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Ischemic stroke and intracranial hemorrhage in extracorporeal membrane oxygenation for COVID-19: A systematic review and meta-analysis

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Abstract

Purpose: Extracorporeal membrane oxygenation (ECMO) is employed to support critically ill COVD-19 patients. The occurrence of ischemic stroke and intracranial hemorrhage (ICH), as well as the implementation of anticoagulation strategies under the dual influence of ECMO and COVID-19 remain unclear. We conducted a systematic review and meta-analysis to describe the ischemic stroke, ICH and overall in-hospital mortality in COVID-19 patients receiving ECMO and summarize the anticoagulation regimens.

Methods: EMBASE, PubMed, Cochrane, and Scopus were searched for studies examining ischemic stroke, ICH, and mortality in COVID-19 patients supported with ECMO. The outcomes were incidences of ischemic stroke, ICH, overall in-hospital mortality and anticoagulation regimens. We calculated the pooled proportions and 95% confidence intervals (CIs) to summarize the results.

Results: We analyzed 12 peer-reviewed studies involving 6039 COVID-19 patients. The incidence of ischemic stroke had a pooled estimate of 2.2% (95% CI: 1.2%–3.2%). The pooled prevalence of ICH was 8.0% (95% CI: 6.3%–9.6%). The pooled estimate of overall in-hospital mortality was 40.3% (95% CI: 33.1%–47.5%). The occurrence of ICH was significantly higher in COVID-19 patients supported with ECMO than in other respiratory ECMO [relative risk=1.75 (95% CI: 1.00–3.07)]. Unfractionated heparin was the most commonly used anticoagulant, and anticoagulation monitoring practice varied among centers.

Conclusions: Ischemic stroke and ICH were common under the double "hit" of COVID-19 and ECMO. The prevalence of ICH was significantly higher in COVID-19 patients supported with ECMO than non-COVID-19 patients requiring ECMO. Individualized anticoagulation regimens may be a good choice to balance thrombosis and bleeding. More detailed research and further exploration are needed to clarify the underlying mechanism and clinical management decisions.

Keywords

COVID-19, extracorporeal membrane oxygenation, ischemic stroke, intracranial hemorrhage, anticoagulation, overall in-hospital mortality

Introduction

Coronavirus disease 2019 (COVID-19)-related acute respiratory distress syndrome (ARDS) has prompted the application of extracorporeal membrane oxygenation (ECMO). Many observational studies, including the Extracorporeal Life Support Organization (ELSO) registry,[1,2] reported outcomes for patients with COVID-19 receiving ECMO that were comparable to non-COVID-19 related ECMO.[3] To date, more than 10,000 COVID-19 patients received ECMO support, with an overall in-hospital mortality of approximately 47%.[4] During ECMO, axial pump flow and direct

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exposure of blood to artificial surface change three elements of the coagulation system (vascular, blood components, and blood flow) into non-physiological state, which significantly impacts on hemostasis.[5] Ischemic stroke and intracranial hemorrhage (ICH) are well-known and severe complications during ECMO.[6,7] The ELSO recommends following existing institutional anticoagulation guidelines but to consider anticoagulation intensity at the higher end of the usual targets in COVID-19 related ECMO.[8] COVID-19 causes inflammatory responses and endothelial dysfunction,[9] leading to a hypercoagulable state and vascular thrombotic processes, which also involve the cerebral microvasculature[10] and may increase the susceptibility of ischemic stroke and ICH.[11,12] Thus, intensified anticoagulation may be justified due to existing micro- or macro-thromboses in a hypercoagulable state and to prevent further thrombosis. The presumed occurrence of ischemic stroke and ICH in COVID-19 patients on ECMO and their impact on mortality are not understood and require further elucidation.

In this systematic review, we focus on ischemic stroke, ICH and overall in-hospital mortality and summarize current knowledge about anticoagulation management strategies under the double "hit" of COVID-19 and ECMO. These meta-analysis data may provide insight into the prevalence of ischemic stroke and ICH in COVID-19 patients that are critically ECMO-treatment and may be instructive for clinicians.

Methods

This study was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[13] (Supplementary Table 1) and Meta-Analysis of Observational Studies in Epidemiology (MOOSE)[14] guidelines, and was registered with PROSPERO (CRD 42020224880) in advance.

Search strategy

Appropriate MeSH terms or keywords: "ECMO", "COVID-19" and "coagulopathy" were adopted to search the Pubmed, Embase, Cochrane, and Scopus databases to October 25, 2021 (Supplementary Table 2). Manual searches of reference lists were performed to identify additional articles.

Inclusion and exclusion criteria

The inclusion criteria of this systematic review and meta-analysis were as follows: (1) above 50 adult patients (aged > 18 years old) were reported; (2) laboratory-confirmed COVID-19 supported with ECMO; (3) the incidences of ischemic stroke, or ICH proven by imaging. (4) overall in-hospital mortality were reported. Reviews, animal studies, in vitro experiments, and conference abstracts were excluded. Only the largest study was included, if there were overlapping patient data. The latest ELSO report[2] was included. No language restrictions were applied.

Data collection

Two reviewers (YJ and YZ) worked independently to exclude nonrelevant studies; disagreements were solved by consultation with the third reviewer (JPL). A standardized form was adopted to extract specific data from included studies. Extracted information included study characteristics (author, year of publication, study design, study duration, number of ECMO centers, study country), patient characteristics (cases, mean/median age, ratio of males, comorbidities, scores describing the severity of the disease), ECMO characteristics (ECMO modes, ECMO system, ECMO duration), the prevalence of ischemic stroke and ICH before ECMO implantation in COVID-19 patients, the incidence ischemic stroke and ICH during ECMO, anticoagulants, target anticoagulation monitoring and overall in-hospital mortality. If studies compared ischemic stroke and ICH in COVID-19 related ECMO with non-COVID-19 patients requiring ECMO, we extracted additionally.

The diagnoses of ischemic stroke and ICH were made based on findings by computed tomography (CT) and/or magnetic resonance imaging of the brain, regardless of clinical symptoms.

Outcomes of interest

The primary outcomes were the incidence of ischemic stroke and ICH during ECMO. The secondary outcomes were overall in-hospital mortality (all-cause mortality of patients during hospital length of stay), the types and usage of anticoagulants, anticoagulation monitoring tools and targets (activated partial thromboplastin time (APTT), anti-factor Xa levels (Anti-Xa), and activated clotting time (ACT)).

Assessment of the study quality and certainty

The Joanna Briggs Institute (JBI) checklist for cohort studies was used to assess studies' quality.[15] The Grading of Recommendations, Assessments, Developments, and

Evaluations (GRADE) approach was used to assess the certainty of evidence.[16] The possibility of publication bias was assessed using the visual assessment of funnel plots.

Statistical analysis

Statistical analysis was performed by STATA version 15.0 (StataCorp LP, College Station, TX, USA). Exact event rates were noted from the reported results in all cases of each included study. Continuous variables were expressed as appropriate as the mean and standard deviation (SD) or the median and interquartile range. Categorical variables were described as counts and percentages. For studies that only reported medians, ranges, and interquartile ranges, the mean and SD were estimated using the methods proposed by Wan et al.,[17] to calculate the pooled mean ECMO duration and the pooled mean age of patients.

The random-effects model[18] was applied to estimate the between-study variance, because included studies were mostly retrospective observational studies, and distinct heterogeneity existed between them. Pooled effect estimates were expressed as estimated rates with 95% confidence intervals (CIs). We assessed statistical heterogeneity using the I^2 statistics, the Chi-squared test and visual inspection of forest plots.[19] Pooled relative risk (RR) was calculated to compare ischemic stroke, ICH and mortality in COVID-19 patients supported with ECMO to non-COVID-19 related ECMO. We performed sensitivity analyses in two ways: by omitting one study at a time to identify influential studies, and by excluding studies with a score less than 9 in the JBI checklist for cohort studies. Subgroup analyses were performed when $p < 0.05$ and $I^2 > 50\%$, to investigate the association between geographical regions (Europe, America, Asia, and International), anticoagulation monitoring tools (APTT, anti-Xa, ACT, and others), the application of routine CT, and the prevalence of intracranial thrombotic and bleeding events. The ELSO report[2] was analyzed into three groups separately based on the time and centers at which COVID-19-related ECMO was started. The terms early- or late-adopting center refers to the selected starting date of 1 May 2020.

Results

Study description

Through screening the study details of 1398 references, we included 12 observational studies with 6039 patients in the systematic review and[2,20–30] meta-analysis (Figure 1). There were eight[20,22,23,26–30] studies (879 patients) from Europe, one[21] study (190 patients) from North America, one[24] study (85 patients) from South America, one[25] study (73 patients) from Asia, and one[2] study (4908 patients) from ELSO international summary. The number of included COVID-19 patients requiring ECMO for each study ranged from 51 to 4908. The average age ranged from 45 to 62 years. More than half were males, ranging from 63% to 83%. The average ECMO duration ranged from 13 to 20 days. Veno-venous (VV) ECMO was the predominant support mode, accounting for 92%–100% (Table 1). The pooled estimates of age, male proportion, and ECMO duration were 49.3 years (95% CI: 48.1–50.5 years), 73% (95% CI: 73%–77%), and 16.8 days (95% CI: 14.3–19.3 days), retrospectively. Hypertension [31% (95% CI: 25%–36%)], diabetes [23% (95% CI: 20%–27%)], and chronic obstructive pulmonary disease [9% (95% CI: 7%–11%)] were the most common comorbidities, with a median Sequential Organ Failure Assessment (SOFA) score of 9.6 (95% CI: 8.6–10.7).

Study quality, certainty of evidence, and risk of bias

Appraisal using the JBI checklist for cohort studies indicated a high level of quality across the 12 included studies for this review and meta-analysis. Nine[2,20–25,29,30] studies had scores no less than 9/11 with a low risk of bias (Supplementary Table 3). The GRADE assessment of primary and secondary outcomes for certainty of evidence was summarized in Supplementary Table 4. The prevalence rates of ischemic stroke, ICH showed high certainty, while overall in-hospital mortality had moderate certainty. The funnel plots revealed apparent asymmetry that suggested the presence of a potential publication bias (Supplementary Figure 1). Sensitivity analysis, including only studies with a lower risk of bias in their JBI score, showed similar estimates for the risk of ischemic stroke (2.1%), ICH (7.1%), and overall in-hospital mortality (43.7%) among all patients (Supplementary Figure 2). In order to avoid double publication between the ELSO report and the other studies, we performed a meta-analysis of ischemic stroke, ICH and overall in-hospital mortality in the remaining 11[20–30] studies (1227 patients) after excluding the ELSO registry data. The pooled prevalence of ischemic stroke, ICH, and overall in-hospital mortality were 4.8%, 10.8%, and 37.2% (Supplementary Figure 3).

Primary and secondary outcomes

The incidence of ischemic stroke in these COVID-19 patients supported with ECMO had a pooled estimate of

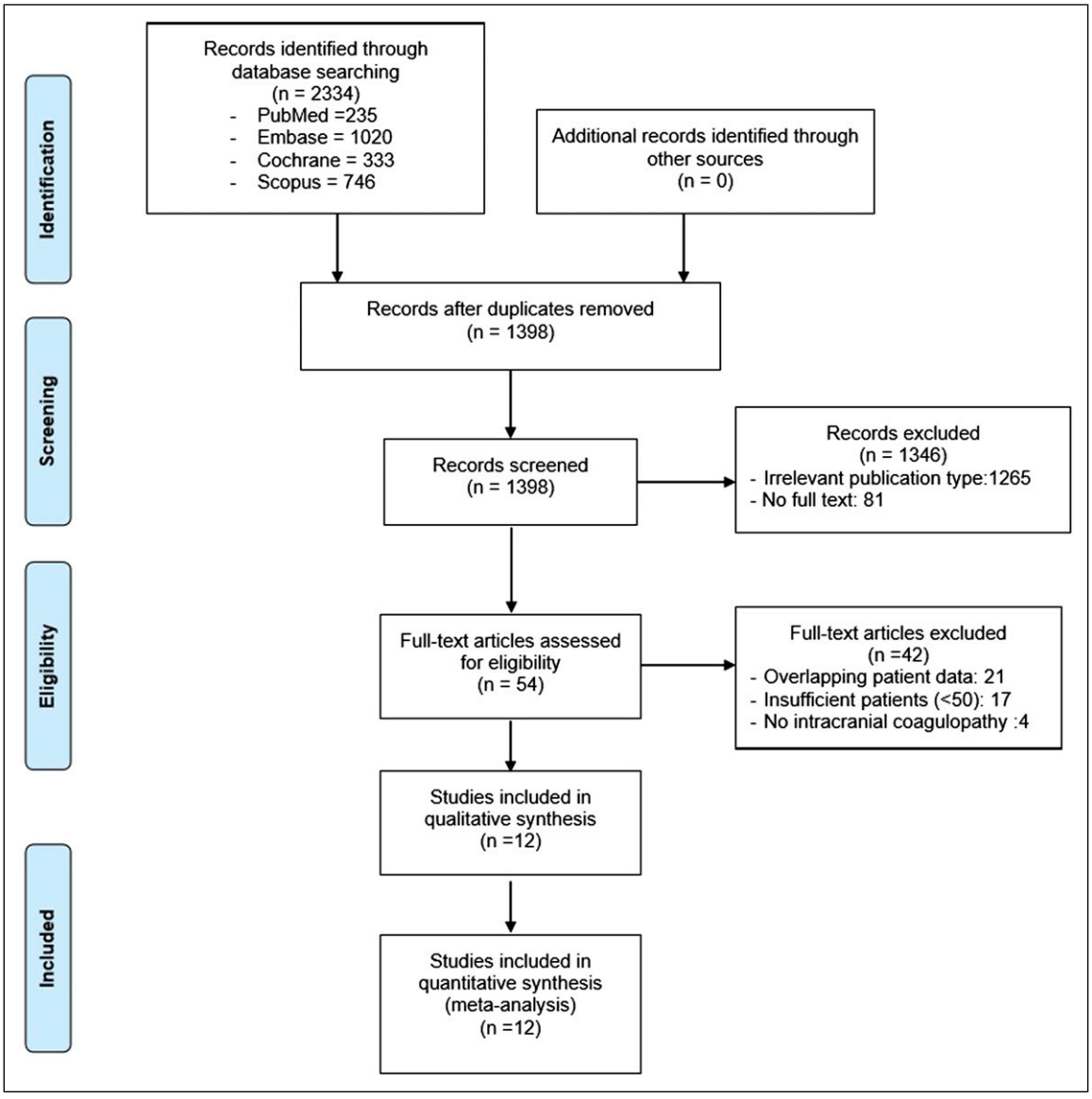

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses flowchart.

2.3% (95% CI: 1.3%–3.3%, $p < 0.001$, 9 studies,[2,20–23,26–29] 5748 patients) (Figure 2). The lowest incidence of ischemic stroke was 0.6%, while the highest was 14.4%. There are large differences between centers in prevalence of ICH, which varied from 4.2% to 24.1%, with a pooled estimate of 8.0% (95% CI: 6.3%–9.6%, $p < 0.001$, 11 studies,[2,20–22,24–30] 5828 patients) (Figure 3).

The overall in-hospital mortality varied widely across included studies; the lowest was 15.1% and the highest was 80.8%, as well as the pooled estimate was 40.3% (95% CI: 33.1%–47.5%, $p < 0.001$, 12 studies,[2, 20-30] 6039 patients) (Figure 4). Eight[20,22,23,25–28,30] studies reported the use of anticoagulants during ECMO, with most patients receiving unfractionated heparin (UFH). The use of argatroban was mentioned for heparin-induced thrombocytopenia in two studies.[22,28] APTT combined with Anti-Xa was the most common anticoagulation monitoring, which was adopted in 5 studies.[20,22,26,27,30] One[23] study referred to APTT and ACT, one[25] study used APTT, and one[28] study adopted Anti-Xa for anticoagulation titration. Different target ranges varied among centers, and anticoagulation targets were modestly upregulated in the presence of thrombosis (Table 1).

Subgroup analysis

The ischemic stroke and ICH and overall in-hospital mortality significantly differed between regional groups.

Table 1. Characteristics and outcomes of included studies.

Study (author, year)	Study period	Centers	Country	Cases	Age (years)	Male	ECMO duration (days)	In-hospital mortality	Ischemic stroke	ICH	Anticoagulants & anticoagulation monitoring
Lebreton 2021	2020.3.8–2020.6.3	17	France	302	52 (45, 58)	235 (78)	14 (8, 26)	163 (54)	6 (3)	27 (12)	UFH APTT (60–75s), anti-xa (0.3–0.5 IU/ml)
Shaef 2021	2020.3.1–2020.7.1	55	USA	190	49 (41, 58)	137 (72)	NA	63 (33)	3 (2)	8 (4)	NA
Arachchillage 2021	2020.3.1–2020.5.31	4	UK	152	47 (range 23, 65)	114 (75)	18 (11, 30)	45 (30)	6 (4)	16 (11)	UFH, argatroban for HIT Anti-xa of 0.2–0.3 IU/ml or equivalent APTT; for patients with thrombosis at the initiation or during ECMO, anti-xa of 0.5–0.7 IU/ml or equivalent APTT
Biancari 2021	2020.3.1–2020.7.31	10	France, Germany, Italy, Sweden, UK	132	51 ± 10	109 (83)	15 ± 11	70 (53)	19 (14)	NA	UFH ACT (160–300 s); APTT (40–60 s)
Diaz 2021	2020.3.3–2020.8.31	13	Chile	85	48 (41, 55)	71 (84)	16 (10, 27)	30 (39)	NA	11 (13)	NA
Yang 2021	2020.1.1–2020.5.31	21	China	73	62 (51, 66)	46 (63)	17 (11, 29)	59 (81)	NA	5 (7)	UFH APTT (60–80 s)
Raasveld 2021	2020.3.1–2020.4.30	13	Netherlands, Belgium, Sweden, Spain	71	52 (47, 57)	57 (80)	13 (7, 20)	26 (37)	1 (1)	7 (10)	UFH APTT-r (1.5–2.0) in 7 centers, (2.0–2.5) in 5 centers, (1.5–2.5) in 1 center; 5 centers combined anti-xa from 0.2 to 1.0 IU/mL; 1 center combined ACT of (180-220s)
Weir-McCall 2021	2019.1.1–2020.4.30	3	UK	64	45 ± 9	49 (77)	NA	18 (28)	3 (5)	9 (14)	UFH Anti-xa (0.3–0.7 IU/ml); APTT-r (1.5–2.0)
Weatherill 2021	2020.3.17–2020.5.26	1	UK	54	46 ± 11	40 (74)	NA	9 (17)	6 (11)	13 (24)	UFH, argatroban for HIT Anti-xa (0.3–0.5 IU/ml)
Garfield 2021	2020.3.17–2020.5.30	1	UK	53	46 ± 8	39 (74)	18 (12, 30)	8 (15)	6 (11)	11 (21)	NA
Doyle 2021	2020.3.2–2020.5.31	1	UK	51	46 (35, 53)	38 (75)	13 (8, 21)	13 (26)	NA	3 (6)	UFH APTT-r (1.5–2.0; 2.0–2.5 if a thrombotic event), anti-xa (0.3–0.7IU/ml; 0.6–1.0 if a thrombotic event)

(continued)

Table 1. (continued)

Study (author, year)	Study period	Centers	Country	Cases	Age (years)	Male	ECMO duration (days)	In-hospital mortality	Ischemic stroke	ICH	Anticoagulants & anticoagulation monitoring
Barbaro 2021 A1	2020.1.1–2020.5.1	236	International	1182	50 (42, 57)	876 (74)	14 (8, 24)	448 (38)	7 (1)	69 (6)	NA
Barbaro 2021 A2	2020.5.2–2020.12.31	236	International	2824	51 (42, 58)	2049 (73)	20 (10, 35)	1488 (53)	54 (2)	195 (7)	NA
Barbaro 2021 B	2020.5.2–2020.12.31	113	International	806	49 (40, 58)	598 (74)	NA	475 (59)	8 (1)	42 (5)	NA

Notes: Continuous data are presented as mean ± standard deviation or median (interquartile range) and categorical data as *n* (percent). ECMO, extracorporeal membrane oxygenation; ICH, intracranial hemorrhage; NA, not available; UFH, unfractionated heparin; APTT, activated partial thromboplastin time; APTT-r, activated partial thromboplastin time ratio; Anti-Xa, anti-factor Xa levels; ACT, activated clotting time; HIT, heparin-induced thrombocytopenia.

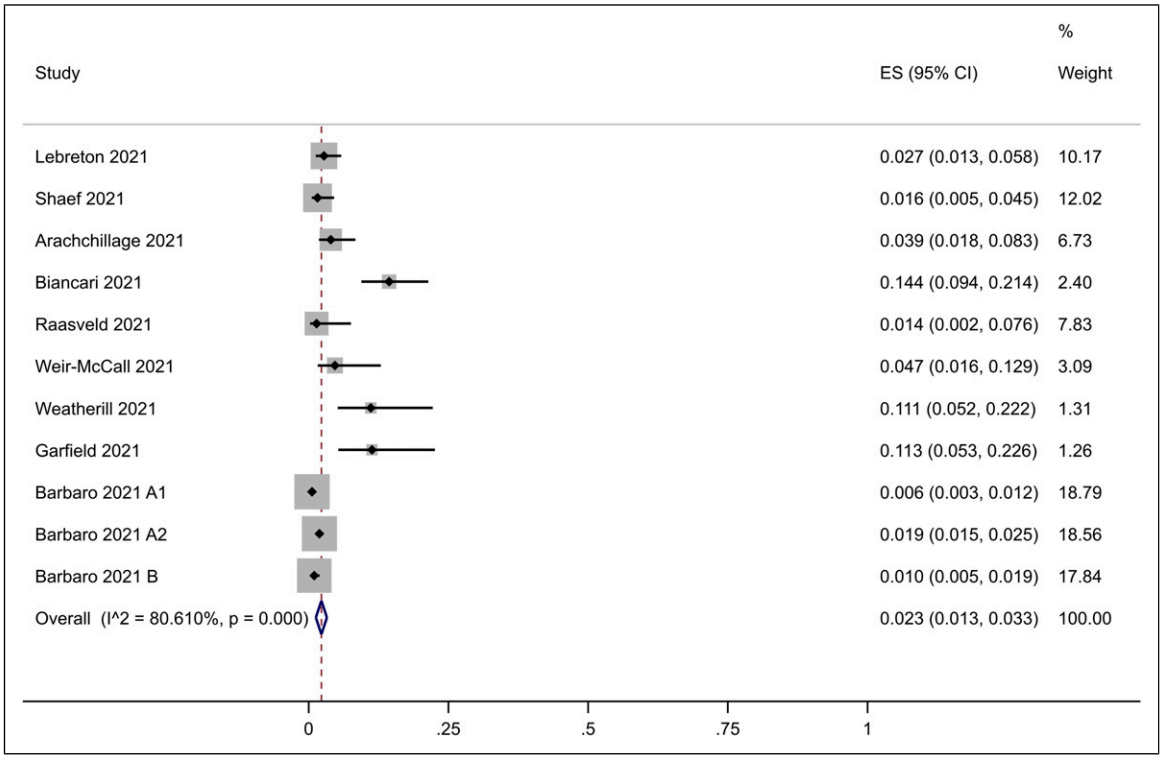

Figure 2. Forest plot of incidence of ischemic stroke in COVID-19-related ECMO.

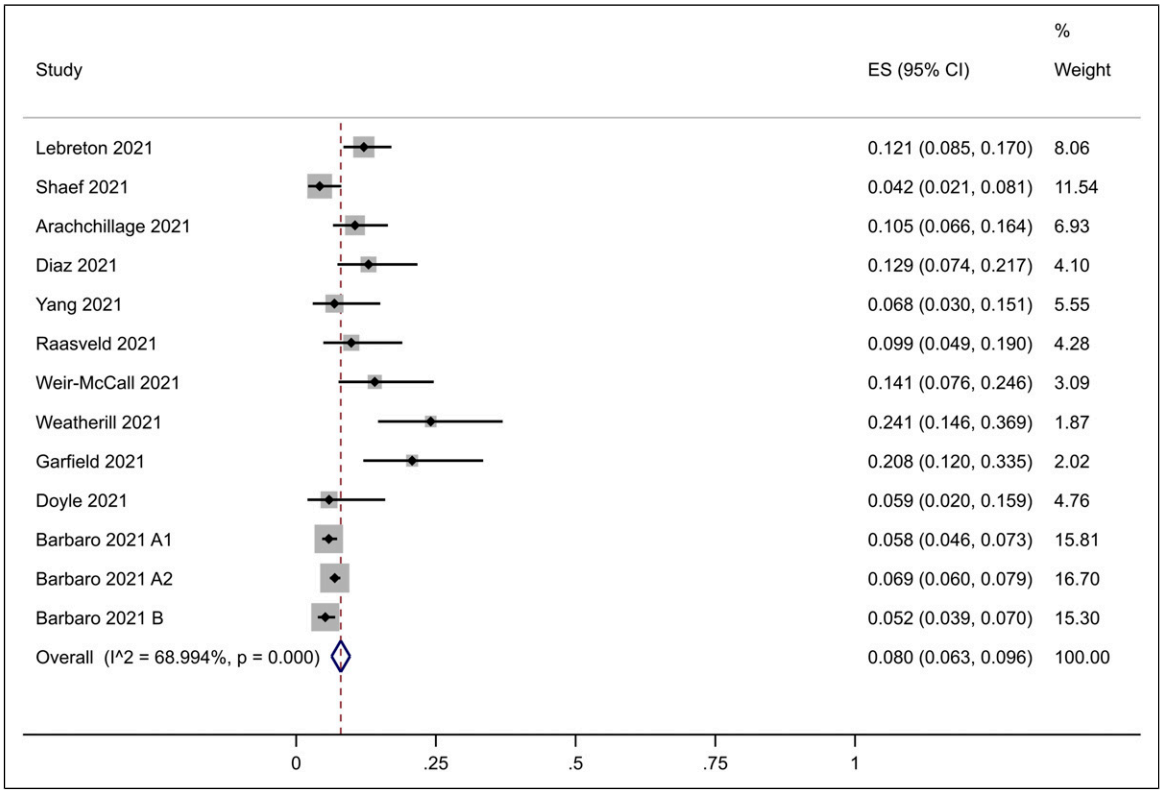

Figure 3. Forest plot of incidence of intracranial hemorrhage in COVID-19-related ECMO.

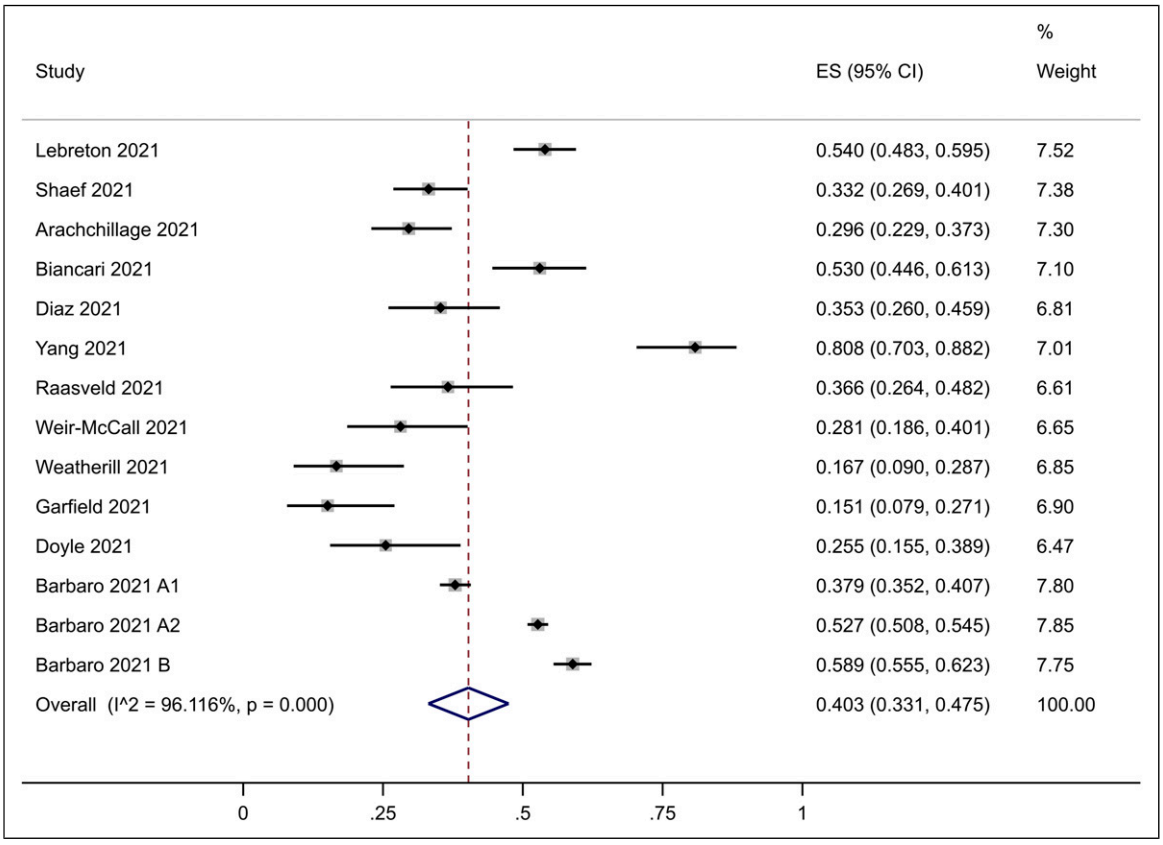

Figure 4. Forest plot of overall in-hospital mortality in COVID-19-related ECMO.

The pooled prevalence of ischemic stroke (5.7% v.s. 1.2%, $p = 0.016$) and ICH (12.3% v.s. 6.1%, $p = 0.010$) were significantly higher in Europe than international registry. However, the pooled overall in-hospital mortality was much lower (32.6% v.s. 49.8%, $p < 0.001$) in Europe (Supplementary Figure 4).

Pooled estimates overlapped between anticoagulation monitoring subgroups. The incidence of ischemic stroke was as high as 14.4% in the study[23] referred to APTT (target range: 40–60s) and ACT (target range: 160–300s). Up to 24.1% complicated with ICH in the study based on Anti-Xa (target range: 0.3–0.5 IU/ml) (Supplementary Figure 5).

In fact, the detection of ischemic stroke and ICH varied among centers. Some centers performed routine CT regardless of neurological symptoms, with a higher detection rate of ischemic stroke (5.0% v.s. 1.9%, $p = 0.053$), and ICH (12.3% v.s.7.1%, $p = 0.098$) than brain CT which was performed for clinical suspicion/symptoms of neurological injury (Supplementary Figure 6).

Comparison of COVID-19 patients requiring ECMO with non-COVID-19 patients supported with ECMO

Of the 12 included studies, 3 studies[27–29] (171 patients) compared COVID-19 related ECMO and non-COVID-19 related ECMO. We extracted and summarized the overall in-hospital mortality, incidence of ischemic stroke and ICH in these studies. Compared to non-COVID-19 patients supported with ECMO, ICH during ECMO [RR = 1.75 (95% CI: 1.00 to 3.07), $p = 0.729$] was significantly higher in COVID-19 related ECMO (Figure 5).

Discussion

This systematic review and meta-analysis aimed to summarize ischemic stroke, ICH, overall in-hospital mortality and anticoagulation practices in COVID-19 patients requiring ECMO, and compare them with non-COVID-19 related ECMO.

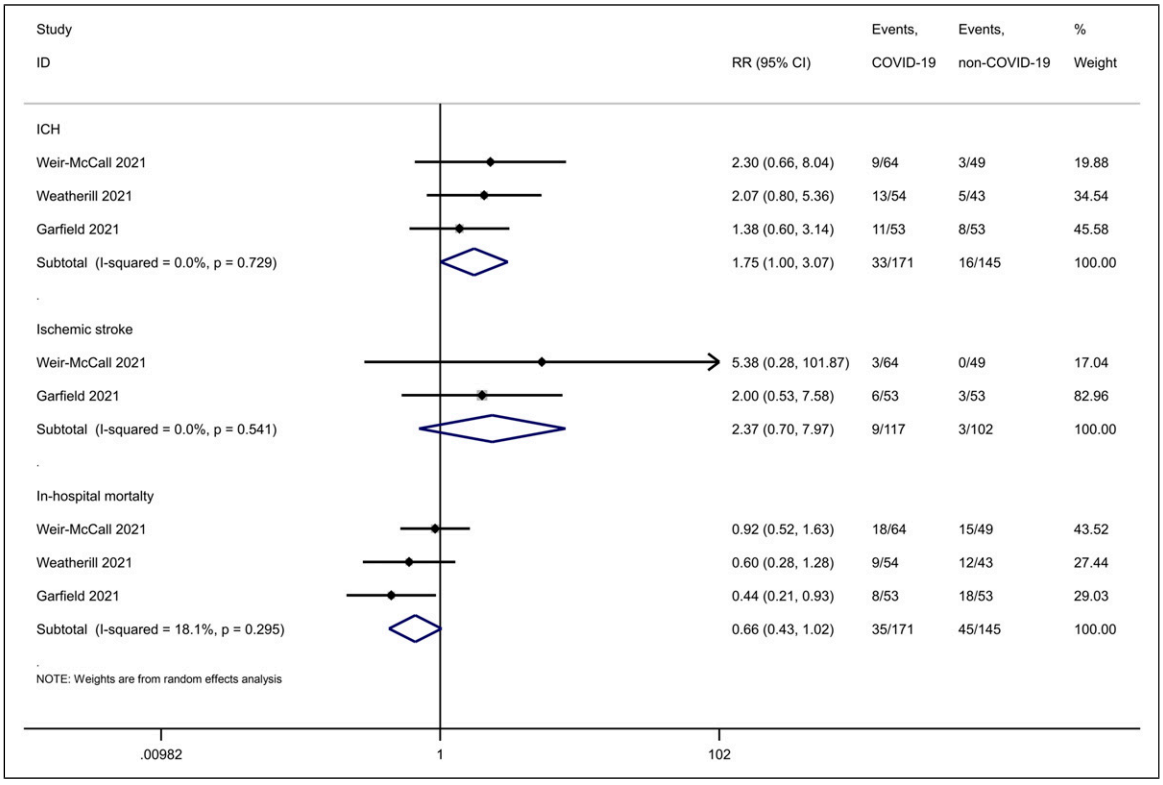

Figure 5. Comparison of the incidence of ischemic stroke and intracranial hemorrhage in the COVID-19 patients requiring ECMO with non-COVID-19 patients supported with ECMO.

The data we included in this study demonstrated an overall prevalence of 2.3% for ischemic stroke, 8.0% for ICH and 40.3% for overall in-hospital mortality among 6039 COVID-19 patients requiring ECMO support. It was reported that patients with COVID-19 infection may be at a greater risk of ischemic stroke than patients with influenza infection.[31] However, this trend is not significant in COVID-19 related ECMO. The prevalence of ICH (8.0%) was significantly higher in COVID-19 related ECMO than previous retrospective analysis of adult VV ECMO from the ELSO registry (4.5%)[3] and the randomized controlled trial-Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) trial (2%).[32]

The occurrence of ischemic stroke and ICH is multifactorial and anticoagulation regimens play an important role to balance bleeding and thrombosis. The prophylactic intermediate or high-dose anticoagulant might be performed to correct the COVID-19 related pro-coagulant state before ECMO.[24] Unfortunately, there was no benefit of therapeutic dosage of heparin in critically ill COVID-19 hospitalized patients,[33] and ICH was more frequent in the higher heparin dose group.[34] Even the use of initial heparin boluses, regardless of previous anticoagulation, and the maintenance of conventional anticoagulation strategy during ECMO, the incidence of ICH was doubled in patients with COVID-19 compared to patients suffering from ARDS attributable to other causes.[35] Additionally, the more intensive anticoagulation regimen due to existing thrombotic event on ECMO[20] may contribute to the higher risk of ICH. There remains no consistent anticoagulation regimen to reduce the occurrence of thrombosis and bleeding events under the double "hit" of COVID-19 and ECMO. Anticoagulation practices require a delicate balancing act.[36] Individualized anticoagulation targets can be a good choice and needs further exploration.

COVID-19 induces endotheliitis, platelet dysfunction or thrombocytopenia and Acquired von Willebrand Syndrome (AVWS).[37–39] As a result, a considerable number of critically ill COVID-19 patients complicated with ischemic stroke and ICH. Doyle et al.[30] reported ischemic stroke of 3.9% and ICH of 15.7% before ECMO implantation. Lang et al.[40] pointed that spontaneous ICH in COVID-19 patients with ARDS not receiving ECMO support are common and similar to non-COVID-19 ARDS.

It was noted that the different prevalence rates of ischemic stroke and ICH among the three groups

became similar after normalizing for the duration of ECMO support (complication rates per 1000 h of ECMO support) in the ELSO registry.[2] Besides the various anticoagulation practices and different ECMO durations, potential factors associated with ICH included a lower pH and renal failure before ECMO.[24]

In our subgroup analysis, we explored the association between region, anticoagulant monitoring and application of routine CT with ischemic stroke, ICH and overall in-hospital mortality. Interestingly, we found that the incidence of ischemic stroke and ICH were approximately 1% and 6% in COVID-19 patients supported with ECMO according to the two publications based on ELSO data,[1,2] which were significantly lower than patients in Europe. More than half of the ELSO registered centers were in North America, and the prevalence of ischemic stroke and ICH in international ELSO reports were consistent with the pooled estimates in the American subgroup in our analysis. However, overall in-hospital mortality was lowest in Europe subgroup.

Routine CT can find clinically silent cerebral microbleeds. The pooled prevalence of ICH and ischemic stroke from four[22,27,28,30] studies received routine CT examination was high at 12.3% (95 CI: 6.3%–18.3%) and 5.0% (95 CI: 6.3%–18.3%), separately. The performance of CT for clinical symptoms happened in about 50% COVID-19 patients on ECMO.[35] In the study by Weatherill et al.,[28] routine whole-body CT imaging was performed in all patients within 24 h of admission for ECMO, which detected ICH of 24.1% and ischemic stroke of 11.1%, comparatively high rates.

The pooled estimate of overall in-hospital mortality was 40.3% of the included data, which is lower than 47% of the ELSO summary, because some of the included studies had short follow-up periods and part of patients were still hospitalized or on ECMO. Studies have shown that ICH can increase mortality,[3,22] but our current meta-analysis cannot explain the relationship between ischemic stroke, ICH and mortality in COVID-19 patients supported with ECMO.

Limitation

We recognize several limitations of our study. The findings and interpretations of this study were limited by the quality of the available evidence, and publication bias existed. The study populations showed high heterogeneity and thus must be interpreted with care. Given that most of these studies were single-center retrospective studies, various confounders may have been introduced due to the lack of risk adjustment or propensity score weighting. Different diagnostic practices, frequency and coverage of imaging examinations, various equipments, anticoagulation management and even differing definitions of ischemic stroke and ICH between studies may confound results. Some factors which may influence the prevalence of ischemic stroke and ICH, such as thrombocytopenia and the use of steroids, were reported in few studies. In the absence of individual patient data, we cannot conclude whether ICH and ischemic stroke will increase mortality. Anticoagulation practice before ECMO implantation was not documented in detail to make further analysis.

Despite its limitations, our study represents the largest data to date on the topic of ischemic stroke and ICH events in COVID-19 patients supported with ECMO. Further studies describing the prevalence, risk factors, and outcomes of ischemic stroke and ICH in critically ill COVID-19 related ECMO are needed to confirm our findings and provide insights into individualized management decisions.

Conclusion

Ischemic stroke and ICH were common under the double "hit" of COVID-19 and ECMO. The prevalence of ICH was significantly higher in COVID-19 patients supported with ECMO than non-COVID-19 patients requiring ECMO. Individualized anticoagulation regimens may be a good choice to balance thrombosis and bleeding. The association between ischemic stroke and ICH and mortality needs further exploration in COVID-19 related ECMO. For some outcomes, imprecision suggested that more data from multicenter and randomized clinical trial studies could help with clarification and offer further insight into personalized anticoagulation strategies and the underlying mechanism.

Authors contributions

Study concept and design: YZ and JL. Acquisition of data, analysis and interpretation of data: YJ and YZ. Drafting of the manuscript: YJ. Critical revision of the manuscript for important intellectual content: YJ, YZ and JL. All authors read and approved the final manuscript.

Declaration of conflicting interests

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Data availability

The data that support the findings of this study are available from the corresponding author, YZ and JL, upon reasonable request.

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Supplemental Material

Supplemental material for this article is available online.

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Appendix

List of abbreviations

COVID-19	Coronavirus disease 2019
ARDS	Acute respiratory distress syndrome
ECMO	Extracorporeal membrane oxygenation
ELSO	Extracorporeal Life Support Organization
ICH	Intracranial hemorrhage
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
MOOSE	Meta-Analysis of Observational Studies in Epidemiology
JBI	Joanna Briggs Institute
GRADE	Grading of Recommendations, Assessments, Developments, and Evaluations
CT	computed tomography
APTT	Activated Partial Thromboplastin Time
Anti-Xa	Anti-factor Xa levels
ACT	Activated Clotting Time
CI	Confidence interval
SD	standard deviation
RR	relative risk
EOLIA	Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome
AVWS	Acquired von Willebrand Syndrome.