortality (OR, 0.48; 95% CI, 0.27–0.83 [z=2.60; p=0.009; χ^2=1.34; p for heterogeneity=0.25; I^2=25%]).

Nosocomial Pneumonia

The results shown in Figure 7 did not indicate a relation between ECMO and nosocomial pneumonia (OR, 1.21; 95% CI, 0.82–1.78 [z=0.94; p=0.35; χ^2=0.10; p for heterogeneity=0.75; I^2=54%]). The I^2 indicated moderate heterogeneity among the studies. However, ECMO might be related to the increase in nosocomial pneumonia seen in the H1N1-ARDS patient subgroup (p=0.03; I^2=0%).

Bleeding Complications

As shown in Figure 8, ECMO was associated with more bleeding complications, as compared to the CMV group (OR, 2.64; 95% CI, 1.60–4.35 [z=3.82; p=0.0001; χ^2=13.69; p for heterogeneity=0.01; I^2=64%]).

Table 1 Baseline characteristics of included studies.

Study	Study Type	ARDS Aetiology	Average Age (yr) ECMO/CMV	Men ECMO/CMV	No. of Patients ECMO/CMV	PaO$_2$/FiO$_2$ ECMO/CMV	ICU LOS (d) ECMO/CMV	Primary Endpoint	ECMO Support Duration (d)	Mechanical Before ECMO	Country/District
Zapol et al. [16]	RCT	Mixed	NA	NA	42/48	NA	NA	30-d mortality, 60-d mortality	NA	NA	NA
Morris et al. [17]	RCT	Mixed	33/38	NA	21/19	62.6/63.8	23.8/24.2	30-d mortality	NA	NA	Utah, USA
Peek et al. [11]	RCT	Mixed	39.9/40.4	59	90/90	75.9/75.0	NA	9	NA	NA	Leicester, UK
Mi et al. [12]	RCT	Mixed	52/54	70/72	125/124	73/72	23/18	60-d mortality	14	NA	NA
Tsai et al. [18]	RCS	Mixed	48/57	69/68	45/45	117.4/121.80	NA	6-mo survival rate	NA	NA	NA
2018 Sahetya et al. [19]	RCS	Mixed	29/52.6	NA/54	5/41	NA	8/17.5	Hospital discharge survival rate	NA	6.4	Washington, USA
Grasselli et al. [20]	RCS	Mixed	54/54	70/62	34/50	72/114	24/11	1-yr mortality	9	1	Milan, Italy
Ullrich et al. [21]	RCS	Mixed	71/13	NA/NA	13/71	NA	31/16	ICU mortality	NA	NA	Böblingen, Germany
Weber-Carstens et al. [22]	RCS	H1N1	42/43	56/60	61/55	87/141	33/27	ICU mortality	NA	NA	Germany
Buchner et al. [23]	RCS	H1N1	50/58	69.2/69.2	13/13	NA	NA	30-d mortality, in-hospital mortality	NA	NA	Baltimore, USA
Wang et al. [24]	RCS	Mixed	NA	NA	42/154	NA	NA	In-hospital mortality, 1-yr mortality	NA	NA	Tianjin and Shandong, China
Davies et al. [25]	RCS	H1N1	36/44	48/47	68/133	NA	22/12	In-hospital mortality, ICU mortality	NA	NA	Australia and New Zealand
Pham et al. [26]	RCS	H1N1	NA	NA	103/157	NA	NA	ICU mortality	NA	<7	France
Lewandows et al. [27]	RCS	Mixed	31.5/33.3	NA	49/73	NA	50.1/31.2 31.2	In-ICU mortality	NA	NA	Berlin, Germany
Beiderlinden et al. [28]	RCS	Mixed	42.2/41.9	NA	32/118	63/100	NA	In-hospital mortality	NA	NA	Germany
Mols et al. [29]	RCS	Mixed	35/43	NA	62/183	96/126	NA	In-hospital mortality	NA	NA	Germany
Munoz et al. [30]	RCS	Mixed	44.6/53.1	60/68	15/52	67/79	44.6/28.4	ICU mortality	NA	8.5	Spain
2011 Noah et al. [31]	RCS	H1N1	36.5/42.8	NA	78/75	54.9/68.4		In-hospital mortality	NA	4.4	England

Data are n unless otherwise indicated.

Abbreviations: ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; CMV, conventional mechanical ventilation; PaO$_2$, partial pressure of oxygen; FiO$_2$, fraction of inspired oxygen; ICU, intensive care unit; LOS, length of stay; RCT, randomised controlled trial; NA, not available; RCS, retrospective control study; mixed ARDS, patients were included regardless of aetiological type; H1N1 ARDS, all the included ARDS patients were infected with H1N1.
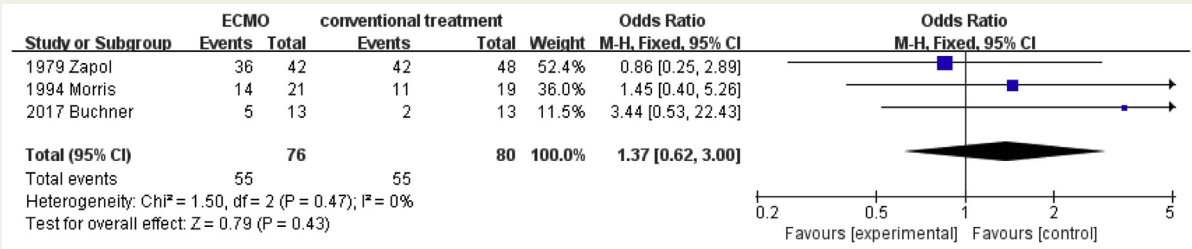
Figure 2 Extracorporeal membrane oxygenation (ECMO) versus conventional mechanical ventilation: 30-day mortality (Mantel–Haenszel statistic [MH], 1.37; 95% confidence interval [CI] –0.62 to 3.00; n=3).

Haemorrhagic Stroke

As shown in Figure 9, ECMO may not be associated with haemorrhagic stroke (OR, 1.00; 95% CI, 0.32–3.08 [z=0.00; p=1.00; χ^2=2.56; p for heterogeneity=0.28; I^2=22%]). After excluding the study by Morris et al. from 1994 [17], the result did not change (p=0.97).

Continuous Renal Replacement Therapy

Extracorporeal membrane oxygenation was also not associated with the incidence of the CRRT (OR, 1.56; 95% CI, 0.91–2.67 [z=1.63; p=0.10; χ^2=6.62; p for heterogeneity=0.08; I^2=55%]). However, the I^2 showed medium heterogeneity between studies (Figure 10).

Acute Physiology, Age, Chronic Health Evaluation II Scores and Sequential Organ Failure Assessment

Figure 11 presents the difference in Acute Physiology, Age, Chronic Health Evaluation II (APACHE II) scores between patients treated with ECMO and CMV (Mantel–Haenszel statistic [MH], 2.70; 95% CI 2.48–2.93 [z=23.73; p<0.00001,

χ^2=46.56; p for heterogeneity <0.00001; I^2=94%]). The ECMO group had a higher score. As can be seen in Figure 12, patients treated with ECMO may have a higher Sequential Organ Failure Assessment (SOFA) score than those treated with CMV (MH, 2.56; 95% CI, 2.47–2.65 [z=54.14; p<0.00001; χ^2=67.65; p for heterogeneity<0.00001; I^2=91%]). However, the I^2 suggested significant heterogeneity among the studies. A sensitivity analysis was done and the results showed that the I^2 decreased to 0% Acute Physiology and Chronic Health Evaluation (APACHE II) after removing the study by Morris et al. [17], and to 25% (SOFA) after removing the studies by Mi et al. [12] and Noah et al. [31]. The p-value remained <0.05, indicating that the APACHE II and SOFA scores were associated with ECMO treatment.

Discussion

H1N1 Acute Respiratory Distress Syndrome

In this meta-analysis, we found that ECMO treatment might increase the ICU mortality of and the incidence of nosocomial pneumonia in patients with H1N1-ARDS.
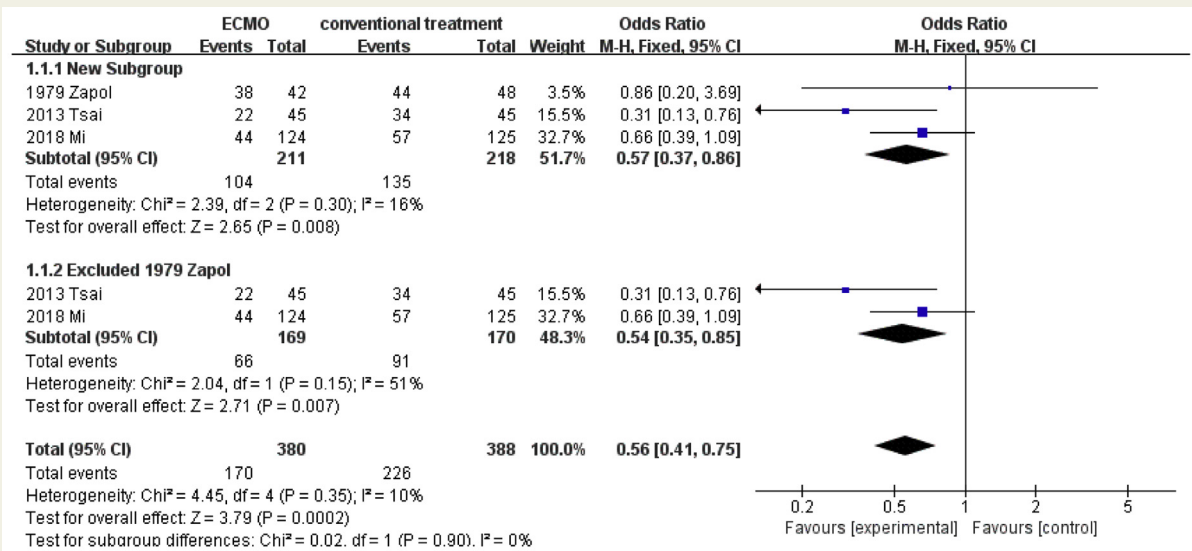

Figure 3 Extracorporeal membrane oxygenation (ECMO) versus conventional mechanical ventilation: 60-day mortality (Mantel–Haenszel statistic [MH], 0.57; 95% confidence interval [CI], 0.37–0.86; n=3).
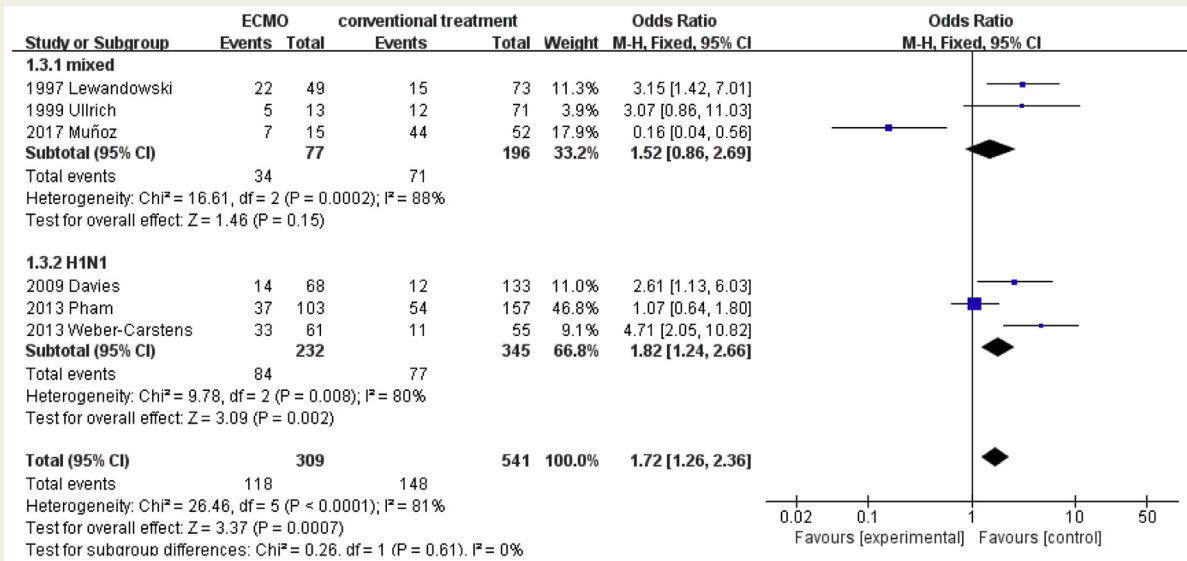
Figure 4 Extracorporeal membrane oxygenation (ECMO) versus conventional mechanical ventilation: Intensive Care Unit mortality (Mantel–Haenszel statistic [MH], 1.72; 95% confidence interval [CI], 1.26–2.36; n=6).

However, there has been no previous high-quality conclusion about ICU mortality. Some possibilities may account for this finding. Firstly, previous studies compared patients with H1N1 ARDS and non-H1N1 ARDS and found that patients with H1N1 ARDS had a more rapidly extensive viral pneumonia with severe lung function impairment, higher body mass indexes (BMIs), higher ICU resource consumption, required ECMO support more often, and needed longer ECMO support times and longer ICU stays [26,32,33], which may be why patients with H1N1 ARDS have a higher ICU mortality rate (in the post-pandemic H1N1 infection period).

Secondly, a recent study showed that ECMO withdrawal failure was the sole factor associated with ICU mortality [34]. As a result, depending on the meta-analysis, a higher incidence of nosocomial pneumonia in the ECMO group may
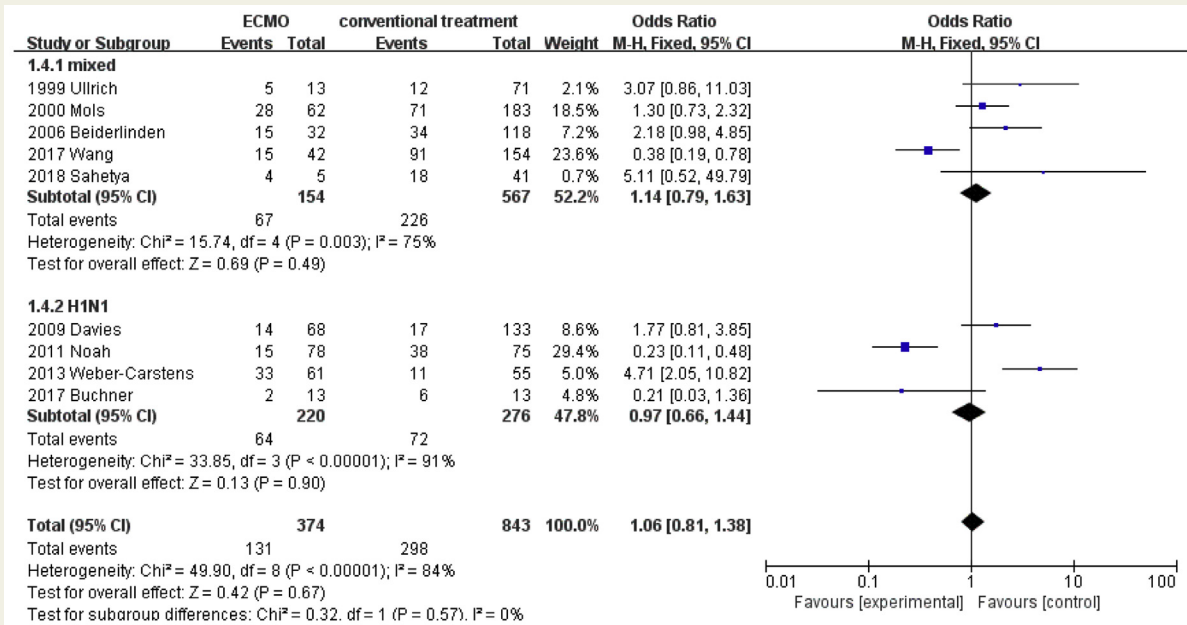

Figure 5 Extracorporeal membrane oxygenation (ECMO) versus conventional mechanical ventilation: in-hospital mortality (Mantel–Haenszel statistic [MH], 1.06; 95% confidence interval [CI], 0.81–1.38; n=9).
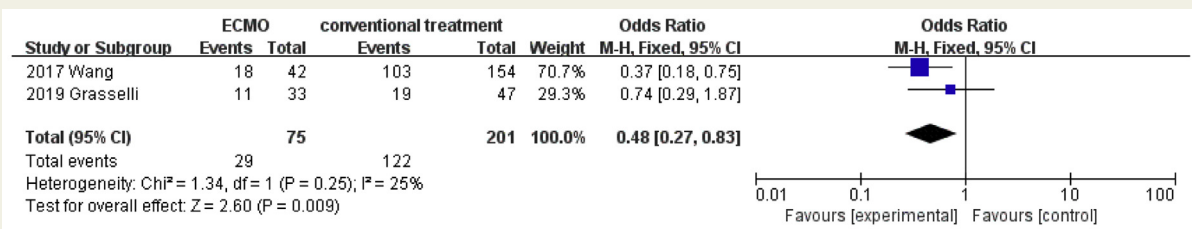
Figure 6 Extracorporeal membrane oxygenation (ECMO) versus conventional mechanical ventilation: 1-year mortality (Mantel–Haenszel statistic [MH], 0.48; 95% confidence interval [CI], 0.27–0.83; n=2).
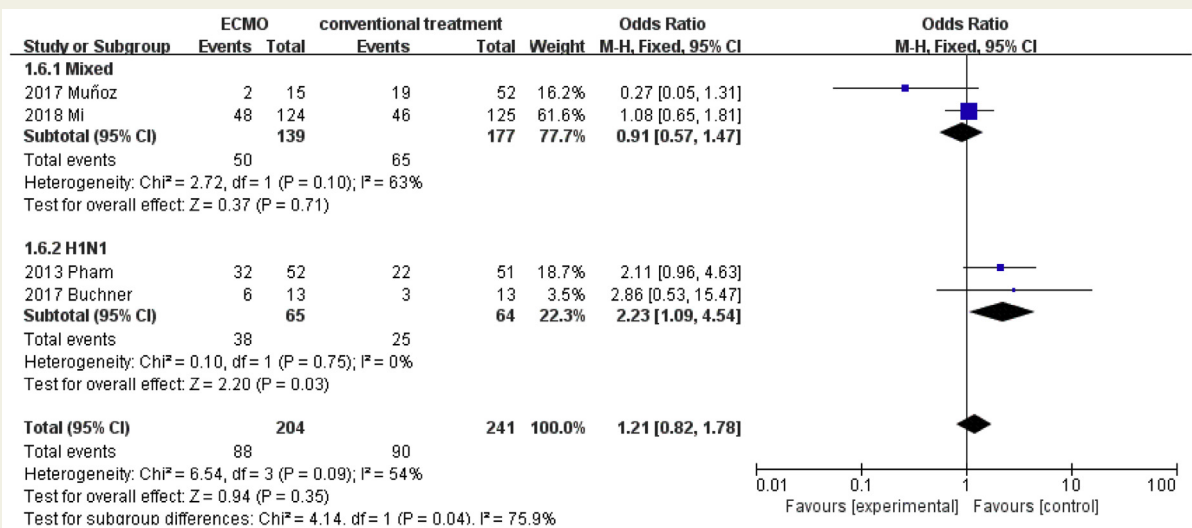

Figure 7 Extracorporeal membrane oxygenation (ECMO) versus conventional mechanical ventilation: nosocomial pneumonia (Mantel–Haenszel statistic [MH], 1.21; 95% confidence interval [CI], 0.82–1.78; n=4).
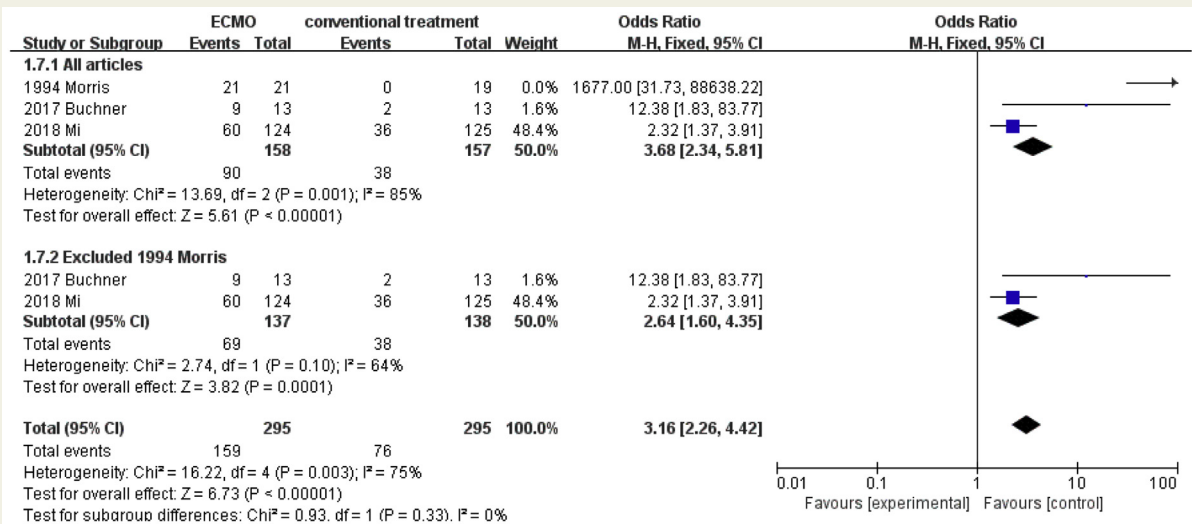

Figure 8 Extracorporeal membrane oxygenation (ECMO) versus conventional mechanical ventilation: bleeding complications (Mantel–Haenszel statistic [MH], 3.68; 95% confidence interval [CI] 2.34–5.81; n=3).
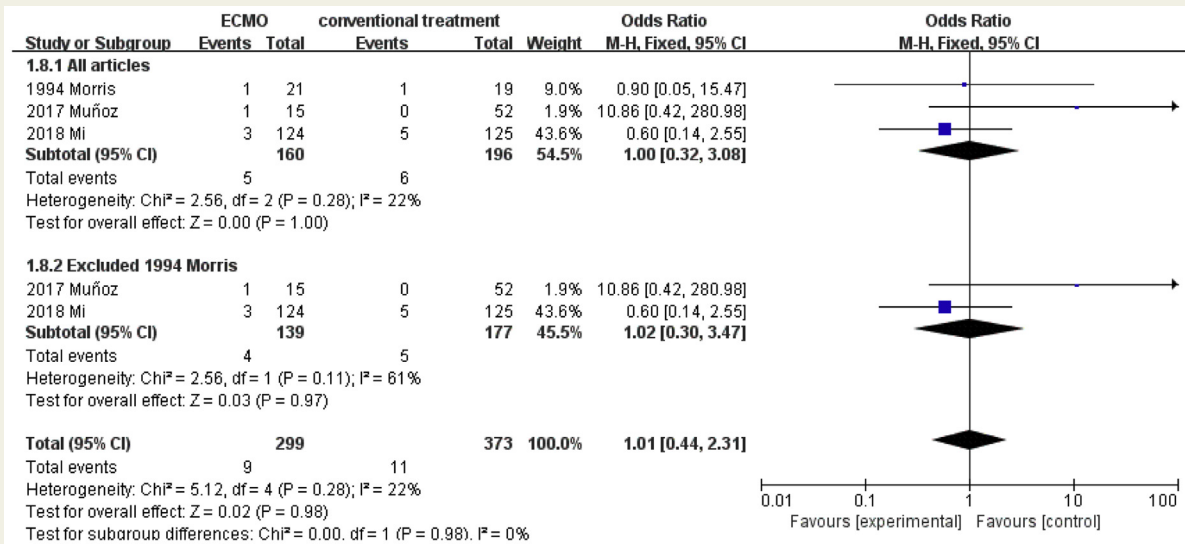
Figure 9 Extracorporeal membrane oxygenation (ECMO) versus conventional mechanical ventilation: haemorrhagic stroke (Mantel–Haenszel statistic [MH], 1.00; 95% confidence interval [CI], 0.32–3.08; n=3).

lead to ECMO withdrawal failure, which then leads to higher ICU mortality. More bleeding complications in the ECMO group may also be a culprit. The present study concludes that patients in the ECMO group have higher SOFA and APACHE II scores when all studies with complete data were combined in the meta-analysis. This may also have occurred in the six included studies [21,22,25-27,30] reporting ICU mortality, with bleeding complications leading to more sicker patients in the ECMO group, followed, as a consequence, by a higher ICU mortality.

In addition, some differences in management deserve attention, such as time to the initiation of ECMO, the application of steroids, and sample size. However, the included studies did not provide complete data for these factors, so it is regrettable that they could not be analysed with specific data, in order to draw conclusions.

Lastly, studies have found that hyperlactataemia before ECMO and higher dynamic driving pressure of patients needing ECMO in first 3 days were independent risk factors for increased ICU mortality [35,36]. Nevertheless, haematological disease, early acute kidney injury, corticosteroid therapy, and early haemodynamic failure might all be associated with the higher mortality rate in H1N1 ARDS [37,38]. Therefore, the influence factors in ICU mortality are numerous, and more rigorous studies are needed to confirm the relationship between ECMO support and the ICU mortality of patients with ARDS.

Sensitivity Analysis

The meta-analysis included four RCTs and 14 RCS. The studies were mostly retrospective and had been published over a long period of time, during which ECMO technology and knowledge regarding the safety of mechanical ventilation changed greatly.

Furthermore, patients with ARDS receiving ECMO, whether as part of an RCT or RCS, were prone to having more serious conditions and higher disease scores (SOFA and APACHE II) (Figures 11 and 12). And as can be seen in Figures 2–12, the results of the analysis id not change, even when RCSs were excluded from the sensitivity analysis.
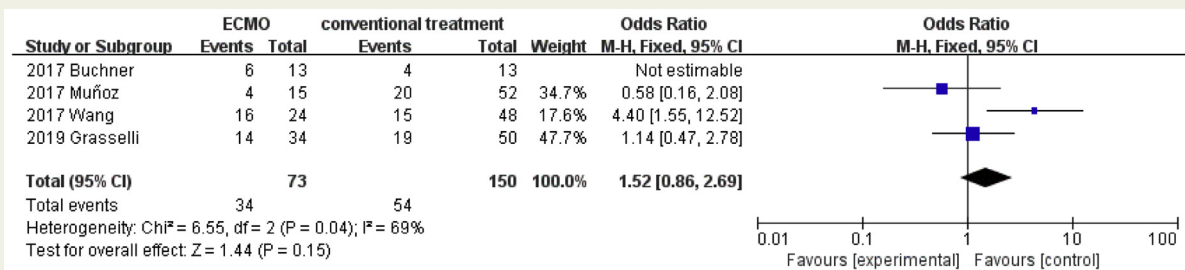

Figure 10 Extracorporeal membrane oxygenation (ECMO) versus conventional mechanical ventilation: continuous renal replacement therapy (Mantel–Haenszel statistic [MH], 1.56; 95% confidence interval [CI], 0.91–2.67; n=4).
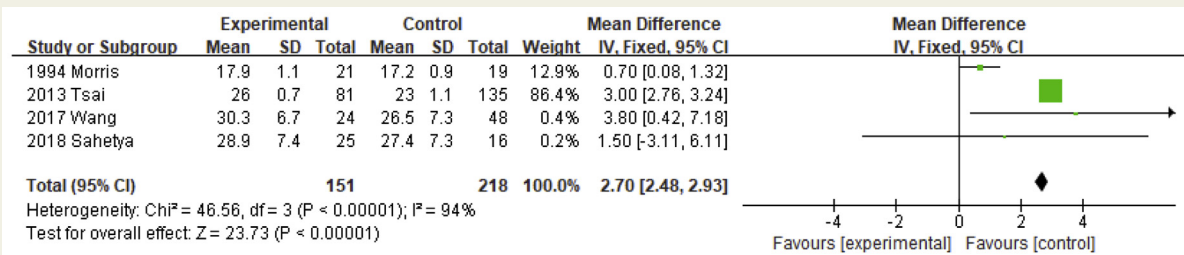
Figure 11 Extracorporeal membrane oxygenation (ECMO) versus conventional mechanical ventilation: Acute Physiology, Age, Chronic Health Evaluation II (APACHE II) score (Mantel–Haenszel statistic [MH], 2.70; 95% confidence interval [CI], 2.48–2.93; n=4).
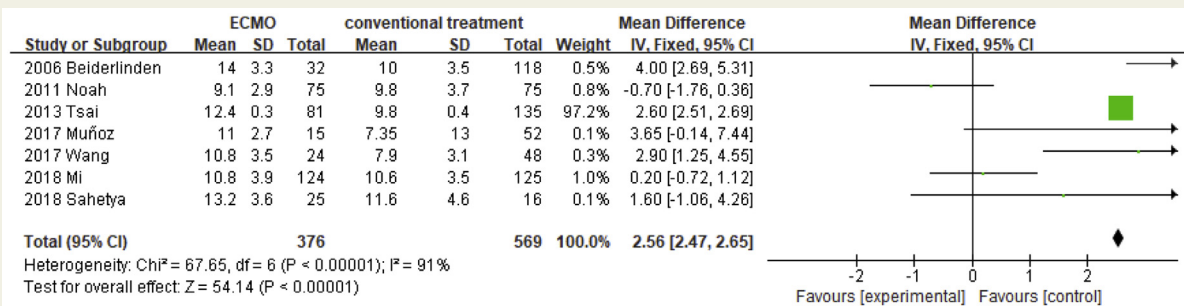

Figure 12 Extracorporeal membrane oxygenation (ECMO) versus conventional mechanical ventilation: Sequential Organ Failure Assessment (SOFA) score (Mantel–Haenszel statistic [MH], 2.56; 95% confidence interval [CI], 2.47–2.65; n=7).

Of the four RCTs, two were published >20 years ago. Subgroup analysis showed that the results did not change after the removal of these two RCTs. Therefore, our conclusion is reliable.

Factors Influencing Extracorporeal Membrane Oxygenation

Combined with the results of this paper and past studies [39], it can be concluded that ECMO plays an important role in the treatment of ARDS and will certainly be included as a standard treatment in future guidelines. However, the factors influencing ECMO treatment have not been clearly stated.

Ultrasound is a convenient and commonly used monitor of the disease course, which is critical for lung assessment and to identify complications in the ICU early. Daily lung ultrasound assessment is recommended during ECMO treatment in patients with ARDS [40]. The lactate clearance within 72 hours of the initiation of ECMO may contribute to risk stratification and the mortality of patients with ARDS [41]. However, some studies do not support this conclusion [42,43]. ECMOnet score [44] has long been concerned with predicting the efficacy of ECMO, and it is also used as a tool to evaluate the indications and time nodes of ECMO in ARDS. Research has found that, in general, obese (BMI >30 kg/m²) patients with refractory ARDS are more likely to need ECMO treatment [45,46], but there is no evidence of the relation between obesity and higher mortality.

Right ventricular hypertrophy is a side effect of ECMO support, which may be attributed to increased afterload and higher BMI. Right ventricular hypertrophy also has a negative impact on ICU mortality [45].

Limitations

Firstly, many important variables influenced the results of the study, such as the duration of ECMO, the CMV settings, number of mechanical ventilation days, prone positioning before ECMO, different populations, and time to initiation of ECMO. With regard to the 14 observational studies included, this review cannot overcome the limitations of primary studies. Most of the studies included in this meta-analysis did not report data on these indicators in detail.

Secondly, even though higher disease severity scores (SOFA and APACHE II) were associated with ECMO treatment, each study outcome included different articles, and more detailed data are needed to see if outcomes are affected by disease severity scores.

Conclusions

The meta-analysis showed that ECMO was associated with reduced 60-day and 1-year mortality, but increased ICU mortality, compared to CMV in patients with ARDS. Extracorporeal

membrane oxygenation may have different effects on different types of ARDS, such as H1N1 ARDS. In the subgroup analysis, ECMO treatment increased ICU mortality and the incidence of nosocomial pneumonia in patients with H1N1 ARDS.

Extracorporeal membrane oxygenation can be used as a standard step in the management of ARDS. It should be used immediately when high-risk criteria are satisfied, rather than as a late-stage rescue therapy in end-stage ARDS or multi-organ failure.

However, the appropriate time at which to use ECMO, the best applicable population, the clinical characteristics of patients, evaluation of efficacy, the best way in which to reduce the complications of ECMO, and the ARDS pathogen type for the best treatment effect are all problems that need to be solved. Therefore, it is hoped that there will be more high-quality research to address these issues.

Funding Sources

Conflicts of Interest

There are no conflicts of interest to disclose.

Author Contributions

J.W. was involved in the study design, data curation, formal analysis, investigation, methodology, project administration, resources, software, validation, visualisation, writing (original draft, final content, writing), and review and editing. Y.W. was involved with data curation, formal analysis, investigation, methodology, resources, validation, visualisation, writing (original draft). X.K.X. and T.W. carried out investigation and validation. G.Z. was involved in the study conceptualisation, project administration, software, supervision, visualisation, writing, review, and editing. All authors read and approved the manuscript.

Acknowledgements

References

[1] Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet. 1967;2:319–23.

[2] Rezoagli E, Fumagalli R, Bellani G. Definition and epidemiology of acute respiratory distress syndrome. Ann Transl Med. 2017;5:282.

[3] Ni YN, Luo J, Yu H, Wang Y-W, Hu Y-H, Liu D, et al. Can body mass index predict clinical outcomes for patients with acute lung injury/acute respiratory distress syndrome? A meta-analysis. Crit Care. 2017;21:36.

[4] Yeligar SM, Chen MM, Kovacs EJ, Sisson JH, Burnham EL, Brown LAS. Alcohol and lung injury and immunity. Alcohol. 2016;55:51–9.

[5] Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, et al. Incidence and outcomes of acute lung injury. N Engl J Med. 2005;353:1685–93.

[6] Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in Intensive Care Units in 50 countries. JAMA. 2016;315:788–800.

[7] Fan E, Dowdy DW, Colantuoni E, Mendez-Tellez PA, Sevransky JE, Shanholtz C, et al. Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. Crit Care Med. 2014;42:849–59.

[8] Griffiths M, Francis McAuley D, Perkins GD, Barrett N, Blackwood B, Boyle A, et al. Guidelines on the management of acute respiratory distress syndrome. BMJ Open Respir Res. 2019;6:e000420.

[9] Ferguson ND, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P, et al. High-frequency oscillation in early acute respiratory distress syndrome. N Engl J Med. 2013;368:795–805.

[10] Jabaudon M, Blondonnet R, Audard J. Encou-RAGE-ing lung protection in patients with acute respiratory distress syndrome under extracorporeal membrane oxygenation. Crit Care Med. 2019;47:1654–5.

[11] Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet. 2009;374:1351–63.

[12] Mi MY, Matthay MA, Morris AH. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med. 2018;379:884–7.

[13] ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307:2526–33.

[14] Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis. 1988;138:720–3.

[15] Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American–European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med. 1994;149:818–24.

[16] Zapol WM, Snider MT, Hill JD, Fallat RJ, Bartlett RH, Edmunds LH, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. JAMA. 1979;242:2193–6.

[17] Morris AH, Wallace CJ, Menlove RL, Clemmer TP, Orme JF Jr, Weaver LK, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. Am J Respir Crit Care Med. 1994;149:295–305.

[18] Tsai HC, Chang C-H, Tsai F-C, Fan P-C, Juan K-C, Lin C-Y, et al. Acute respiratory distress syndrome with and without extracorporeal membrane oxygenation: a score matched study. Ann Thorac Surg. 2015;100:458–64.

[19] Sahetya SK, Brower RG, Stephens RS. Survival of patients with severe acute respiratory distress syndrome treated without extracorporeal membrane oxygenation. Am J Crit Care. 2018;27:220–7.

[20] Grasselli G, Scaravilli V, Tubiolo D, Russo R, Crimella F, Bichi F, et al. Quality of life and lung function in survivors of extracorporeal membrane oxygenation for acute respiratory distress syndrome. Anesthesiology. 2019;130:572–80.

[21] Ullrich R, Lorber C, Röder G, Urak G, Faryniak B, Sladen RN, et al. Controlled airway pressure therapy, nitric oxide inhalation, prone position, and extracorporeal membrane oxygenation (ECMO) as components of an integrated approach to ARDS. Anesthesiology. 1999;91:1577–86.

[22] Weber-Carstens S, Goldmann A, Quintel M, Kalenka A, Kluge S, Peters J, et al. Extracorporeal lung support in H1N1 provoked acute respiratory failure: the experience of the German ARDS Network. Dtsch Arztebl Int. 2013;110:543–9.

[23] Buchner J, Mazzeffi M, Kon Z, Menaker J, Rubinson L, Bittle G, et al. Single-center experience with venovenous ECMO for influenza-related ARDS. J Cardiothorac Vasc Anesth. 2018;32:1154–9.

[24] Wang ZY, Li T, Wang C-T, Xu L, Gao X-J. Assessment of 1-year outcomes in survivors of severe acute respiratory distress syndrome receiving extracorporeal membrane oxygenation or mechanical ventilation: a prospective observational study. Chin Med J (Engl). 2017;130:1161–8.

[25] Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators, Davies A, Jones D, Baily M, Beca J, Bellomo R, Blackwell N, et al. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. JAMA. 2009;302:1888–95.

[26] Pham T, Combes A, Rozé H, Chevret S, Mercat A, Roch A, et al. Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis. Am J Respir Crit Care Med. 2013;187:276–85.

[27] Lewandowski K, Rossaint R, Pappert D, Gerlach H, Slama KJ, Weidemann H, et al. High survival rate in 122 ARDS patients managed according to a clinical algorithm including extracorporeal membrane oxygenation. Intensive Care Med. 1997;23:819–35.

[28] Beiderlinden M, Eikermann M, Boes T, Breitfeld C, Peters J. Treatment of severe acute respiratory distress syndrome: role of extracorporeal gas exchange. Intensive Care Med. 2006;32:1627–31.

[29] Mols G, Loop T, Geiger K, Farthmann E, Benzing A. Extracorporeal membrane oxygenation: a ten-year experience. Am J Surg. 2000;180:144–54.

[30] Muñoz J, Santa-Teresa P, Tomey MJ, Visedo LC, Keough E, Barrios JC, et al. Extracorporeal membrane oxygenation (ECMO) in adults with acute respiratory distress syndrome (ARDS): a 6-year experience and case-control study. Heart Lung. 2017;46:100–5.

[31] Noah MA, Peek GJ, Finney SJ, Griffiths MJ, Harrison DA, Grieve R, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). JAMA. 2011;306:1659–68.

[32] Töpfer L, Menk M, Weber-Carstens S, Spies C, Wernecke K-D, Uhrig A, et al. Influenza A (H1N1) vs non-H1N1 ARDS: analysis of clinical. course. J Crit Care. 2014;29:340–6.

[33] Díaz E, Rodríguez A, Martin-Loeches I, Lorente L, Del Mar Martín M, Pozo JC, et al. Impact of obesity in patients infected with 2009 influenza A(H1N1). Chest. 2011;139:382–6.

[34] Kim G, Koh Y, Lim C-M, Huh JW, Jung SH, Kim JB, et al. The effect of an improvement of experience and training in extracorporeal membrane oxygenation management on clinical outcomes. Korean J Intern Med. 2018;33:121–9.

[35] Chiu L-C, Hu H-C, Hung C-Y, Chang C-H, Tsai F-C, Yang C-T, et al. Dynamic driving pressure associated mortality in acute respiratory distress syndrome with extracorporeal membrane oxygenation. Ann Intensive Care. 2017;7:12.

[36] Lazzeri C, Bonizzoli M, Cianchi G, Batacchi S, Terenzi P, Cozzolino M, et al. Lactate and echocardiography before veno-venous extracorporeal membrane oxygenation support. Heart Lung Circ. 2018;27:99–103.

[37] Martin-Loeches I, Díaz E, Vidaur L, Torres A, Laborda C, Granada R, et al. Pandemic and post-pandemic influenza A (H1N1) infection in critically ill patients. Critical Care. 2011;15:R286.

[38] Hernández Garcés H, Navarro Lacalle A, Lizama López L, Zaragoza Crespo R. Risk factors associated to noninvasive ventilation failure in primary influenza A pneumonia in the critical care setting. Med Intensiva. Epub ahead of print 7 January 2020, https://doi.org/10.1016/j.medin.2019.11.007.

[39] Bartlett RH. Extracorporeal membrane oxygenation for acute respiratory distress syndrome: EOLIA and beyond. Crit Care Med. 2019;47:114–7.

[40] Mongodi S, Pozzi M, Orlando A, Bouhemad B, Stella A, Tavazzi G, et al. Lung ultrasound for daily monitoring of ARDS patients on extracorporeal membrane oxygenation: preliminary experience. Intensive Care Med. 2018;44:123–4.

[41] Bonizzoli M, Lazzeri C, Cianchi G, Boddi M, Cozzolino M, Di Valvasone S, et al. Serial lactate measurements as a prognostic tool in venovenous extracorporeal membrane oxygenation support. Ann Thorac Surg. 2017;103:812–8.

[42] Beurtheret S, Mastroianni C, Pozzi M, D'Alessandro C, Luyt C-E, Combes A, et al. Extracorporeal membrane oxygenation for 2009 influenza A (H1N1) acute respiratory distress syndrome: single-centre experience with 1-year follow-up. Eur J Cardiothorac Surg. 2012;41:691–5.

[43] Voelker MT, Busch T, Bercker S, Fichtner F, Kaisers UX, Laudi S. Restrictive transfusion practice during extracorporeal membrane oxygenation therapy for severe acute respiratory distress syndrome. Artif Organs. 2015;39:374–8.

[44] Pappalardo F, Pieri M, Greco T, Patroniti N, Pesenti A, Arcadipane A, et al. Predicting mortality risk in patients undergoing venovenous ECMO for ARDS due to influenza A (H1N1) pneumonia: the ECMOnet score. Intensive Care Med. 2013;39:275–81.

[45] Lazzeri C, Bonizzoli M, Cianchi G, Batacchi S, Terenzi P, Cozzolino M, et al. Body mass index and echocardiography in refractory ARDS treated with veno-venous extracorporeal membrane oxygenation. J Artif Organs. 2017;20:50–6.

[46] Galvagno SJ Jr, Pelekhaty S, Cornachione CR, Deatrick KB, Mazzeffi MA, Scalea TM, et al. Does weight matter? Outcomes in adult patients on venovenous extracorporeal membrane oxygenation when stratified by obesity class. Anesth Analg. 2020;131:754–61.