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The Performance of Extracorporeal Membrane Oxygenation in Various Viral Pneumonia Pandemics: A Meta-Analysis and Systematic Review

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Abstract: *Objective:* To compare the effects of extracorporeal membrane oxygenation (ECMO) and routine mechanical ventilation on mortality and the risk of associated adverse events in patients with severe viral pneumonia. *Methods:* PubMed, the Cochrane Library, Embase, Web of Science, and other databases were searched to collect case-control or cohort studies on prognoses associated with ECMO treatment for viral pneumonia. Search terms included extracorporeal membrane oxygenation, ECMO, viral pneumonia, COVID-19, influenza, MERS, and others. According to the PICOS principle, two evaluators independently screened the literature, extracted the data, cross-checked the data, and extracted the data again. Two researchers evaluated the risk of bias in the included studies according to the Newcastle-Ottawa Scale (NOS) and cross-checked the results. Meta-analysis was performed using RevMan 5.3 software. *Results:* Nine studies were included for analysis, encompassing a total of 4,330 patients, which were categorized into ECMO and CMV groups. There were no significant differences between the two groups in most baseline data; however, the ECMO group had a lower oxygenation index, and some studies reported higher SOFA scores in the ECMO group compared to the CMV group. There was no significant difference in in-hospital mortality between the two groups. The length of ICU stay, total hospital stay, and total mechanical ventilation time were longer in the ECMO group than in the CMV group. In terms of adverse events, there was no significant difference in the occurrence of kidney injury between the two groups. Bleeding events were reported in two studies, with more bleeding events occurring in the ECMO group. According to the subgroup analysis of different virus types, there were no statistical differences in the above aspects among patients with swine flu, novel coronavirus, and MERS. *Conclusion:* ECMO has a certain degree of positive significance in the treatment of severe viral pneumonia, but there is no significant difference in the treatment outcome of ECMO across different epidemic periods. The timing of ECMO treatment, patient management, and withdrawal evaluation still need further research.

Keywords: Extracorporeal membrane oxygenation; Viral pneumonia pandemic; Meta-analysis

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1. Introduction

Pneumonia is a common disease and a major factor in the aggravation or death of patients. It is often associated with atypical bacteria, viruses, or pathogens, with viral pneumonia being a very significant category. In recent years, improvements in PCR multiple testing techniques have identified a large number of viral pneumonia cases, increasing the diagnosis rate and improving our understanding of viruses as pathogens for both mild and severe respiratory infections [1]. Generally, adenoviruses, cytomegaloviruses, parainfluenza viruses, respiratory syncytial virus (RSV), influenza A and B viruses, and the coronavirus family are responsible for most viral pneumonia. For more than two decades, influenza A and B viruses and coronaviruses such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and novel coronavirus (COVID-19) have repeatedly caused epidemics and pandemics worldwide [2], significantly impacting global life and economies.

Viral pneumonia can cause diffuse alveolar damage, lung cell exfoliation, edema, and hyaline membrane formation, resulting in acute respiratory distress syndrome (ARDS). Without rapid intervention, it can progress to multi-organ failure [3]. Treatment for severe viral pneumonia is primarily supportive. Antivirals such as acyclovir, ribavirin, palivizumab, oseltamivir, zanamivir, amantadine, and rimantadine are available and effective in specific cases. Patients with severe viral pneumonia admitted to an intensive care unit (ICU) typically receive mechanical ventilation to correct hypoxia, in addition to appropriate antiviral therapy when possible. For the most critical patients, extracorporeal membrane oxygenation (ECMO) is considered to improve oxygenation and carbon dioxide removal, reducing the need for ventilator support (e.g., low tidal volume and low airway pressure) and allowing lung rest. This strategy, along with protective ventilation, buys time for primary disease treatment and lung repair [4].

ECMO proved to be an effective management option during the 2009 influenza A (H1N1) outbreak [5]. It has also played an indispensable role during the COVID-19 pandemic. Initial ECMO outcome data in the early stages of the COVID-19 pandemic showed a disproportionately high mortality rate, possibly due to poor patient selection early on [6]. In 2021, data from a large multicenter cohort study and the Extracorporeal Life Support Organization (ELSO) registry for COVID-19 ECMO patients suggested improved survival compared to earlier reports [7]. Currently, ECMO is recommended only for severe patients who fail to respond to other ventilation therapies early on, due to its high cost and numerous complications [8].

With the development of technology and varying types of viral pneumonia, ECMO strategies and therapeutic effects differ. We performed a systematic review and meta-analysis of available data to compare the effects of ECMO versus conventional mechanical ventilation on mortality and the risk of related adverse events in patients with severe viral pneumonia.

2. Materials and methods

2.1. Study inclusion criteria

(1) Study types: Case-control studies and cohort studies.

(2) Subjects: Patients with viral pneumonia treated with ECMO, regardless of race, nationality, and disease duration. Patients in the control group received mechanical ventilation.

(3) Outcome measures: Incidence of complications or mortality.

2.2. Exclusion criteria

(1) Repeated publications;

(2) Articles without full text;

(3) Literature with inconsistent outcome indicators;
(4) No valid data or data that could not be extracted, even after contacting the authors.

2.3. Literature search strategy

Databases such as PubMed, the Cochrane Library, Embase, and Web of Science were searched to collect case-control or cohort studies on the prognosis of patients with viral pneumonia treated with ECMO. The search period extended from the establishment of each database until September 5, 2023. A combination of subject-specific terms and unrestricted keywords was used, adjusted for the unique characteristics of each database. English search terms included extracorporeal membrane oxygenation (ECMO), and viral pneumonia (including COVID-19, influenza, and MERS), among others. Chinese search terms included extracorporeal membrane oxygenation, extracorporeal life support therapy, viral pneumonia, influenza A, influenza B, and novel coronavirus.

2.4. Document selection and data extraction

Two independent researchers selected the literature, extracted the information, and cross-checked the data. If discrepancies occurred, a third party was consulted, and the author was contacted to supplement any insufficient data. Initially, titles and abstracts were read to exclude irrelevant literature. Then, the full text was reviewed to determine final inclusion. Data extraction included:

(1) Basic information: study name, author, study type, country, and publication date.
(2) Basic characteristics of the subjects: sample size, grouping, age, gender, disease type, and treatment mode.
(3) Key elements of risk of bias assessment.
(4) Outcome indicators and indicators of interest.

2.5. Risk of bias assessment

The risk of bias in the included studies was evaluated by two researchers using the Newcastle-Ottawa Scale (NOS), and the results were cross-checked. The NOS consists of three dimensions, eight items, and a total of nine points. Higher scores indicate a lower risk of bias.

2.6. Statistical analysis

Meta-analysis was performed using RevMan 5.3 software. Continuous variables were reported as mean ± standard deviation. If the original research used median and quartiles, these were converted to mean and standard deviation using an online calculator (https://smcgrath.shinyapps.io/estmeansd).

3. Results

3.1. Literature screening

A total of 1,628 relevant studies were initially screened, and 9 studies were finally included. The screening process is shown in **Figure 1**. Among these studies, 4 focused on influenza patients, 1 on Middle East respiratory syndrome (MERS), and 4 on the novel coronavirus (COVID-19). A total of 4,330 patients were included in the 9 studies, with 386 patients treated with ECMO and 3,944 patients treated with mechanical ventilation.

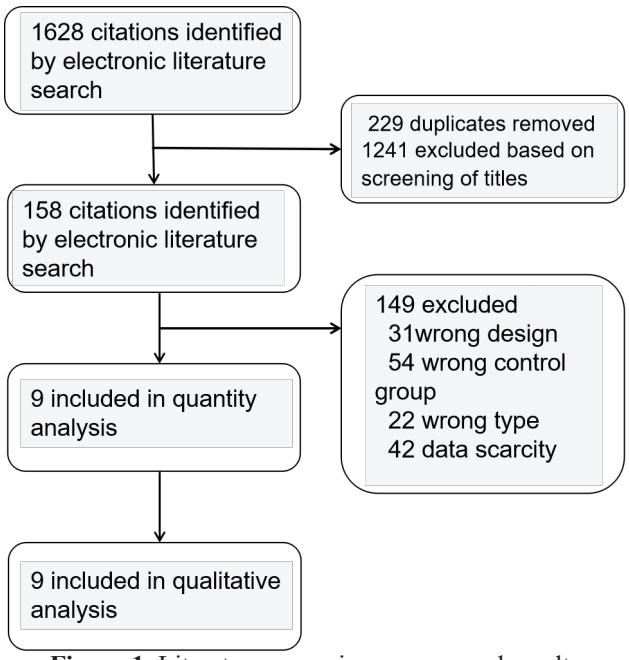


Figure 1. Literature screening process and results

3.2. Basic characteristics and quality analysis of literature

The 9 included studies were retrospective medical record control studies or cohort analyses. The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the literature, and the results are shown in **Table 1**. The basic information of the patients in each study is shown in **Table 2**. The subjects of the nine studies were adult patients admitted to the ICU during viral pneumonia-related pandemics. Most of the patients were male, with an average age between 36 and 70 years, a median oxygenation index of less than 100 mmHg, and a median SOFA score of 6 or greater.

Forest plot analysis of the oxygenation index and SOFA score (**Figures 2** and **3**) showed that the oxygenation index was lower in the ECMO group ($P < 0.001$). While the SOFA score was higher in the ECMO group than in the control group in some studies, there was no significant difference in the SOFA score between the two groups in general ($P = 0.26$).

Table 1. Quality assessment of the included literature NOS scale scores

Study names	Year	Selection	Comparability	Ending	Total score
Andrew Davies	2009	* * * *	**	**	8
Antoine Roch	2010	* * * *	**	* * *	9
Jessica Buchner	2017	* * * *	*	* * *	8
Jing FANG	2021	* * * *	*	* * *	8
Mohammed S. Alshahrani	2018	* * * *	**	* * *	9
Muhtadi Alnababteh	2021	* * * *	**	**	8
Ta'i Pham	2012	* * * *	**	**	8
Shahzad Shaef	2021	* * * *	**	**	8
Xiao Yang	2020	* * * *	**	**	8

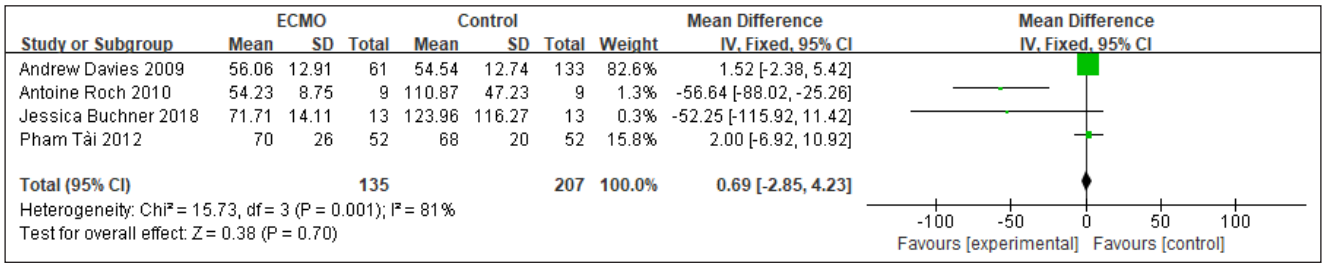


Figure 2. Oxygenation index analysis

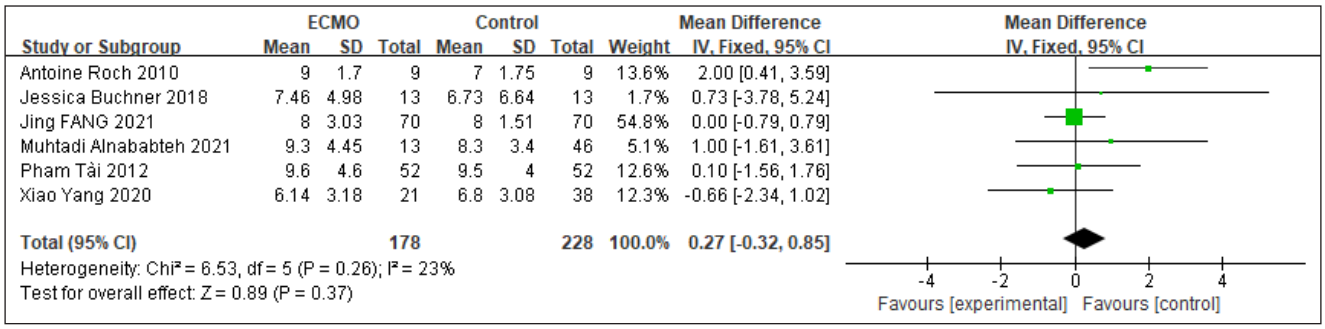
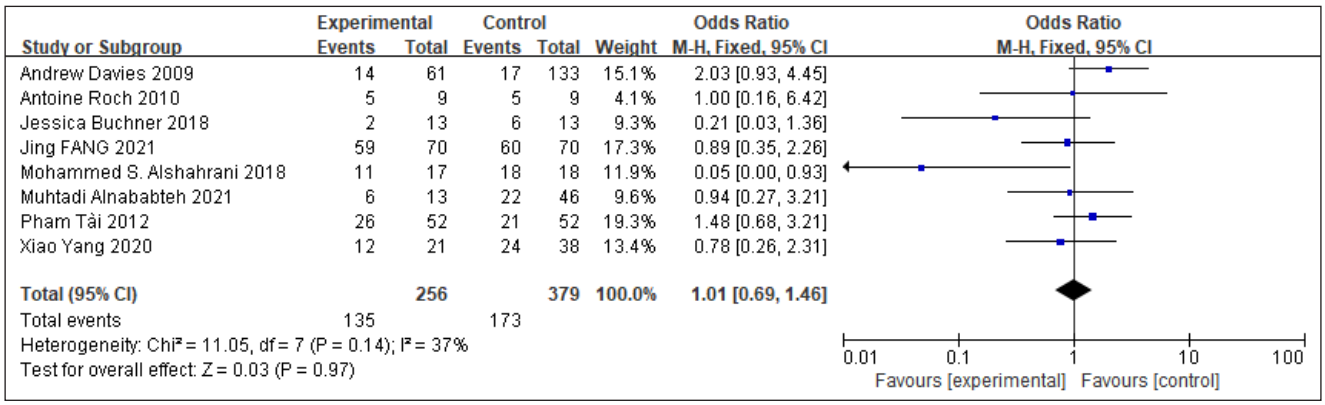


Figure 3. SOFA score analysis

3.3. Meta-analysis and subgroup analysis

3.3.1. Main outcome measures: number of in-hospital deaths

A total of 8 studies reported in-hospital deaths (**Figure 4**). A total of 256 patients received ECMO and 379 patients were in the mechanical ventilation group. The random-effects model meta-analysis showed no significant difference in in-hospital mortality between the two groups (P = 0.14). Only the results from the Mohammed S. Alshahrani 2018 study indicated that the number of deaths in the ECMO group was lower than that in the mechanical ventilation group. Subgroup analysis according to disease type, showed that in patients with COVID-19, the treatment effect of the ECMO group was improved, but the overall difference was not significant (P = 0.26).



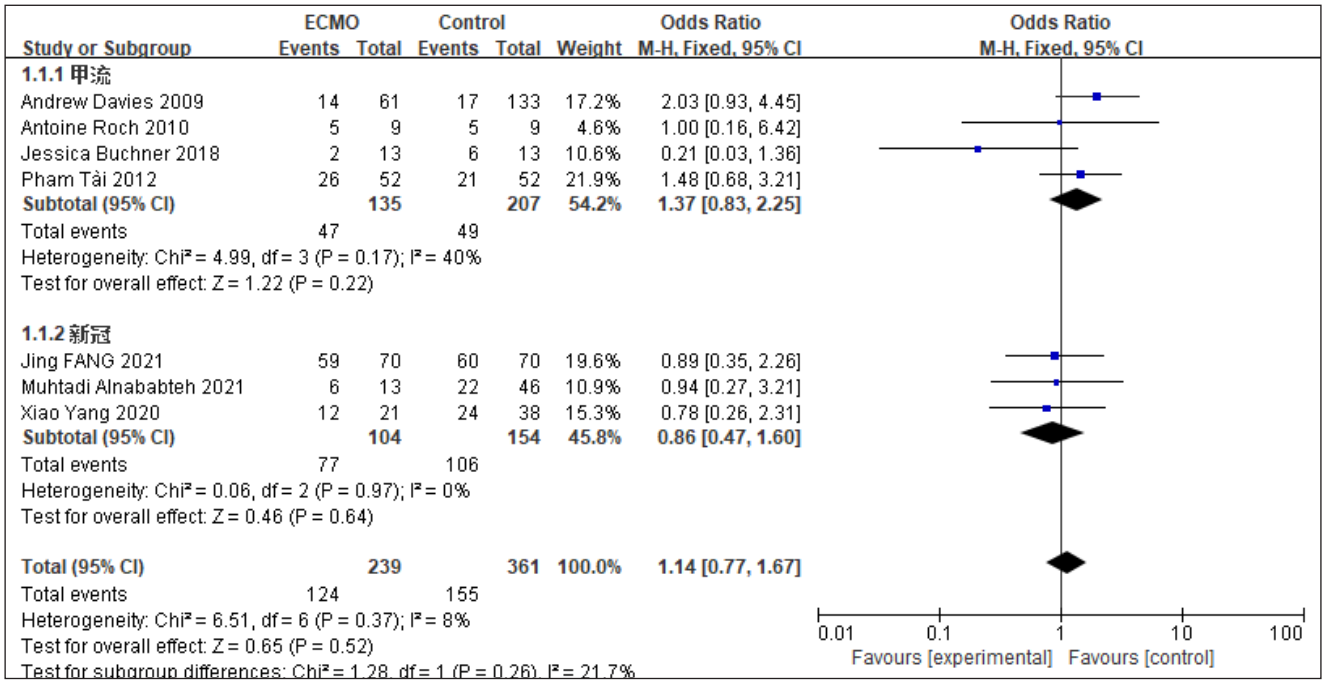
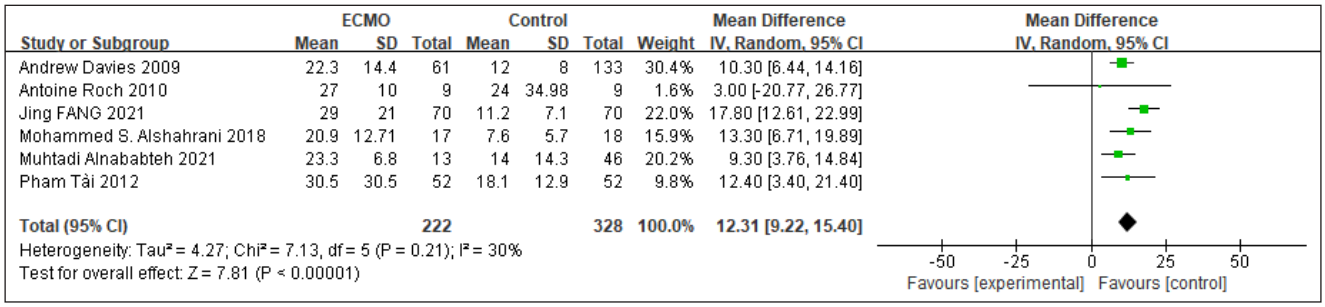


Figure 4. Analysis of in-hospital deaths and subgroup analysis

3.3.2. Secondary outcomes: length of ICU stay, total length of hospital stay, and duration of mechanical ventilation

ICU length of stay and total length of stay were reported in six and five studies, respectively, involving patients with influenza, COVID-19, and MERS (**Figures 5** and **6**). The random-effects model meta-analysis suggested that the length of ICU stay and the total length of hospital stay were longer in the ECMO group than in the mechanical ventilation group ($P < 0.00001$ for both ICU stay and total hospital stay). According to the subgroup analysis based on virus type, there was no statistically significant difference in the duration of ICU stay among patients with different diseases ($P = 0.41$). Although the study by Mohammed S. Alshahrani in 2018 suggested that the ECMO group had a relatively shorter total hospital stay, statistical significance did not indicate a significant difference. Furthermore, there was no significant variation in the total length of hospital stay between the ECMO group and the mechanical ventilation group based on clinical condition ($P = 0.13$).

The total duration of mechanical ventilation was reported in six studies (**Figure 7**), involving 218 patients in the ECMO group and 323 patients in the mechanical ventilation group. The random-effects meta-analysis suggested that the duration of mechanical ventilation was longer in the ECMO group than in the control group ($P < 0.00001$). Subgroup analysis based on influenza, COVID-19, and MERS showed that in different diseases, the ECMO group had a longer duration of mechanical ventilation, with no significant difference among the three subgroups ($P = 0.06$). In addition, except for one study (Antoine Roch 2010), the duration of mechanical ventilation in the other groups was statistically different.



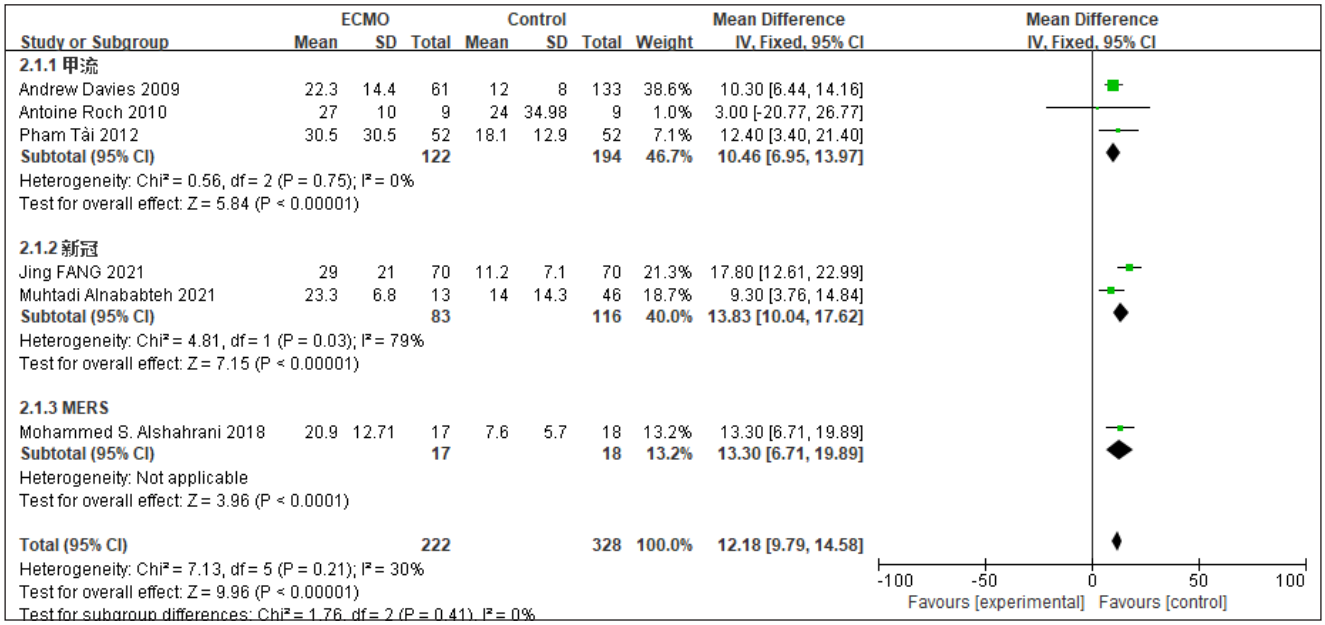
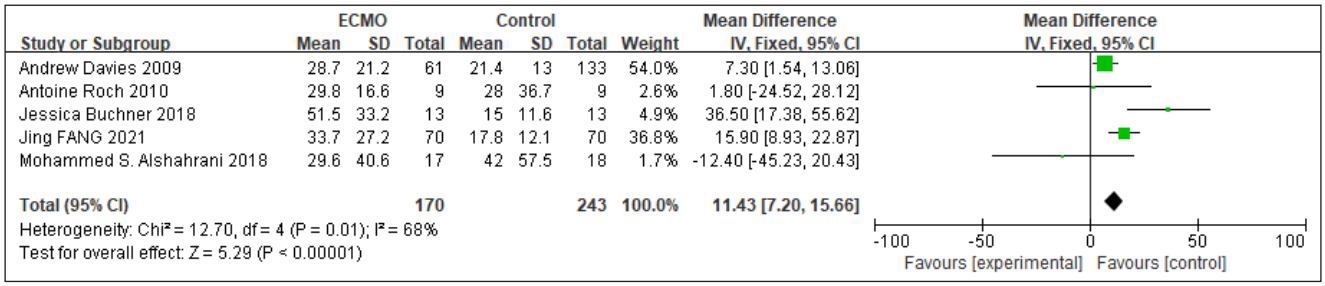


Figure 5. ICU length of stay and subgroup analysis



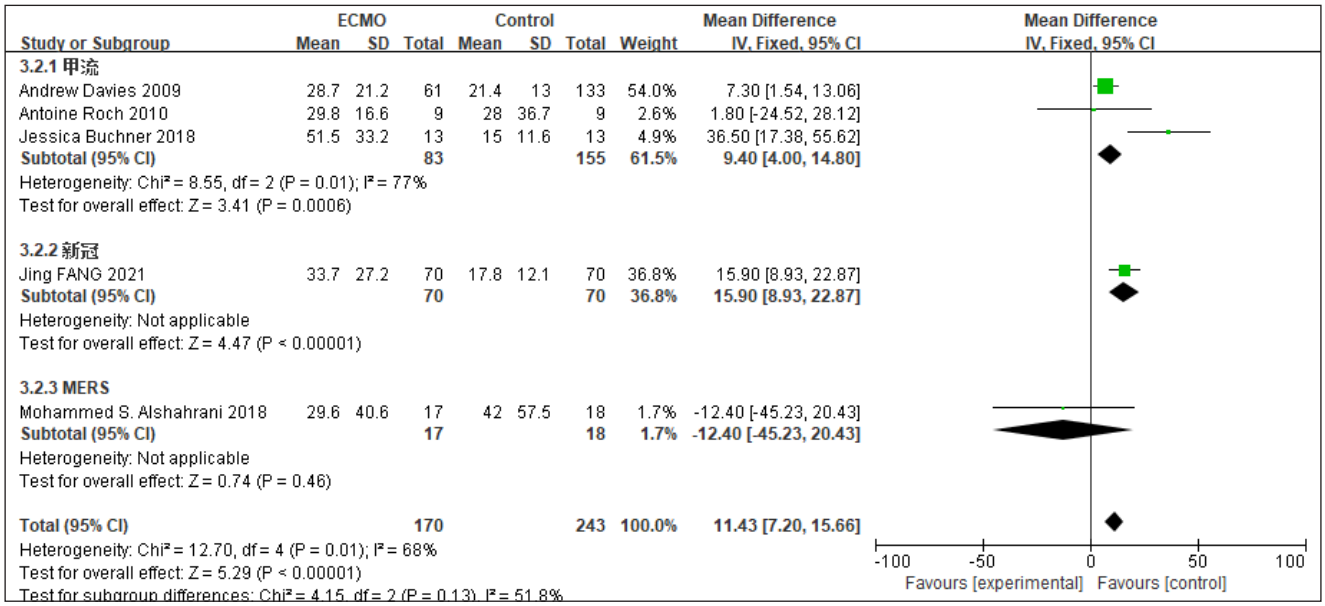


Figure 6. Analysis of total length of stay and subgroup analysis

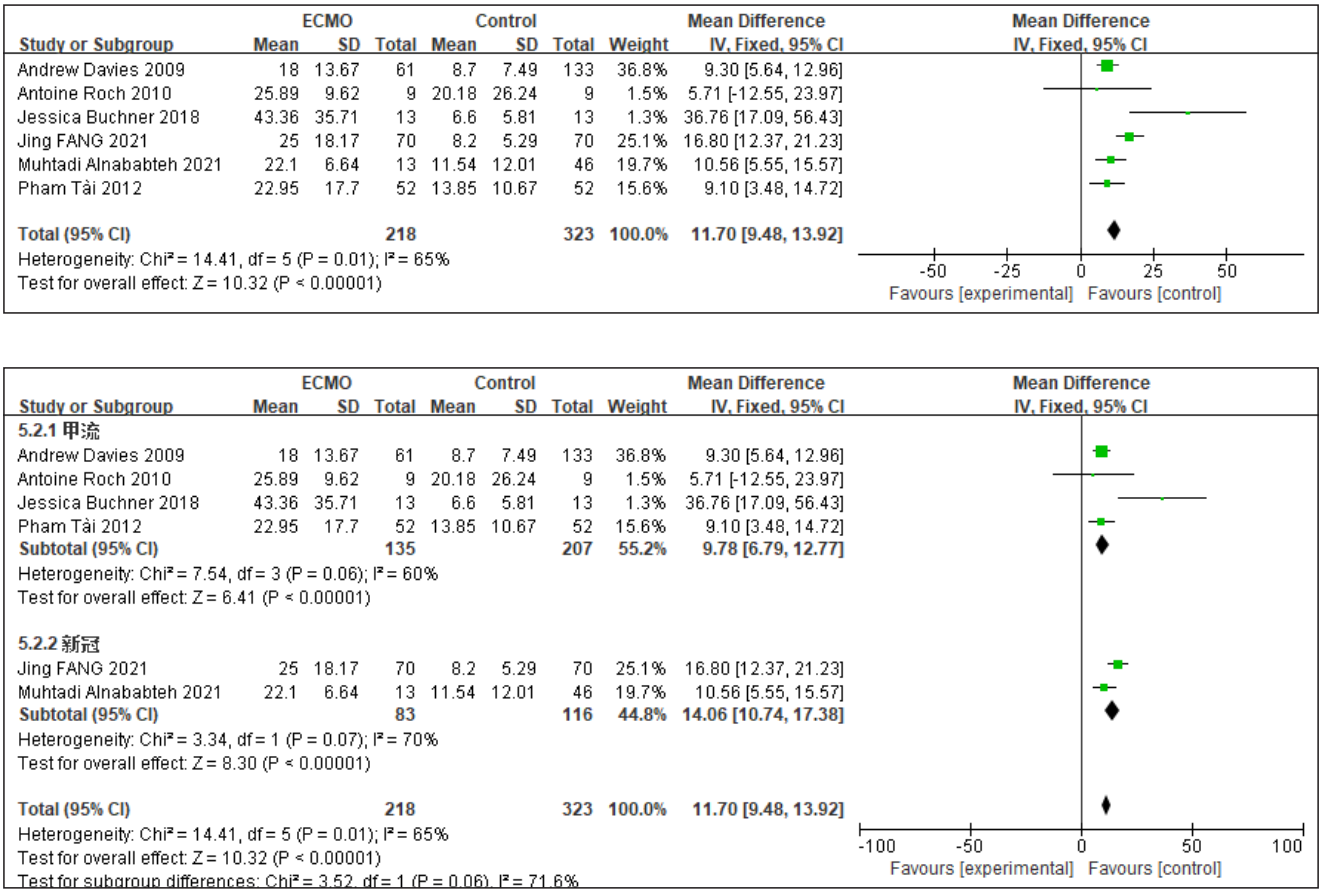
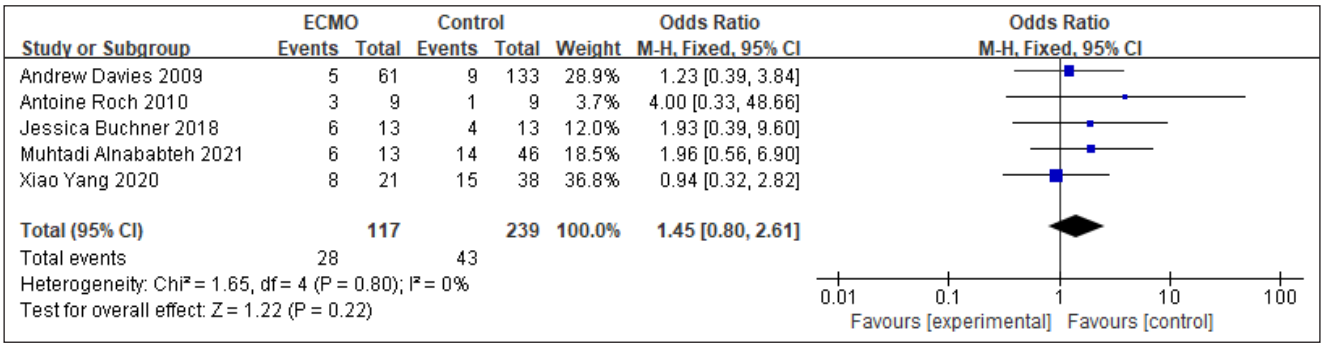


Figure 7. Analysis of duration of mechanical ventilation and subgroup analysis

3.3.3. Adverse events: renal injury and bleeding events

Five studies reported the occurrence of kidney injury (**Figure 8**). The meta-analysis suggested that kidney injury occurred in relatively more patients in the ECMO group, but the data were not statistically different across studies, and there was no overall difference ($P = 0.80$). Subgroup analysis for influenza and COVID-19 revealed comparable incidences of kidney injury between the two groups across both diseases ($P = 0.68$).



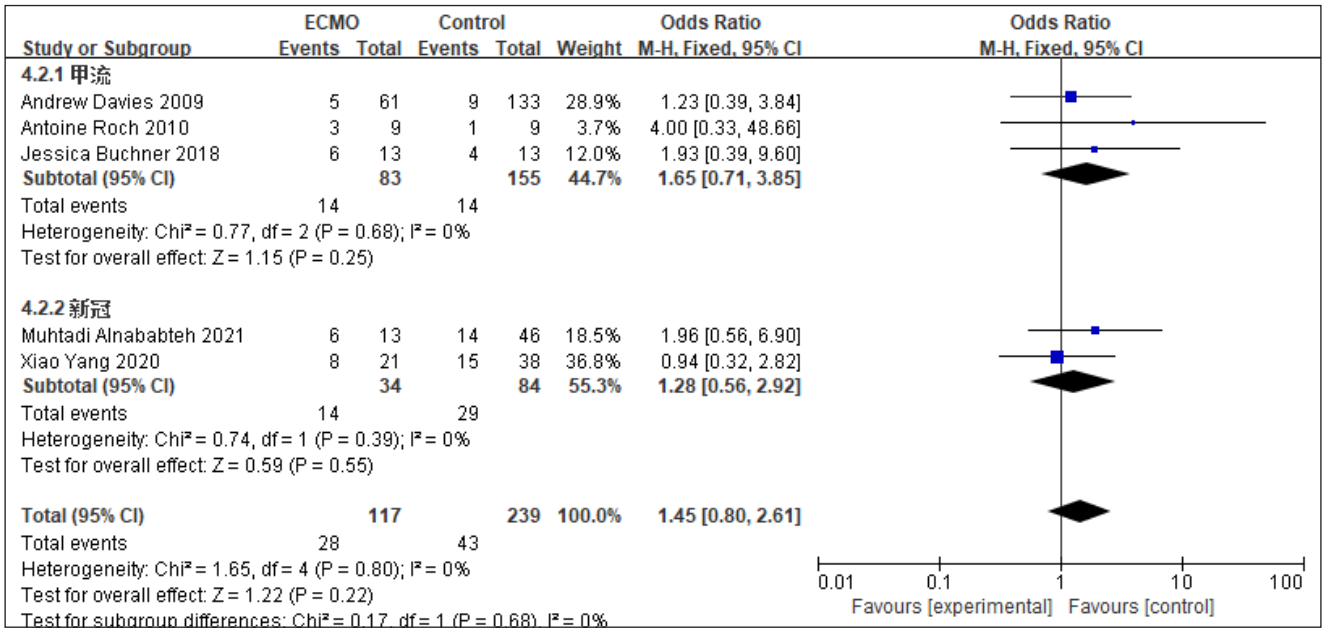


Figure 8. Renal injury analysis and subgroup analysis

Bleeding events were reported in two studies involving patients with COVID-19 (**Figure 9**), totaling 26 patients in the ECMO group and 59 patients in the mechanical ventilation group. Meta-analysis revealed a significant prolongation of bleeding time in the ECMO group compared to the mechanical ventilation group ($P = 0.001$).

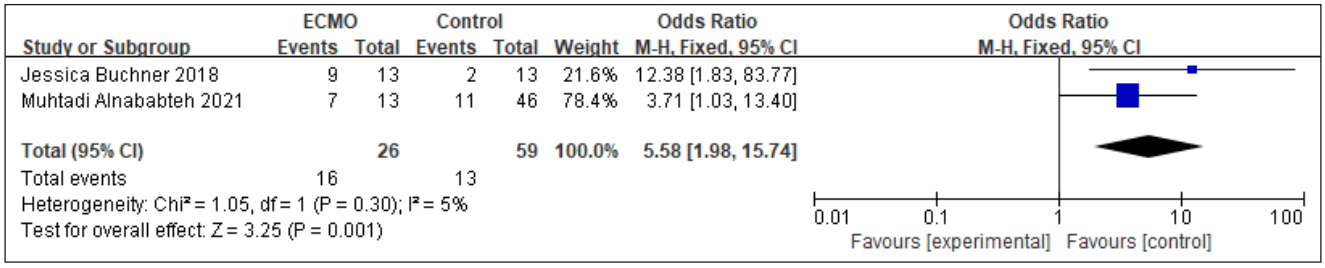


Figure 9. Analysis of bleeding events and subgroup analyses

4. Discussion

ECMO, as a new means of mechanical support for the heart and lungs, plays an increasingly important role in each epidemic of viral pneumonia [9]. However, due to its high economic cost, higher technical requirements, and increased risk of complications, the timing of ECMO application is still approached cautiously in clinical practice [10].

In this study, it was found that in different periods, patients with more severe lung conditions were selected for ECMO treatment, with a lower oxygenation index, but there were no obvious distinctions in the overall severity score of the disease. As observed, there was no significant difference in overall in-hospital mortality between the ECMO group and the mechanical ventilation group. To some extent, this indicates that the treatment effect of ECMO is indeed positive.

In subgroup analyses, patients assigned to ECMO had significantly longer durations of care, whether in

mechanical ventilation, length of stay in the ICU, or total length of stay. This may be related to the more severe lung conditions in patients, but it may also be related to patient management. During the course of treating the condition, managing patients with ECMO involves multiple weaning stages, and clinicians may adopt a more cautious strategy.

Due to incomplete reporting of adverse events, only renal injury and bleeding time were included in the analysis. In patients with poor oxygenation, hypoxia may cause kidney injury. In multiple studies, there has been no significant difference in the incidence of kidney injury between patients receiving ECMO and those receiving mechanical ventilation, despite lower initial oxygenation indexes. This also suggests the importance of ECMO in organ protection. Not surprisingly, however, the risk of bleeding was also significantly higher with ECMO. As an extracorporeal circulation support system, the operation of the ECMO system often requires anticoagulant drug support, and the current circulation pipeline also has anticoagulant coating. The effect of extracorporeal circulation on the coagulation and inflammatory system will also cause coagulation dysfunction, leading to an increase in bleeding events.

In this subgroup analysis, no significant difference was shown in the outcome of ECMO treatment during different disease epidemics. This may be relevant to the severity of the patient's condition. Although there have been innovations and advances in ECMO materials and management techniques in the past ten years, the length of hospital stay and mechanical ventilation time of patients are still long, indicating that there is still room for progress in ECMO management and weaning.

Firstly, although ECMO has been used to treat many patients with severe or critical COVID-19 in China, there is a scarcity of detailed information for further analysis and interpretation. The role of ECMO in the management of COVID-19 remains uncertain. Currently, there is a lack of clinical data from various regions, necessitating collaboration among registries and clinical research groups worldwide to conduct high-quality multicenter studies that can provide more prospective observational and randomized experimental data support.

Additionally, the benefit of ECMO for patients with COVID-19 is limited. Critically ill patients with viral pneumonia have high mortality rates, as seen in H1N1 influenza and MERS cases, and ECMO does not significantly improve clinical outcomes in these patients. Similar challenges may arise for critically ill COVID-19 patients as well. In addition to potential mortality risks, ECMO can lead to longer ICU stays, reduced bed turnover rates, and higher medical costs. Furthermore, ECMO serves as a supportive measure that does not directly address septic shock or coagulopathy experienced by the patient; improper invasive procedures or inadequate daily management may even increase these risks. Therefore, evaluating whether ECMO improves survival rates for COVID-19 patients compared to traditional mechanical ventilation therapy requires future high-quality prospective observational or randomized trials similar to those conducted after ten years following the H1N1 epidemic.

In addition, it is crucial to understand the indications and timing of ECMO in the management of COVID-19. Several studies have demonstrated that early initiation of ECMO in ARDS can significantly enhance clinical outcomes, particularly among younger patients. However, when ECMO is initiated more than 10 days after invasive ventilator use for COVID-19, the likelihood of successful treatment diminishes substantially. Therefore, experts recommend initiating ECMO before MODS or severe ventilator-associated lung injury occurs. Some guidelines propose using ECMO as a rescue therapy following the failure of standard treatment protocols. Nevertheless, the feasibility of early ECMO application may be limited in smaller or underqualified medical centers due to inadequate availability of equipment and specialists. Ethical concerns may also arise regarding patient selection and optimal timing for initiating ECMO due to resource constraints.

The choice of ECMO mode is another crucial consideration. For patients with pulmonary infection

and respiratory failure, VV mode is the primary preference. However, COVID-19 can lead to multi-system dysfunction, and some critically ill patients may experience myocardial injury, myocarditis, and circulatory failure. Therefore, it becomes necessary to assess if VAV-ECMO support is required during treatment and when VA-ECMO mode should be activated. The indications for treatment in such cases are currently lacking high-quality research results. Furthermore, there is a need for further exploration in ECMO management to optimize ventilation and fluid management strategies.

The last question is, potential harms or complications associated with ECMO raise concerns that require further research on effective prevention methods. Notably, lymphocyte counts and IL-6 concentrations show significant differences between COVID-19 survivors and non-survivors due to the influence of ECMO use; thus, Henry suggests closely monitoring immune indicators in ECMO patients. Anticoagulation plays a vital role in ECMO treatment as both deficiency and excess can result in fatal complications. Achieving balance in flow velocity within the ECMO circuit along with appropriate dosing of anticoagulant drugs requires effective monitoring techniques. Timely screening for thrombotic events within the tubing system also needs accurate attention. Reducing the risk of nosocomial infections holds great importance as they pose direct life-threatening situations for ECMO patients while putting medical staff at significant risk due to potential body fluid splashes during operation. Henceforth, establishing an independent ICU unit dedicated solely to ECMO treatment managed by a professional team following standardized protocols becomes imperative.

Disclosure statement

The authors declare no conflict of interest.

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