

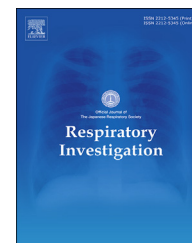


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## Review

# A systematic review and meta-analysis comparing the clinical characteristics and outcomes of COVID-19 and influenza patients on ECMO

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## ABSTRACT

**Background:** Extracorporeal membrane oxygenation (ECMO) is a valuable rescue therapy to treat refractory hypoxemia caused by influenza. The present meta-analysis aimed to compare the clinical characteristics and outcomes of ECMO between COVID-19 and influenza.

**Methods:** We searched the PubMed, Cochrane Library, SCOPUS, and Web of Science databases from inception to May 1, 2021. The included studies compared the clinical characteristics and outcomes of ECMO between adults with COVID-19 and those with influenza. **Results:** The study included four retrospective cohorts involving a total of 129 patients with COVID-19 and 140 with influenza who were treated using ECMO. Clinical characteristics were similar between the COVID-19 and influenza groups, including body mass index (BMI), diabetes mellitus, hypertension, and immunocompromised status. A higher proportion of patients with COVID-19 on ECMO were male (75.9% vs. 62.9%;  $P = 0.04$ ). There was no difference between the groups in terms of illness severity based on sequential organ failure assessment (SOFA) score or serum pH. Patients with COVID-19 had a longer mean duration of mechanical ventilation before ECMO (6.63 vs. 3.38 days;  $P < 0.01$ ). The pooled mortality rate was 43.8%. The mean ECMO duration (14.13 vs. 12.55 days;  $P = 0.25$ ) and mortality rate (42.6% vs. 45.0%;  $P = 0.99$ ) were comparable between the groups.

**Conclusion:** Clinical characteristics, ECMO duration, and mortality were comparable between patients with COVID-19 and those with influenza who required ECMO to treat refractory hypoxemia. The duration of mechanical ventilation before ECMO did not influence outcomes. Patients with COVID-19 benefit from ECMO salvage therapy similarly to those with influenza.

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**Abbreviations:** ARDS, acute respiratory distress syndrome; BMI, body mass index; COVID-19, coronavirus disease 2019; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation; HTN, hypertension; ICU, intensive care unit; MERS, Middle East respiratory syndrome; SOFA, sequential organ failure assessment.

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## 1. Introduction

In early December 2019, a novel viral respiratory disease was discovered and termed coronavirus disease 2019 (COVID-19), which has resulted in a worldwide pandemic. COVID-19 can present with a wide variety of clinical manifestations, from a mild flu-like illness to severe respiratory failure due to acute respiratory distress syndrome (ARDS). Advancements in management and therapies to reduce morbidity and mortality among patients with COVID-19 are still being pursued as the disease continues to spread across the globe. At present, there are few therapeutic options for COVID-19, and if lung-protective mechanical ventilation and recruitment maneuvers fail to treat refractory hypoxia or hypercapnia, extracorporeal membrane oxygenation (ECMO) is often required to provide temporary organ support. The benefits of ECMO have been studied among critically ill patients with ARDS during the 2009H1N1 influenza and the 2014 Middle East respiratory syndrome (MERS) outbreak [1–3]. This has resulted in the increasing use of ECMO as a salvage therapy for patients with ARDS suffering from seasonal influenza [4,5]. Due to the similarities shared by COVID-19 and influenza, several studies have compared the clinical characteristics and outcomes between hospitalized patients with COVID-19, including those who were critically ill, and those with seasonal influenza [6–9]. In general, critically ill patients with COVID-19 have more comorbidities and are more likely to develop respiratory and extra-respiratory complications. As a result COVID-19 has a higher mortality rate than influenza, even in patients who are critically ill [7–9]. ECMO is a resource-intensive, highly specialized, demanding, and expensive form of life support that can lead to significant complications; its benefits remains less clear in severe COVID-

19 than in influenza. Previous observational studies have demonstrated that critically ill patients with influenza are more likely to be initiated on ECMO than those with COVID-19, although this did not necessarily improve mortality [6,7,10]. Few studies have compared clinical characteristics and outcomes between patients with COVID-19 and those with influenza on ECMO. The present systematic review and meta-analysis used published evidence to compare clinical characteristics and outcomes between patients with COVID-19 and those with influenza who required ECMO.

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## 2. Materials and methods

The present systematic review was conducted and presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Ethical approval and informed consent were not required as this was a systematic review and meta-analysis of previously published studies. The protocol was registered and published in the International Prospective Register of Systematic Reviews (PROSPERO) under reference number CRD42021249317.

### 2.1. Search criteria and selection

A literature search was performed in the PubMed, Cochrane Library, SCOPUS, and Web of Science databases from inception to May 1, 2021, using the keywords and respective Medical Subjects Headings (MeSH) terms: “COVID-19,” “severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),” “ECMO,” “extracorporeal life support (ECLS),” and “influenza”. Two authors (W.C. and B.S.) independently reviewed the titles and abstracts of all search results for eligibility. If an article was

considered potentially eligible, both authors independently examined the full article for inclusion. Disagreements between the authors were resolved by consensus-based discussion. If no consensus was reached, a third reviewer (B.M.) made the final decision. To detect additional studies, we searched the reference lists of all retrieved articles for more eligible studies.

## 2.2. Inclusion and exclusion criteria

We included studies that: (1) compared outcomes of clinical characteristics and mortality between critically ill patients with COVID-19 (population) and those with influenza (comparison) who received ECMO (intervention); (2) involved adult patients (aged  $\geq 18$  years) with COVID-19 or influenza; (3) had a cross-sectional, case-control, or cohort design; (4) diagnosed COVID-19 or H1N1 infection using real-time reverse transcription-polymerase chain reaction from a nasopharyngeal or oropharyngeal swab. We excluded studies that: (1) were systematic reviews, literature reviews, case reports, case series, editorials, commentaries, or opinion articles, although the references of such articles were screened for articles meeting our inclusion criteria; (2) discussed infectious outbreaks other than the COVID-19 pandemic; (3) were conducted on animals or in vitro; (4) were published in languages other than English if no translated version was available.

## 2.3. Data collection and synthesis

The extracted data from the full texts of the included studies were compiled into a standardized form. The following information was collected and summarized in Table 1: study design, period of patient enrollment, clinical characteristics, and associated outcomes. Descriptive statistics were reported as means  $\pm$  standard deviations (SDs). Any disagreements or discrepancies regarding the extracted data were resolved via discussion between two authors (W.C. and B.S.), or with a third researcher (B.M.).

## 2.4. Outcomes

The primary outcomes of interest were differences in mortality or ECMO duration between critically ill patients with COVID-19 and those with H1N1 influenza patients requiring ECMO. The secondary outcomes were differences in clinical characteristics between the two populations. The following clinical characteristics were collected: patient demographics (age, sex, and body mass index [BMI]), comorbidities (hypertension [HTN], diabetes mellitus [DM], and immunocompromised status), sequential organ failure assessment (SOFA) score at intensive care unit (ICU) admission, pre-ECMO pH, and duration of mechanical ventilation.

**Table 1 – Summary of clinical characteristics and outcomes of cohort studies.**

ECMO	Charlton et al. [28]	Cousin et al. [29]	Jäckel et al. [30]	Luyt et al. [14]
Study design	Single-center, retrospective	Multi-center, retrospective	Single-center, retrospective	Single-center, retrospective
Country	UK	France	Germany	France
COVID-19 enrollment	April 2020–May 2020	March 2020–May 2020	April 2020–May 2020	March 2020–April 2020
Influenza enrollment	2018–2019	January 2014–May 2020	October 2010–June 2020	2017–2020
COVID-19 (N)	34	30	15	50
Influenza (N)	26	22	47	45
COVID-19 age (Y)	46.30 $\pm$ 7.50	57.00 $\pm$ 11.11	60.80 $\pm$ 9.56	48.00 $\pm$ 10.37
Influenza age (Y)	43.10 $\pm$ 8.70	55.00 $\pm$ 8.89	52.70 $\pm$ 13.93	58.00 $\pm$ 11.85
COVID-19 male N (%)	27 (79.4)	24 (80.0)	11 (73.3)	36 (72.0)
Influenza male N (%)	18 (69.2)	14 (63.6)	28 (59.6)	28 (62.2)
COVID-19 BMI (kg/m <sup>2</sup> )	31.90 $\pm$ 6.00	33.00 $\pm$ 6.67	27.80 $\pm$ 4.67	NR
Influenza BMI (kg/m <sup>2</sup> )	30.60 $\pm$ 7.80	30.00 $\pm$ 5.93	27.50 $\pm$ 8.15	NR
COVID-19 HTN N (%)	8 (23.5)	7 (31.8)	5 (33.3)	NR
Influenza HTN N (%)	5 (19.2)	2 (9.1)	20 (42.8)	NR
COVID-19 DM N (%)	4 (11.8)	10 (33.3)	2 (13.3)	NR
Influenza DM N (%)	2 (7.7)	2 (9.1)	8 (17.0)	NR
COVID-19 immunocompromised N (%)	NR	3 (10.0)	0 (0)	1 (2.0)
Influenza immunocompromised N (%)	NR	1 (4.5)	8 (17.0)	4 (8.9)
COVID-19 SOFA score	NR	10.00 $\pm$ 3.70	10.00 $\pm$ 2.22	12.00 $\pm$ 2.96
Influenza SOFA score	NR	11.00 $\pm$ 3.70	8.00 $\pm$ 2.22	15.00 $\pm$ 5.19
COVID-19 pre-ECMO pH	7.30 $\pm$ 0.10	7.37 $\pm$ 0.07	7.30 $\pm$ 0.13	NR
Influenzae pre-ECMO pH	7.30 $\pm$ 0.20	7.35 $\pm$ 0.12	7.28 $\pm$ 0.12	NR
COVID-19 ventilated pre-ECMO (D)	4.90 $\pm$ 1.70	6.00 $\pm$ 3.70	4.60 $\pm$ 3.41	11.00 $\pm$ 5.19
Influenzae ventilated pre-ECMO (D)	2.40 $\pm$ 2.50	3.00 $\pm$ 2.96	1.10 $\pm$ 1.85	7.00 $\pm$ 2.96
COVID-19 ECMO duration (D)	13.20 $\pm$ 5.60	11.00 $\pm$ 5.19	11.30 $\pm$ 11.85	21.00 $\pm$ 17.78
Influenzae ECMO duration (D)	12.30 $\pm$ 8.00	11.00 $\pm$ 9.63	8.90 $\pm$ 7.63	18.00 $\pm$ 17.04
COVID-19 mortality N (%)	16 (47.1)	16 (53.3)	6 (40.0)	17 (34.0)
Influenzae mortality N (%)	8 (30.8)	10 (45.5)	27 (57.4)	18 (40.0)

**Abbreviations:** BMI, body mass index; D, days; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation; HTN, hypertension; N, numbers; SOFA, sequential organ failure assessment; Y, years.

## 2.5. Quality assessment

The quality of individual observational studies was assessed by two researchers (W.C. and B.S.) using the Newcastle–Ottawa Scale (NOS), which contains nine items. Briefly, the NOS scale assesses three important features of studies: adequacy of the selection of exposed and non-exposed cohorts, comparability of groups, and adequacy of outcome assessment, with a total score ranging from 0 to 9 [11]. The study quality can be divided into three groups: low quality, 0–3; moderate quality, 4–6; high quality, 7–9. During the quality assessment of the included studies, any disagreements were resolved by discussion or by a third researcher (B.M.).

## 2.6. Statistical analysis

A meta-analysis was performed for the primary and secondary outcomes using the Review Manager (RevMan) software, Version 5.4, The Cochrane Collaboration, 2020. Dichotomous outcomes were assessed using the Mantel–Haenszel statistical method and measured in odds ratios (ORs) with 95% confidence intervals (CIs). Continuous outcomes were evaluated using the inverse variance statistical method and measured in terms of standard mean difference (SMD). The inverse variance method accounts for the differing sample sizes of individual studies by weighting studies based on the variance of their estimates: small studies with large variances have less weighting and large studies with small variances have more weighting. Pooled ORs, SMDs, and 95% CIs were calculated using DerSimonian and Laird's random-effects model, and extracted outcomes were pooled by weighted averages [12]. Statistical heterogeneity among studies was assessed using  $I^2$  statistics, with high heterogeneity defined as an  $I^2$  value of  $\geq 50\%$  [13]. All P-values  $< 0.05$  were considered statistically significant. Publication bias was examined by visual inspection of the funnel plot.

## 3. Results

### 3.1. Study selection

A total of 625 studies were identified in the initial search of the PubMed database, and 850 studies were identified from other databases and sources. After removing duplicates and those not meeting the inclusion criteria (by title, abstract, and full text), four eligible observational studies were included in the present review (Fig. 1).

### 3.2. Study characteristics

The study characteristics of the four included studies are described in Table 1. All of them retrospective cohort studies. Two of the studies were from France, one was from Germany, and the other was from the UK. A total of 269 patients requiring ECMO were described—129 with COVID-19 and 140 with influenza. The patients with COVID-19 were recruited between March and May 2020, while those with influenza were recruited between 2010 and 2020. The quality assessment of the studies is shown in Table 2: three of the studies had the maximum score of nine, and one by Luyt et al. had a score of eight [14].

### 3.3. Demographics and comorbidities

Mean age was comparable between patients with COVID-19 and those with influenza on ECMO (53.03 vs. 52.20 years;  $P = 0.57$ ; Table 1 and Fig. 2). A higher proportion of patients with COVID-19 were male (75.9% vs. 62.9%;  $P = 0.04$ ; Table 1 and Fig. 3). The mean BMI was similar between the groups (30.90 vs. 29.37  $\text{kg}/\text{m}^2$ ;  $P = 0.15$ ).

Comorbidities of DM, HTN, and immunocompromised status were common in both groups. The prevalences of DM

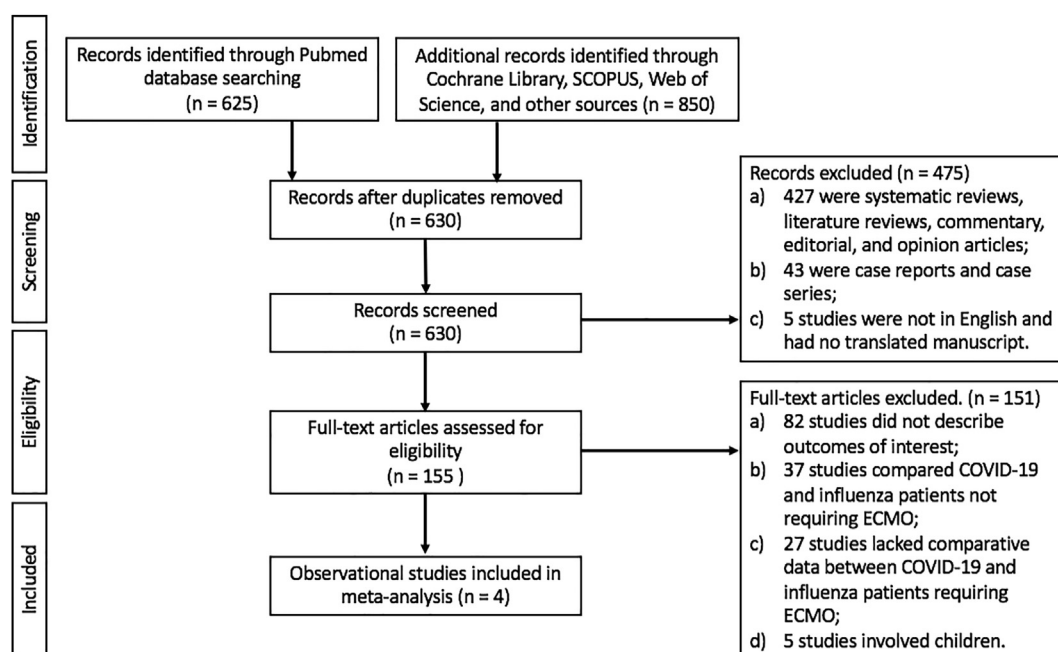


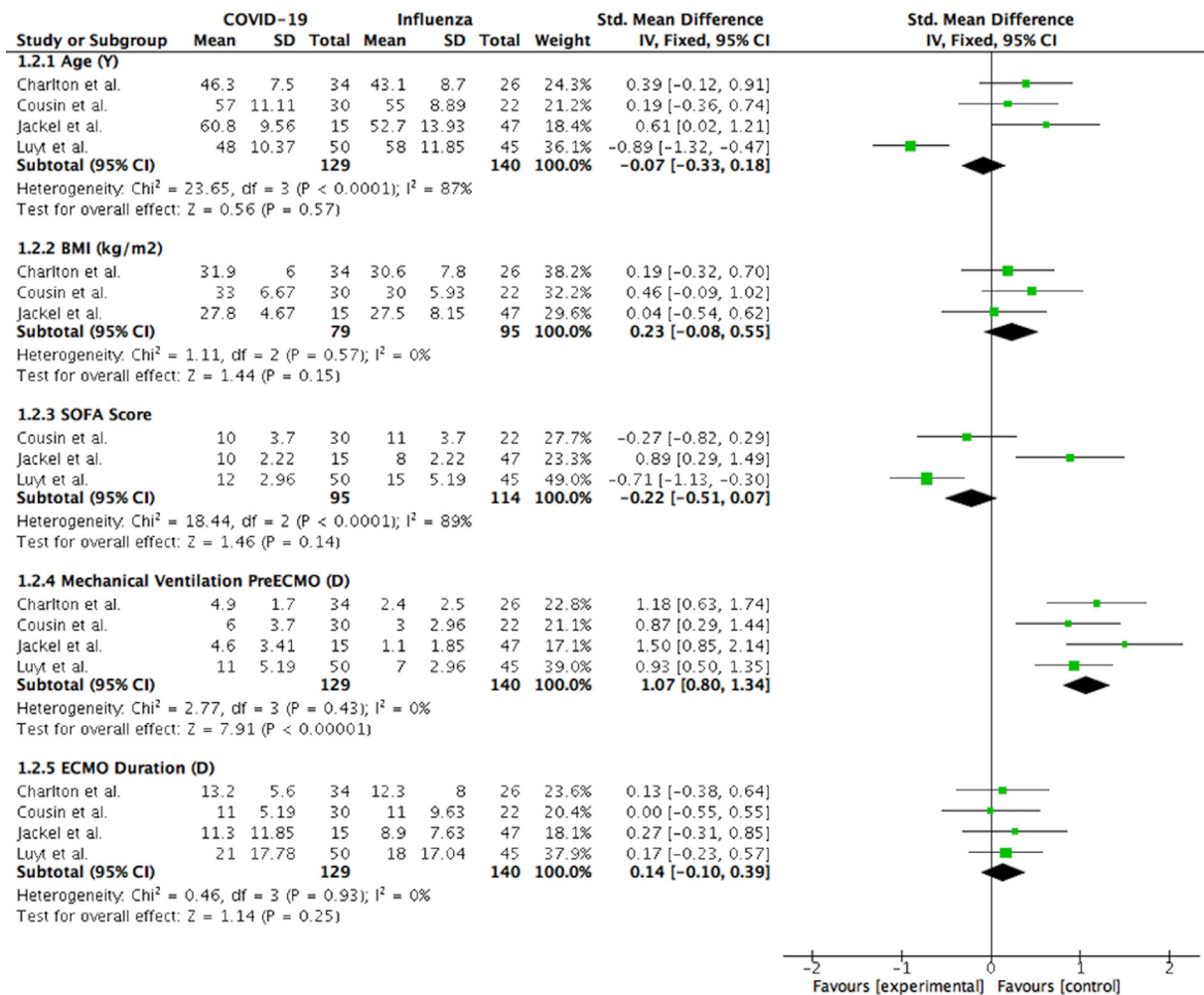
Fig. 1 – Flow diagram of study selection.

**Table 2 – Results of the Newcastle–Ottawa Scale [11] in the four cohort studies.**

1. Representatives of the exposed cohorts
  2. Selection of the non-exposed cohorts
  3. Ascertainment of exposure
  4. The outcome of interest was not present at the start of the study
- Comparability: Study controls were compared for the most important factor and additional factors
- a) Assessment of the outcome
  - b) Enough follow-up for the outcome
  - c) Adequacy of follow-up

Author(s)	Cohort Studies	Selection				Comparability	Outcome			Total Of 9 Scores
		1	2	3	4	(**)	a	b	c	
Charlton et al. [28]	Single-center, retrospective	*	*	*	*	**	*	*	*	9
Cousin et al. [29]	Multi-center, retrospective	*	*	*	*	**	*	*	*	9
Jackel et al. [30]	Single-center, retrospective	*	*	*	*	**	*	*	*	9
Luyt et al. [14]	Single-center, retrospective	*	*	*	*	*	*	*	*	8

Abbreviations: NR, non-representative; \* one positive variable; \*\* two positive variable.



**Fig. 2 – Forrest plot of patients with COVID-19 and those with influenza requiring ECMO support. Clinical characteristics of age, BMI, SOFA score, days from mechanical ventilation to ECMO initiation, and outcome of ECMO duration were assessed. Standard mean differences were calculated by inverse variance statistical method with a random-effects model. Abbreviations: BMI: body mass index; CI, confidence intervals; df, degree of freedom; ECMO, extracorporeal membrane oxygenation; IV, inverse variance; SD, standard deviation; SOFA, sequential organ failure assessment.**

(20.3% vs. 12.6%;  $P = 0.28$ ) and HTN (25.3% vs. 28.4%;  $P = 0.66$ ) were comparable. The proportion of immunocompromised patients was similar between groups (4.2% vs. 11.4%;  $P = 0.37$ ; Table 1 and Fig. 3). Luyt et al. identified immunocompromised status in patients who had undergone solid-organ transplant or those with underlying vasculitis requiring treatment using chronic immunosuppressant, such as corticosteroids [14].

### 3.4. Pre-ECMO variables

Upon ICU admission, illness severity was similar between patients with COVID-19 and those with influenza (mean SOFA

score: 10.67 vs. 11.33;  $P = 0.14$ ). The serum pH levels before ECMO initiation were comparable between groups, ranging from 7.30 to 7.37 in the patients with COVID-19 and from 7.28 to 7.35 in those with influenza (Table 1). Patients with COVID-19 had a longer mean duration of mechanical ventilation prior to ECMO initiation (6.63 vs. 3.38 days;  $P < 0.01$ ; Table 1 and Fig. 2).

### 3.5. Outcomes

The mean ECMO duration was similar between patients with COVID-19 and those with influenza (14.13 vs. 12.55 days;

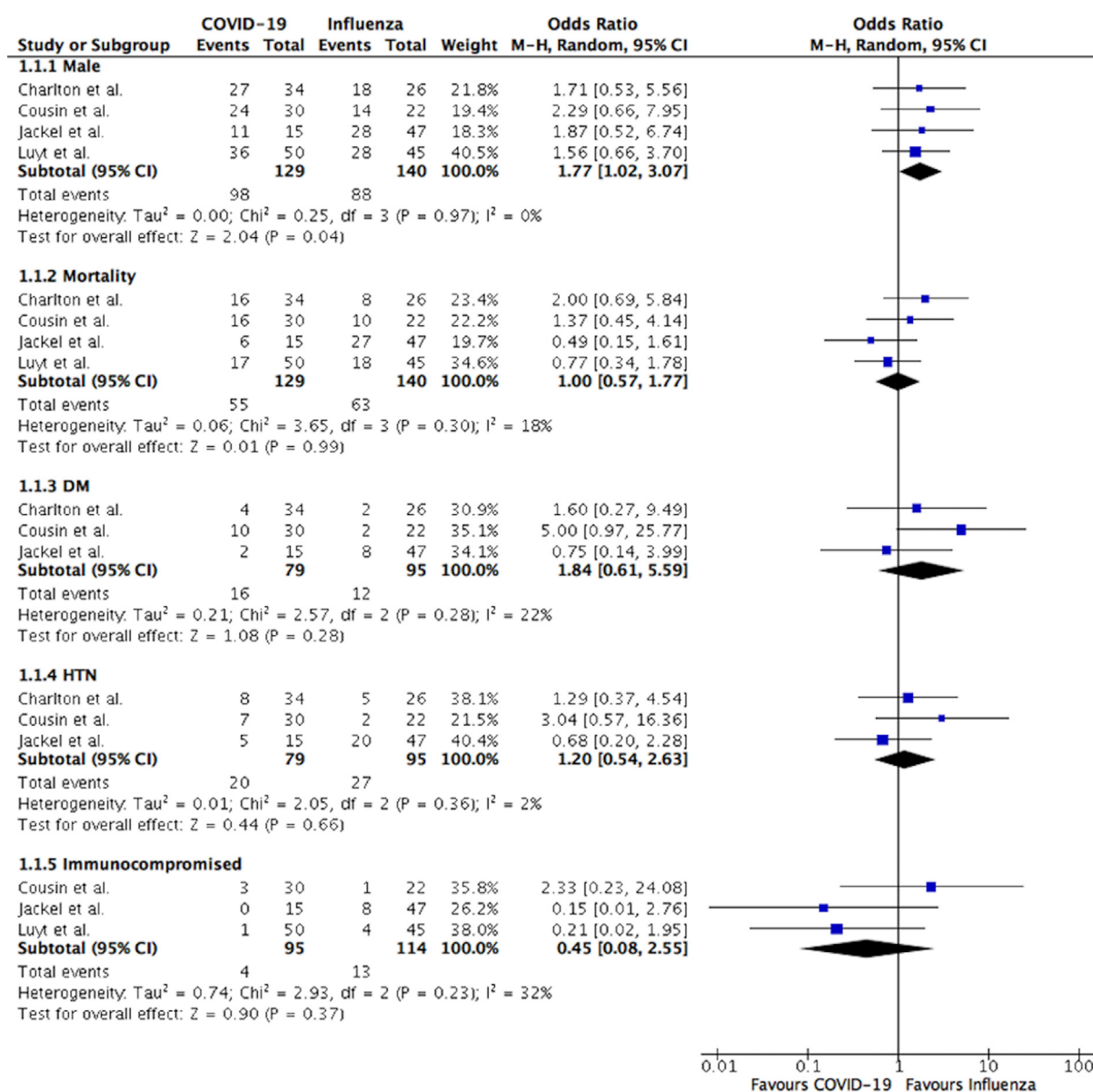


Fig. 3 – Forrest plot of patients with COVID-19 or influenza requiring ECMO support. Clinical characteristics of male sex, diabetes mellitus, hypertension, immunocompromised status, and outcome of mortality were assessed. The odds ratio was calculated using the Mantel–Haenszel method with a random-effects model. Abbreviations: CI, confidence intervals; df, degree of freedom; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation; HTN, hypertension; M – H, Mantel–Haenszel.

$P = 0.25$ ). The pooled mortality rate among all patients was 43.8% (118/269). The mortality rate did not differ between the groups (42.6% vs. 45.0%;  $P = 0.99$ ).

#### 4. Discussion

We reviewed four studies with comparative data describing 129 patients with COVID-19 and 140 with influenza requiring ECMO, with a pooled mortality rate of 43.8%. The demographics and comorbidities were similar between the groups. A higher proportion of patients with COVID-19 on ECMO were male. There was no difference between the two groups in terms of illness severity according to serum pH levels or SOFA score upon ICU admission. Patients with COVID-19 receiving ECMO had a longer duration of mechanical ventilation prior to ECMO initiation. Lastly, the ECMO duration and mortality rate were comparable.

It is likely that clinical characteristics were similar between patients with COVID-19 and those with influenza on ECMO because clinicians applied similar selection criteria. Advanced age, morbid obesity, and multiple comorbidities, especially those that are disabling, incurable, or life-threatening, are associated with lower survival rates and are listed as contraindications to ECMO in the Extracorporeal Life Support Organization 2017 and updated 2020 guidelines [15–18]. The comparable outcomes indicate that refractory respiratory failure can be treated in a similar manner in both viral syndromes. Neither mortality nor ECMO duration differed significantly between the two groups. Sex difference has not been shown to affect survivability among ECMO patients [19,20]. The higher rate of men among patients with COVID-19 is unsurprising because men with this disease are known to have a greater likelihood of severe illness and hospitalization [7,8,20].

Correctly timing ECMO is challenging in practice. Initiating the treatment too soon may unnecessarily subject the patient to a risky and costly procedure, but clinicians who wait too long risk missing the window in which the therapy could make a difference. The current guidelines caution against ECMO in patients intubated for longer than 7–10 days [15,16]. However, many centers are reluctant to withhold this potentially life-saving salvage therapy in critically ill patients [18,19], especially those with COVID-19, which follows a more indolent course initially and takes longer to reach a point of clinical decompensation [21–23]. For this reason, it is unsurprising that patients with COVID-19 showed a longer duration of mechanical ventilation before ECMO initiation. In addition, COVID-related ARDS often demonstrates a unique atypical phenotype of significant gas exchange derangements with relatively preserved lung compliance [23–25]. The work of breathing is, therefore, less taxing to patients, with less resultant dyspnea and distress. In contrast, the fulminant nature and low lung compliance of influenza-related ARDS can result in ventilation challenges and may necessitate earlier ECMO initiation. Moreover, concerns about depleting valuable healthcare resources in the catastrophic COVID-19 pandemic may have led to more cautious and delayed use of ECMO in patients with COVID-19 than in those with influenza [15].

The strength of our study was that it was the only meta-analysis to objectively compare clinical characteristics and

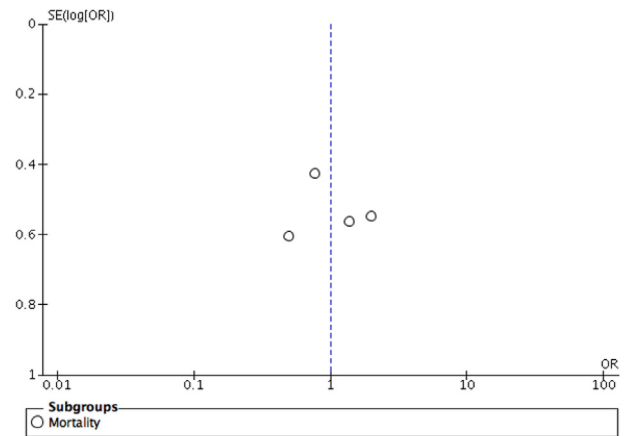


Fig. 4 – Funnel plot for primary outcome of mortality.

outcomes between patients with COVID-19 and those with influenza on ECMO therapy. The rapid COVID-19 pandemic did not allow for more structured and methodical criteria for initiating salvage ECMO. To further improve COVID-19 management, researchers must ascertain the parallels and differences between severe COVID-19 and the better-studied influenza.

There were several limitations to the present meta-analysis. Few studies have described the outcomes and characteristics of both critically ill patients with COVID-19 and those with influenza, and the total number of subjects was therefore small and the results were susceptible to heterogeneity, selection, and publication bias. Predictors associated with clinical outcomes could have been missed. Moreover, existing case series reviewing COVID-19 and influenza separately were highly variable in the type of data collected, so meta-analytic pooling of data became nearly impossible. For this reason, we limited our analysis to studies that provided comparative data on both viral syndromes. As further experience is gained in the unfolding COVID-19 pandemic, we believe more data will become available. Additionally, the dissimilarities between the two study populations, with enrollments period of several months for patients with COVID-19 but several years for influenza patients, likely also predisposed the study to selection and publication bias. Although we only included four studies, the funnel plot was symmetrical, with all studies within the threshold indicating a low probability of publication bias (Fig. 4).

Despite similarities in clinical characteristics and outcomes, critically ill patients with COVID-19 are a unique population. Their further delineation and characterization in the context of ECMO should continue as more data are collected. For instance, thromboembolism during ECMO occurs more frequently in patients with COVID-19 than in those without (63.6% vs. 18.2%;  $P < 0.05$ ) because the viral infection causes a prothrombotic state in the context of extracorporeal circulation [26]. The risk of bleeding is also increased in COVID-19 because there is a higher prevalence of disseminated intravascular coagulation and sepsis-induced thrombocytopenia [27].



## 5. Conclusion

In the midst of the ongoing pandemic, the challenges in patient selection and timing of ECMO initiation are significant barriers preventing the escalation of care in critically ill patients with COVID-19. Because few comparative data were available, it was initially unclear whether the outcomes of patients with COVID-19 would be similar to those of influenza patients on ECMO. In our meta-analysis of four cohort studies involving 129 patients with COVID-19 and 140 with influenza, critically ill patients requiring ECMO support had comparable clinical characteristics, ECMO duration, and mortality. Patients with COVID-19 had a longer duration of mechanical ventilation prior to ECMO. Until more data are available, patients with COVID-19 in refractory respiratory failure can be treated similarly to those with influenza.

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## Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, or publication of this article.

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