Journal of the American Heart Association

ORIGINAL RESEARCH

Association Between Cerebral Microbleeds and Neurological Outcomes in Patients Who Underwent Extracorporeal Membrane Oxygenation

Zhipeng Xu, MD; Jingchen Zhang, MD; Xing Fang, MD; Yongwei Yu, MD; Mi Xu, MD; Tong Li, MD; Jueyue Yan, MD

BACKGROUND: Cerebral microbleeds (CMBs) are common and varied in patients receiving extracorporeal membrane oxygenation (ECMO). Here, the authors describe CMB findings in patients receiving ECMO and their association with clinical factors.

METHODS AND RESULTS: A total of 138 patients receiving ECMO were enrolled and categorized as venovenous and venoarterial. Blood coagulation profiles during ECMO support and Glasgow Coma Scale (GCS) scores within 7 days were recorded. Patients with CMBs exhibited prolonged activated clotting time ($P<0.001$), decreased fibrinogen levels ($P<0.001$), reduced platelet counts ($P<0.001$), and extended prothrombin time ($P<0.001$). A significant correlation ($P<0.05$) was observed between the presence of CMBs and most coagulation parameters among all patients. Patients with venoarterial ECMO had significantly higher activated partial thromboplastin time, activated clotting time, and prothrombin time compared with those with venovenous ECMO (all $P<0.05$). Patients with a less severe CMB burden exhibited higher GCS scores and better neurological injury outcomes at both 7 and 90 days. CMB burden in all patients with ECMO was significantly correlated ($P<0.05$) with most blood coagulation profiles and neurological injury.

CONCLUSIONS: CMB burdens after ECMO are common, varied, and associated with a variety of clinical conditions. These findings may guide ECMO management.

Key Words: cerebral microbleeds ■ extracorporeal membrane oxygenation ■ neurological deficit

Extracorporeal membrane oxygenation (ECMO) is a life-saving mechanical support used to manage severe cardiopulmonary failure. This innovative technology provides temporary support to the heart and lungs by oxygenating the blood outside the body and then returning it to the patient's circulatory system. While venovenous ECMO focuses on providing respiratory support by oxygenating blood and removing carbon dioxide, venoarterial ECMO additionally offers cardiac support by assisting or completely taking over the heart's pumping function. Neurological function assessment is of paramount importance during ECMO operation, as the therapy can have significant implications for brain health.

Intracranial hemorrhage is a recognized neurological complication in patients who have experienced ECMO, with a reported incidence ranging from 2% to 21%.[1] This serious condition can lead to various adverse outcomes, including neurological deficits and death. However, despite the prevalence of intracranial

Correspondence to: Jueyue Yan, MD, Department of Critical Care Medicine, The First Affiliated Hospital, Zhejiang University School of Medicine, No. 79 Qingchun Road, Hangzhou 310003, Zhejiang Province, China. Email: yan814122408@163.com

Preprint posted on ResearchSquare February 16, 2024. https://doi.org/10.21203/rs.3.rs-3953116/v1.

This article was sent to Neel S. Singhal, MD, PhD, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.037029

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- This observational study demonstrated that cerebral microbleeds are common and associated with blood coagulation profiles and neurological injury in patients who experienced extracorporeal membrane oxygenation.

What Are the Clinical Implications?

- This study provides evidence that cerebral microbleed burden is associated with neurological injury in patients who experienced extracorporeal membrane oxygenation.
- Further study of the underlying mechanisms of cerebral microbleed is warranted and may guide extracorporeal membrane oxygenation management.

Nonstandard Abbreviations and Acronyms

ACT	activated clotting time
aPTT	activated partial thromboplastin time
CMB	cerebral microbleed
mRS	modified Rankin Scale
SOFA	Sequential Organ Failure Assessment
STRIVE	Standards for Reporting Vascular Changes on Neuroimaging

hemorrhage, there is a notable lack of research on cerebral microbleeds (CMBs) in patients with ECMO. Existing studies on this topic are limited to case reports,[2,3] and there is a need for more comprehensive investigations to understand the prevalence and impact of CMBs in this specific patient population.

CMBs are small lesions (2–5 mm in diameter) that exhibit low signal on magnetic resonance imaging (MRI) T2 or susceptibility-weighted sequences. It is important to realize that there are different types of CMBs in the brain, and that their pathologies are often overlapping and their pathophysiological mechanisms are similar.[4] CMBs are a radiological indicator of cerebral small vessel disease, which occurs in older adults and cerebrovascular diseases.[4] Among these, CMBs are of particular concern because of their association with an increased risk of future hemorrhagic stroke, ischemic stroke, more severe cognitive decline, and dementia in the general population.[4,5] It is essential to note that these potential complications can have a profound impact on the long-term health and quality of life of patients with ECMO.

Recent studies[3,6] have shown the incidence of CMB in patients who have received ECMO support. CMB is suggested as a complication in patients with ECMO with rates of 2% to 21%.[1,7,8] However, our understanding of CMBs in patients who have experienced ECMO is limited.

Since ECMO has grown rapidly, its positive effect on survival rates has become more evident. For example, recent studies have shown that the survival rate for patients undergoing venoarterial ECMO, which is used primarily for cardiogenic shock and cardiac failure, ranges from 39% to 50% depending on the severity of the condition and timely initiation of the therapy.[9,10] In contrast, venovenous ECMO, used mainly for severe respiratory failure, is associated with higher survival rates. A systematic review and meta-analysis reported a survival rate of 72.3% for venovenous ECMO in trauma patients with acute hypoxic respiratory failure.[9] Another study highlighted that by optimizing ECMO treatment protocols, survival rates for adult patients with acute fulminant myocarditis improved from 66.7% to 89.1%.[11] The lack of comprehensive research on CMBs in patients with ECMO illustrates the significant gap in our understanding of the neurological implications of this life-saving therapy. Given the potential impact of CMBs on patient outcomes, further investigation into the prevalence and impact of CMBs in patients with ECMO is warranted. Understanding the relationship between ECMO (venoarterial and venovenous) and CMBs could provide valuable insights for clinical management and contribute to the development of strategies to minimize the risk of neurological complications after ECMO support. Venoarterial ECMO is primarily used for patients with cardiogenic shock and cardiac failure. It requires higher levels of anticoagulation because it supports not only respiratory function but also sufficient hemodynamic support. This increases the risk of bleeding and thrombotic complications, necessitating more stringent coagulation monitoring and management.[9,10] In contrast, venovenous ECMO is primarily used for patients with severe respiratory failure, with relatively lower anticoagulation requirements, although it still needs to prevent thrombosis in the extracorporeal circuit.[9,11]

In view of the above, we aimed to explore the incidence and number of CMBs, as well as their clinical implications after ECMO support (venoarterial and venovenous). Our study cohort also investigated the association between CMBs (venovenous and venoarterial) and clinical outcomes. By clarifying the differences between these 2 modes, we hope to optimize coagulation management strategies and reduce the risk of severe complications such as cerebral hemorrhage, thus improving the safety and efficacy of ECMO treatment. The primary aim was to explore the association of coagulation profile derangements with the frequency and severity of CMBs among patients undergoing ECMO. In addition, the secondary

objectives encompass assessing the relationship between varying degrees of CMBs and the modified Rankin Scale (mRS) scores at 90 days and cerebral performance category scores. We hypothesize that derangements in coagulation profiles may be associated with the burden of CMBs in patients who have undergone ECMO.

METHODS

The data that support the findings of this study are available on request from the corresponding author.

This study was approved by the First Affiliated Hospital of Zhejiang University (No. 2020-IIT-1163).

Participants

This study was conducted at a single center, specifically the intensive care unit of the First Affiliated Hospital of Zhejiang University School of Medicine. We enrolled patients who received ECMO treatment from August 2020 to December 2023 in this study. These patients included those who received venoarterial ECMO and venovenous ECMO support. Exclusion criteria consisted of: (1) age younger than 18 years; (2) history of cerebral disorders such as cerebrovascular accident, intracranial tumor, central nervous system immune disease, and dementia; (3) inability to undergo cerebral MRI examination; (4) modes converted during ECMO operation; and (5) death within 90 days after explanation of ECMO.

Clinical Information

The clinical data for this study were meticulously gathered through an inpatient data management system, capturing a wide array of demographic information. Medical histories include cardiovascular risk factors such as hypertension, hyperlipidemia, diabetes, smoking, recently prescribed medications, and previous strokes. Blood coagulation parameters during the ECMO operation were recorded. This comprehensive assessment included activated clotting time (ACT), prothrombin time (PT), D-dimer levels, activated partial thromboplastin time (aPTT), and fibrinogen levels. In addition to these parameters, the study also incorporated several other critical markers of patient status and response during ECMO treatment. This encompassed the highest Sequential Organ Failure Assessment (SOFA) score, the maximum lactate level recorded, the lowest hemoglobin level observed, and the worst Glasgow Coma Scale (GCS) score.

Patient Management Under ECMO

Blood gas analysis was conducted on all patients 1 hour before and after ECMO initiation. This was followed by subsequent reviews every 4 hours during the ECMO operation. All patients received heparin anticoagulant therapy, administered as a loading dose before ECMO. Heparinization was adjusted at least once daily based on aPTT values: for venovenous ECMO it was maintained at 1.5 to 2 times the upper normal range (60–80 seconds), and for venoarterial ECMO at 2 to 2.5 times the upper normal range (80–100 seconds), as well as clinical tolerance. Heparin was discontinued in cases of bleeding and reintroduced when bleeding was controlled. Bleeding that leads to heparin discontinuation refers to any clinical bleeding (from the ECMO site, central or arterial lines, tracheal secretions, ear, nose, or throat), with or without hemodynamic effects with or without a decrease in hemoglobin levels as determined by the attending physician. During the ECMO procedure, all patients were routinely administered sedatives and analgesics, while monitoring sedation depth using a bispectral index. If conditions were stable, it was recommended to discontinue sedative and analgesic medications every 24 hours. The GCS score was assessed by specialized intensive care unit physicians or neurologists based on a bispectral index score ≥80 or if the bispectral index score did not increase after discontinuation of anesthetic drugs.

Magnetic Resonance Imaging

All eligible patients underwent MRI with a GE HDx 3.0T magnetic resonance scanner using a combined head and spine coil. Participants underwent conventional MRI plain scan and swan sequence scan. Conventional MRI plain scan sequence and parameters: fast spin echo T1 fluid-attenuated inversion recovery sequence, TR 1930 milliseconds, TE 22 milliseconds or RT 2500 milliseconds, TE 9 milliseconds, T 720 milliseconds in axial and sagittal planes, matrix 320×224, excitation times 1; propeller sequence T2WI, TR 6400 milliseconds, TE 134 milliseconds, matrix 320×320, excitation times 1.5; FSE axial T2 fluid-attenuated inversion recovery sequence, TR 8502 milliseconds, TE 162 milliseconds, TI 2100 milliseconds, matrix 256×192, excitation times 1; diffusion weighted imaging sequence, TR 4800 milliseconds, TE 80 milliseconds, matrix 96×130, excitation number 2; in the horizontal plane, the field of view was 24 cm×24 cm, the thickness was 6 mm, and the interval was 1 mm. The sagittal field of view was 22 cm×22 cm with 5-mm slice thickness and 1-mm interval.

The Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) consensus criteria were used to rate MRI markers of cerebral small vessel disease. In susceptibility-weighted imaging, CMBs appeared as homogenous, rounded hypointense lesions ranging in size from 2 to 10 mm. CMB burden was categorized as low (<10 CMB), moderate (10–30 CMB), and high (>30 CMB), as previously reported.[6] Figure 1 shows the

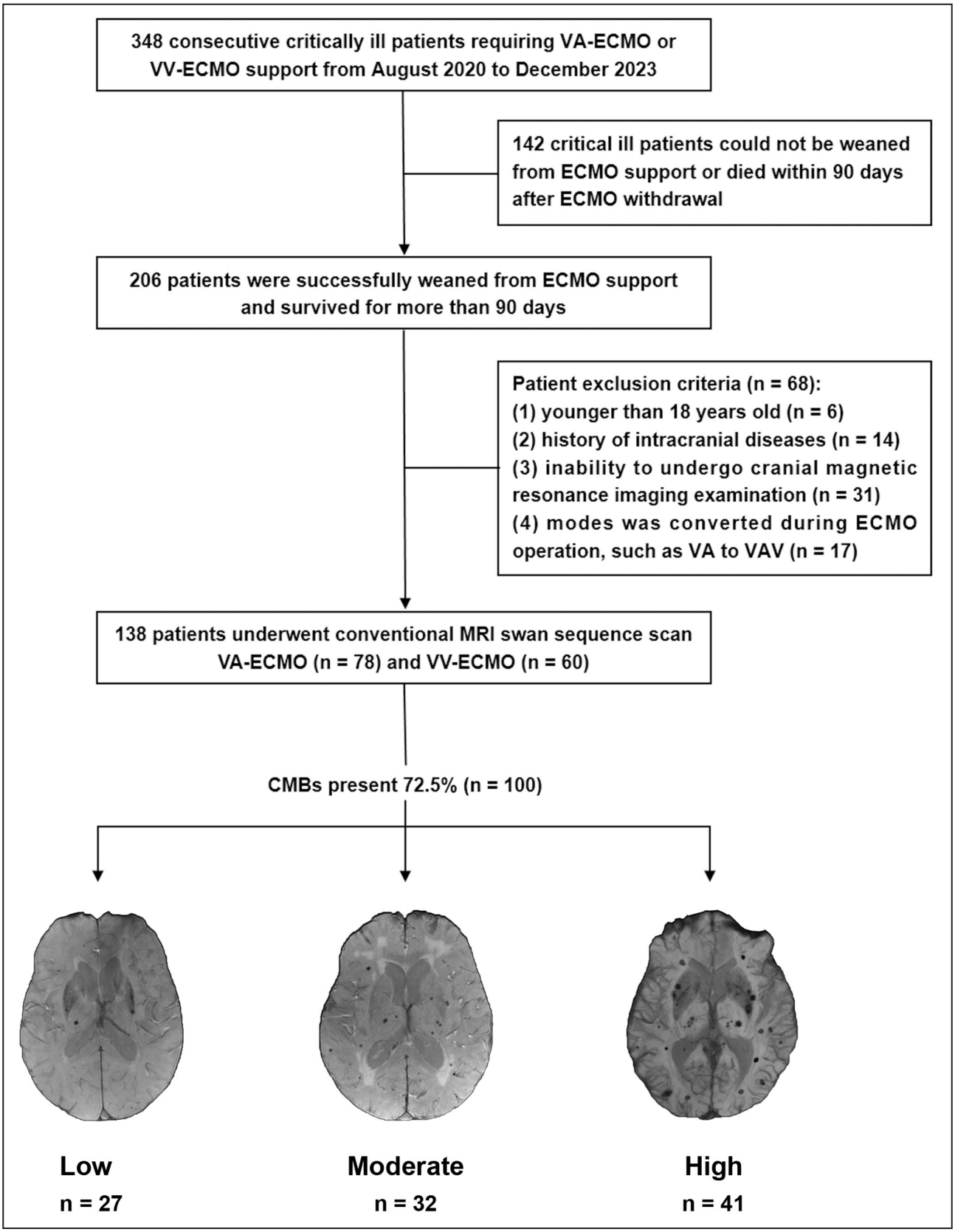

Figure 1. Study flow diagram and stratification of CMBs burden.
CMB indicates cerebral microbleeds; ECMO, extracorporeal membrane oxygenation; MRI, magnetic resonance imaging; VA, venoarterial; and VV, venovenous.

stratification of CMB burden. In the present investigation, we categorized the burden of CMBs as follows: CMB 0 for absence of CMBs, CMB 1 for low burden, CMB 2 for moderate burden, and CMB 3 for high burden.

Informed consent was obtained from all participants or their legal guardians.

Statistical Analysis

Continuous variables with a normal distribution are expressed as mean±SD, while skewed distributions are shown as medians and interquartile ranges. Categorical variables are presented as frequencies and percentages. Categorical variables were analyzed using a χ^2 or Fisher exact test as appropriate, and continuous variables were compared using *t* test (for continuous normally distributed data) or Mann–Whitney *U* test (for continuous, nonnormally distributed data) between the 2 groups.

General linear regression models were used to explore the relationship between CMB count, clinical outcomes, and blood parameters. General logistic regression models were used to explore the relationship between presence of CMBs, clinical outcomes, and blood parameters. This was done by controlling for key covariates: age, sex, hypertension, diabetes, hyperlipidemia, smoking, and ECMO operation time. Separate statistical analyses were conducted for patients with venoarterial and venovenous ECMO.

Statistical analysis and plotting were conducted in R version 4.2.3 (R Foundation for Statistical Computing), and $P<0.05$ was considered significant.

RESULTS

Figure 1 shows the flow chart of our study participants. Between August 2020 and December 2023, 348 patients underwent ECMO treatment at the Department of Critical Care Medicine, the First Affiliated Hospital, Zhejiang University School of Medicine. Among these patients, 142 were unable to be weaned from ECMO or survived 90 days after weaning. In addition, 68 patients were excluded from the study for various reasons. Specifically, 6 patients were excluded because of their age younger than 18 years, 14 based on a documented history of central nervous system disease, 31 because of incomplete MRI or poor image quality, and 17 because of mode switching during ECMO. Our final data analysis included 138 patients with ECMO (mean age, 53.44±8.96 years; 47.10% men); of the 138 patients, 78 (56.52%) received venoarterial ECMO support, while 60 (43.48%) received venovenous ECMO. Baseline characteristics for our patients are shown in the Table. Patients who underwent venoarterial ECMO support had increased CMB burden and poorer mRS scores than patients with venovenous ECMO support. Figure S1 shows the comparison of blood coagulation profiles between patients who received venoarterial ECMO and venovenous ECMO. Patients who underwent venoarterial ECMO had significantly higher aPTT, ACT, and PT compared with those who underwent venovenous ECMO (all $P<0.05$). Figure S2 shows the comparison of clinical outcomes in patients who received venoarterial ECMO and venovenous ECMO.

Figure 2A illustrates the association between CMBs and various blood coagulation parameters within the study cohort. A significant correlation ($P<0.05$) was observed between the presence of CMB and most coagulation parameters across all patients. Further analyses revealed specific associations: patients with CMB exhibited prolonged ACT (Figure 2B; $P<0.001$), decreased fibrinogen levels (Figure 2C; $P<0.001$), reduced platelet counts (Figure 2D; $P<0.001$), and

Table. Characteristics of the Study Population

	All patients	Venovenous ECMO	Venoarterial ECMO	*P* value
Total, n	138	60	78	
Age, mean±SD, y	53.44±8.96	52.60±10.80	54.09±7.25	0.959
Men, n (%)	65 (47.10)	24 (40.00)	41 (52.56)	0.196
Smokers, n (%)	45 (32.61)	17 (28.33)	28 (35.90)	0.449
Drinkers, n (%)	33 (23.91)	13 (21.67)	20 (25.64)	0.733
Hypertension, n (%)	67 (48.55)	32 (53.33)	35 (44.87)	0.416
Diabetes, n (%)	20 (14.49)	9 (15.00)	11 (14.10)	>.99
Hyperlipidemia, n (%)	16 (11.59)	6 (10.00)	10 (12.82)	0.807
Total WMH burden, n (IQR)	3 (2–5)	3 (2–4)	3 (2–5)	0.026
Presence of lacunes, n (%)	19 (13.77)	4 (6.67)	15 (19.23)	0.034
CMB burden, n (IQR)	2 (0–3)	1 (0–2)	2 (1–3)	<0.001
Presence of CMB, n (%)	100 (72.46)	32 (53.33)	68 (87.18)	<0.001
mRS, n (IQR)	3 (2–4)	3 (2–3)	3 (3–4)	0.001

CMB indicates cerebral microbleed; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; mRS, modified Rankin Scale; WMH, white matter hyperintensity.

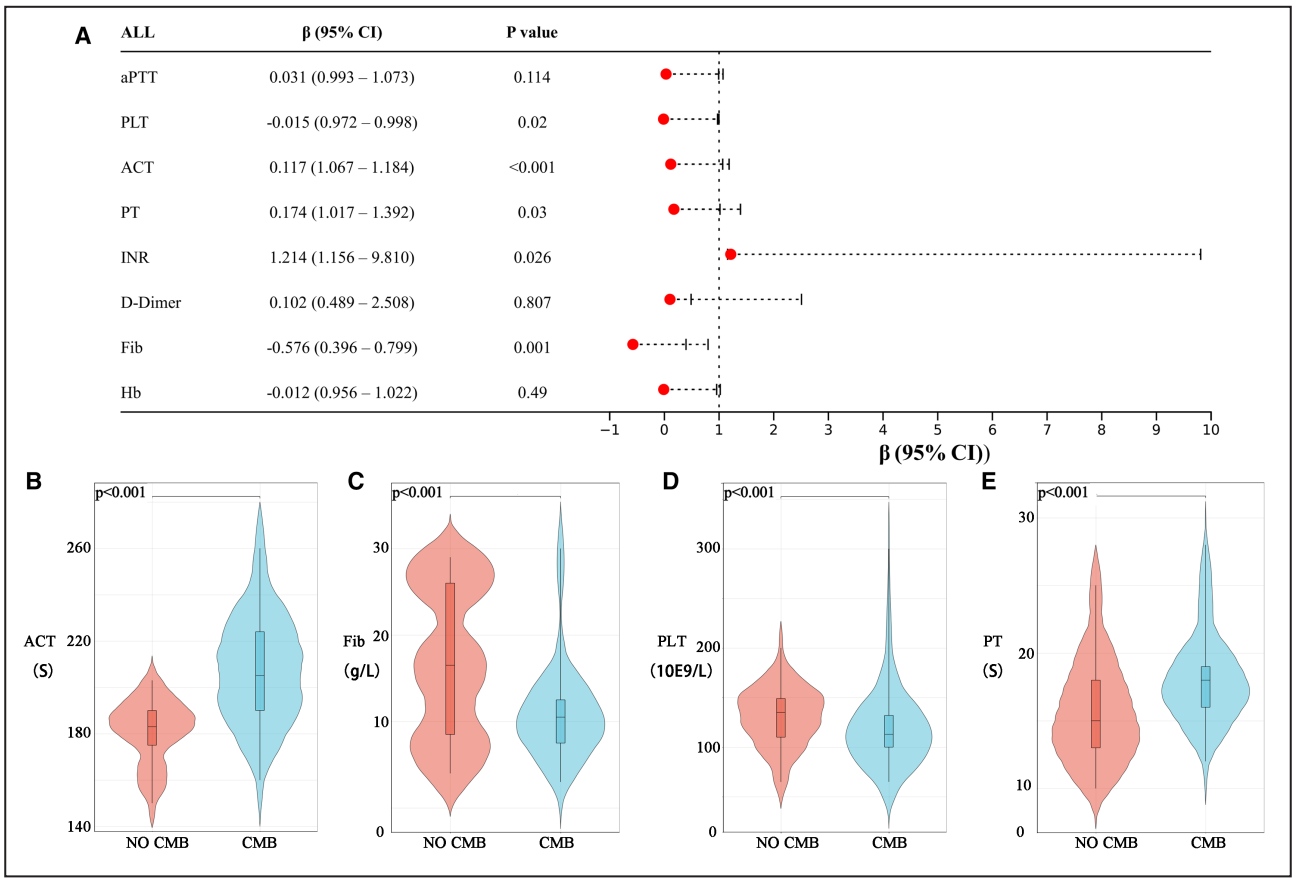

Figure 2. Association between CMBs and blood coagulation parameters.
A, The association between CMB and blood coagulation parameters. Multivariable regression was used to explore the association while adjusting for age, sex, hypertension, diabetes, hyperlipidemia, smoking, and ECMO operation time. Comparison of CMB presence in (**B**), Fib (**C**), PLT (**D**), and PT (**E**). Patients who survived ECMO with CMBs had significantly higher coagulation levels than those without CMBs. ACT indicates activated clotting time; aPTT, activated partial thromboplastin time; ECMO, extracorporeal membrane oxygenation; Fib, fibrinogen; Hb, hemoglobin; INR, international normalized ratio; PLT, platelet; and PT, prothrombin time.

extended PT (Figure 2E; *P*<0.001). Figure S3 shows that in patients with venovenous ECMO support, the presence of CMB significantly correlated with ACT (*P*=0.046); Figure S4 shows that in patients with venoarterial ECMO support, the presence of CMB correlated with ACT (*P*=0.003).

Consistent with observed trends, the burden of CMB was significantly correlated (*P*<0.05) with the majority of blood coagulation parameters across all patients (Figure 3A). Specific findings include an association between high CMB burden and prolonged ACT (Figure 3B; *P*<0.001), reduced fibrinogen levels (Figure 3C; *P*<0.001), decreased platelet counts (Figure 3D; *P*<0.001), and extended PT (Figure 3E; *P*<0.001).

Figure S5 illustrates that in patients with venovenous ECMO, elevated D-dimer levels (*P*<0.001), prolonged ACT (*P*<0.001), and PT (*P*=0.020), along with reduced PLT levels (*P*<0.001), are associated with an increased burden of CMBs. Figure S6 indicates that in patients with venoarterial ECMO, prolonged ACT (*P*<0.001), aPTT (*P*=0.020), PT (*P*<0.001), along with lower PLT (*P*=0.020) and fibrinogen levels (*P*<0.001), may contribute to an increased CMB burden.

In our prospective cohort study of patients with ECMO, we analyzed the correlation between CMB severity and neurological outcomes measured by the GCS scores at 7 and 90 days and the mRS score at 90 days. Figure 4A illustrates the trends in GCS scores at 7 and 90 days, alongside the 90-day mRS outcomes across different levels of CMB burden. Figure 4B presents the variations in 7-day and 90-day GCS scores among the CMB burden subgroups, with nearly all enrolled patients demonstrating an improvement in their 90-day GCS score (all *P*<0.05). Figures 4C through 4E indicate that patients with a less severe CMB burden exhibited higher GCS scores and better mRS outcomes at both 7 and 90 days (all *P*<0.001).

Figures S5 and S6 show the association between CMB burden and clinical outcomes. We showed that CMB and CMB burden significantly correlated with all clinical outcomes in our study cohort (all *P*<0.001).

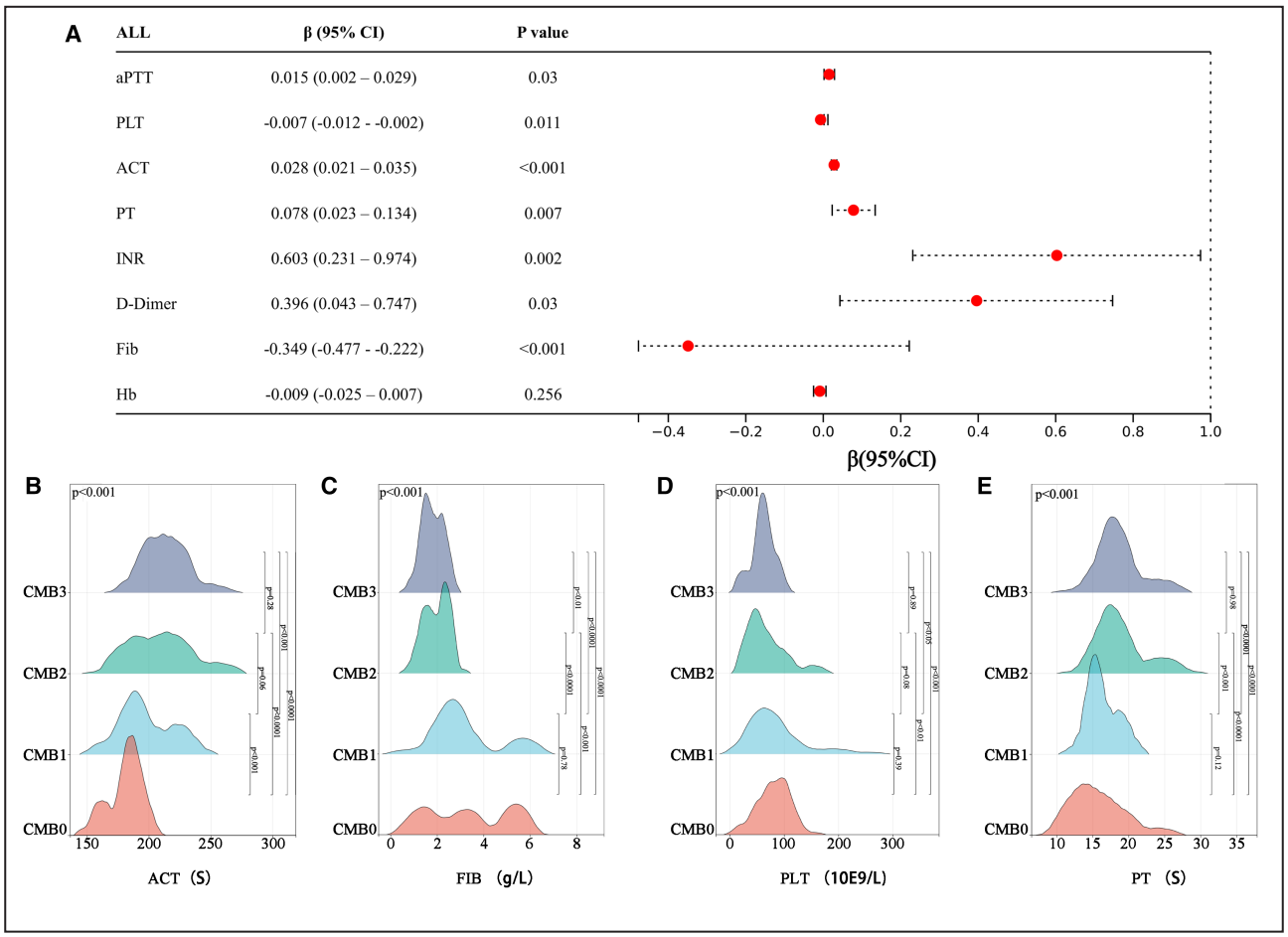

Figure 3. Association between CMB burden and blood coagulation parameters.
A, The association between CMB burden and blood coagulation parameters. Multivariable regression was used to explore the association while adjusting for age, sex, hypertension, diabetes, hyperlipidemia, smoking, and ECMO operation time. Comparison of CMB burden in ACT (**B**), Fib (**C**), PLT (**D**); and PT (**E**). ECMO survivors with a high CMB burden had significantly higher coagulation levels. ACT indicates activated clotting time; aPTT, activated partial thromboplastin time; ECMO; extracorporeal membrane oxygenation; Fib, fibrinogen; Hb, hemoglobin; INR, international normalized ratio; PLT, platelet; and PT, prothrombin time.

DISCUSSION

Since practice variations among different types of ECMO exist and little is known about how it correlates with neurologic injury and coagulation parameters, we conducted an observational, prospective study. In the present study we found that CMB was the most common radiological finding in our ECMO cohort. We found that these radiological findings varied among the different types of ECMO used in our study participants. We also found that CMB was associated with blood coagulation parameters and neurologic injury in patients who underwent ECMO. Although causation cannot be proven in this cross-sectional, noninterventional study, the findings are intriguing. These findings show that levels of these blood coagulation parameters during ECMO support may lead to impaired neurological outcomes.

The pathophysiology of venoarterial ECMO and venovenous ECMO associated with cerebral changes in patients who experienced ECMO differs. Here, we showed that CMB burden and other small vessel disease markers were higher in patients who underwent venoarterial ECMO than in those who underwent venovenous ECMO. CMBs are radiological markers of hemorrhage-prone cerebral small vessel disease identified by blood-sensitive MRI sequences.[12] CMBs are one of the most common radiological findings in patients who undergo ECMO and indicate prior microhemorrhage. In addition, a recent study[6] showed that the presence of CMBs after ECMO support commonly involves the splenium of corpus-callosum and their etiopathogenesis may be independent of microvascular lipohyalinosis. In patients undergoing venoarterial ECMO, hemodynamics often exhibit significant disarray, leading to hypotension and tissue hypoperfusion. This compromised hemodynamic state can surpass the human brain's autoregulatory capacity, culminating in ischemia and hypoxia-induced disruption of the

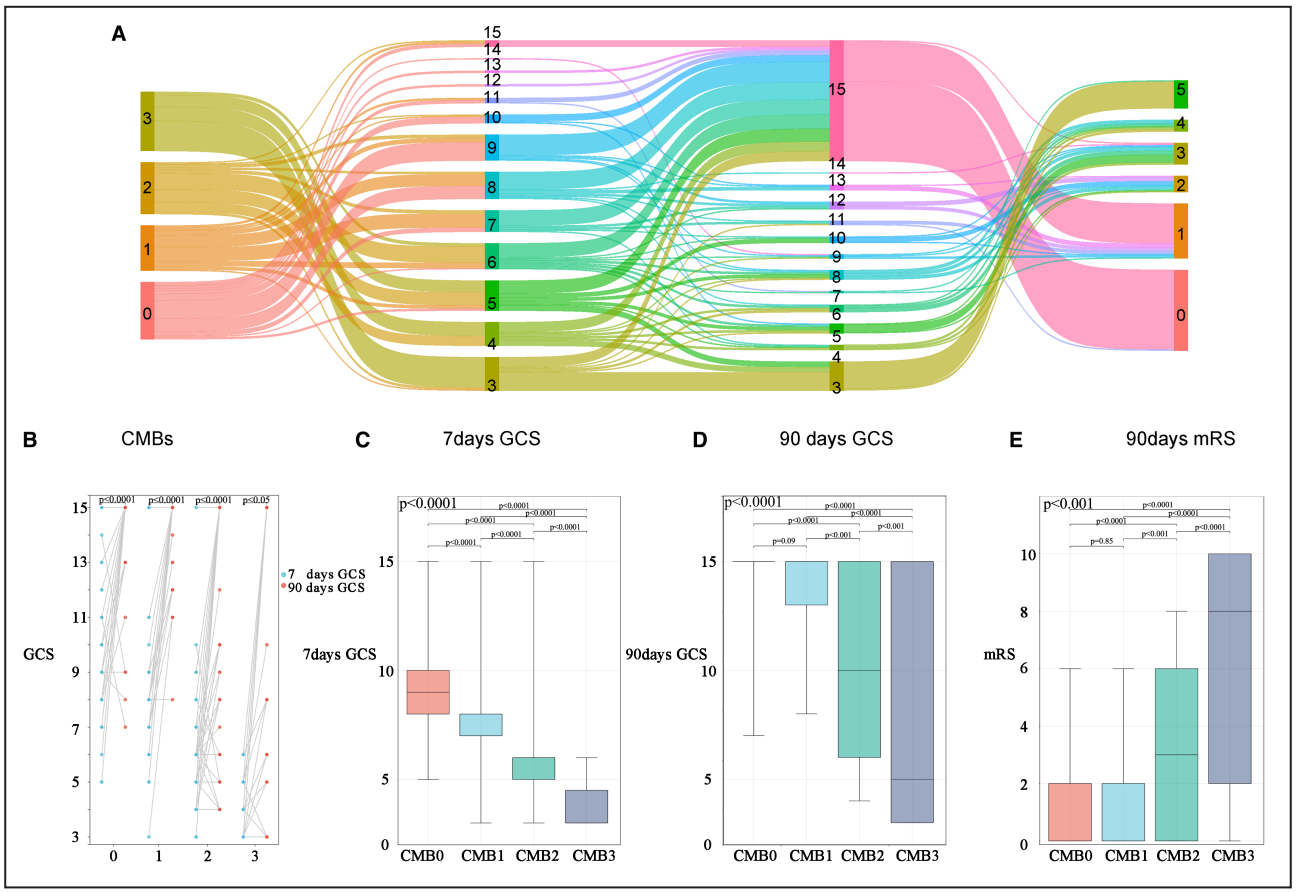

Figure 4. Association between cerebral microbleed (CMB) burden and neurological outcomes measured by the Glasgow Coma Scale (GCS) at 7 and 90 days and the modified Rankin Scale (mRS) at 90 days.
Multivariable regression was used to explore the association while adjusting for age, sex, hypertension, diabetes, hyperlipidemia, and smoking. **A**, Trends in GCS scores at 7 and 90 days, alongside the 90-day mRS outcomes across different CMB burdens. **B**, The variations in 7-day and 90-day GCS scores among CMB burden subgroups. **C** through **E**, Patients with a less severe CMB burden exhibited higher GCS scores and better mRS outcomes at both 7 and 90 days.

blood–brain barrier, ultimately resulting in damage to brain cells. Moreover, patients with venoarterial ECMO have dual circulatory systems, comprising the endogenous heart and the ECMO system. This heightens the potential for cerebral embolism in the event of a thrombotic incident within the ECMO circuit.[13] Furthermore, the nonpulsatile nature of blood flow in the ECMO system may contribute to cerebral damage, compounding the challenges faced by these patients. In contrast, patients receiving venovenous ECMO experience deterioration in lung function, with a lesser impact on tissue perfusion.[14] Notably, the brain in patients with venovenous ECMO depends on pulsatile blood flow from the heart. This mitigates any risks associated with patients with venoarterial ECMO.[15] Radiological incidence of CMB in patients receiving ECMO varies from 2% to 19%.[16,17] CMBs have received less attention because the use of MRI is not routine in adult patients with ECMO.[3,18] Here, we showed that patients who underwent venoarterial ECMO had a higher burden of CMBs compared with patients with venovenous ECMO. The distinctive hemodynamic profiles and tissue hypoxia severity observed in patients with venoarterial ECMO compared with patients with venovenous ECMO may underpin the heightened risk of more severe CMBs. This discrepancy underscores the critical importance of understanding the nuanced physiological dynamics at play in different ECMO modes. It also emphasizes the implications for cerebral health.

The 2 ECMO therapies used in our study differed in terms of laboratory parameters and neurologic injury. There are studies that support mechanical differences between the 2 most commonly used ECMO therapies (venoarterial and venovenous), which may explain differences in blood laboratory parameters and neurologic injury.[19,20] Specifically, differences in anticoagulation management include the use of heparin versus direct thrombin inhibitors such as bivalirudin and variations in monitoring practices such as using ACT or anti-Xa levels.[21] There is, however, very

little information suggesting that blood laboratory parameters and neurologic injury incidence differ. It is important to note that there is a substantial amount of variation in the methods employed by ECMO clinicians worldwide regarding weaning strategies, managing ECMO flow, cannulation techniques, and ventilator management.[19,22] We noticed a difference between laboratory values and SOFA scores between the 2 ECMO therapies.

It is suggested that patients with venoarterial ECMO have higher anticoagulation requirements.[23] Patients who experienced ECMO showed higher ACT, APTT, international normalized ratio D-dimer, and PT, and lower fibrinogen levels than patients with venovenous ECMO. Of note, these blood parameters are considered factors that lead to cerebral hemorrhage[24,25] and small vessel disease.[26,27] The study identified several contributory factors that influenced both the incidence and severity of CMBs in these vulnerable patients. Most notably, a robust correlation was found between the occurrence and severity of microbleeds and derangements in coagulation parameters during ECMO support. Patients with more prolonged or severe coagulopathy were more likely to develop microbleeds and experience an increased CMB burden. We also showed that ACT was associated with CMB presence and burden in both patients with venoarterial ECMO and those with venovenous ECMO. ACT elevations are associated with CMBs in patients with ECMO[1,24] and this finding was reiterated in our study.

The presence of CMBs, regardless of whether they manifested before or during ECMO treatment, exhibited a significant association with neurological function prognosis in survivors. A discernible correlation was observed between CMB burden, as evaluated based on CMB grade, and long-term neurological prognosis. Patients with more numerous or confluent microbleeds, reflecting a higher CMB grade, had poorer neurological function recovery. Our study also revealed that patients with a lower CMB burden exhibited higher GCS scores at both 7 and 90 days after injury. Furthermore, these patients were more likely to be fully awake (GCS=15) and reported higher quality of life based on mRS scores. This finding is in line with CMB morbidity in patients with ECMO.[28–30] This causes significantly longer hospital stays and higher health care costs.

In the present study, we applied MRI sequences to facilitate a comprehensive assessment and categorization of CMBs in patients with ECMO. The MRI sequence allowed for detailed visualization and grading of microbleeds in the brain. This provided significant insights into the relationship between CMBs and neurological prognosis in patients with ECMO. Based on these insights, we recommend targeted anticoagulation management strategies for patients who experienced ECMO exhibiting a sluggish neurological recovery trajectory. Clinicians should exercise caution with overly aggressive anticoagulation to avoid exacerbating microbleed progression in these at-risk individuals. Precisely defined anticoagulation targets and frequent monitoring of coagulation status could help balance the risks of clotting versus bleeding complications. Our results suggest that ACT seems to be a specific measure for monitoring. Compared with other coagulation function indexes, ACT directly reflects anticoagulant drug intensity. It is posited that more judicious anticoagulation approaches have the potential to mitigate both the incidence and worsening of detrimental CMBs over time. This could translate into improved long-term neurological outcomes for survivors of ECMO. The study underscores the value of MRI sequences for CMB characterization and grading. This provides prognostic information not readily discernible through other modalities. The findings highlight the need for individualized anticoagulation regimens tailored to each patient's unique risk profile. With further research, optimized anticoagulation management strategies may help optimize functional recovery for the growing population of patients who undergo ECMO. Overall, the investigation provides novel insights into mechanisms of ECMO-associated brain injury with implications for improving neurological outcomes.

Our findings can be used to generate many hypotheses, but there are several limitations that need to be considered. First, this investigation represents the first comprehensive clinical study of patients with ECMO employing the susceptibility-weighted imaging of MRI. Consequently, the absence of extensive large-scale and high-quality clinical research as a reference necessitates a cautious interpretation of the findings. Nonetheless, the results yield clinically significant conclusions. Second, given that ECMO is predominantly an urgent medical event, MRI, especially susceptibility-weighted imaging, is not routinely included in physical examinations. This makes it challenging to ascertain whether patients who underwent ECMO had previously experienced CMBs. This potential confounding factor was mitigated to the maximum through exclusion criteria. However, a notable association between CMB and the intensity of anticoagulation during ECMO and the neurological prognosis of patients who survive ECMO was observed. Last, it is important to note that this study was conducted at a single center. Although the relatively limited number of included patients met the criteria for successful ECMO withdrawal and underwent safe and stable MRI examinations, the study's single-center design may limit the generalizability of the findings. Nevertheless, it is worth noting that larger multicenter studies have been initiated to address these limitations and provide further insights into the topic.

In conclusion, we showed that the presence and burden of CMB in patients who experienced ECMO were associated with their blood coagulation parameters during ECMO operation and their neurological deficit after ECMO. The change in ACT is more closely related to CMB occurrence and severity. During ECMO operation, appropriate anticoagulation and monitoring methods may reduce CMB occurrence and improve neurological prognosis.

ARTICLE INFORMATION

Received June 7, 2024; accepted September 5, 2024.

Affiliation

Department of Critical Care Medicine, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China.

Acknowledgements

Author Contributions: Designed the study, analyzed, interpreted, and wrote the manuscript: Z.X., Y.Y., M.X., J.Z., H.C., and J.Y.; data collection: Z.X., T.L., H.C., and J.Y.; and revision of the manuscript: Z.X. and J.Y.

Sources of Funding

This research was supported by Zhejiang Provincial Natural Science Foundation of China under grant number LY22H150005, Medical and Health Research Project of Zhejiang province (No. 2022505672), Zhejiang Traditional Chinese Medicine Administration (2023ZL082), and Medical Science and Technology Project of Zhejiang Province (2023RC018).

Disclosures

None.

Supplemental Material

Figures S1–S6

REFERENCES

1. Fletcher-Sandersjoo A, Thelin EP, Bartek J Jr, Broman M, Sallisalmi M, Elmi-Terander A, Bellander BM. Incidence, outcome, and predictors of intracranial hemorrhage in adult patients on extracorporeal membrane oxygenation: a systematic and narrative review. *Front Neurol*. 2018;9:548. doi: 10.3389/fneur.2018.00548
2. Gijs J, Lambert J, Meyfroidt G, Demeestere J. Cerebral microbleeds and intracerebral hemorrhage associated with veno-venous extracorporeal membrane oxygenation. *Acta Neurol Belg*. 2018;118:513–515. doi: 10.1007/s13760-018-0975-z
3. Le Guennec L, Bertrand A, Laurent C, Roze H, Chastre J, Combes A, Luyt CE. Diffuse cerebral microbleeds after extracorporeal membrane oxygenation support. *Am J Respir Crit Care Med*. 2015;191:594–596. doi: 10.1164/rccm.201411-2118LE
4. Duering M, Biessels GJ, Brodtmann A, Chen C, Cordonnier C, de Leeuw FE, Debette S, Frayne R, Jouvent E, Rost NS, et al. Neuroimaging standards for research into small vessel disease-advances since 2013. *Lancet Neurol*. 2023;22:602–618. doi: 10.1016/S1474-4422(23)00131-X
5. Akoudad S, Wolters FJ, Viswanathan A, de Bruijn RF, van der Lugt A, Hofman A, Koudstaal PJ, Ikram MA, Vernooij MW. Association of cerebral microbleeds with cognitive decline and dementia. *JAMA Neurol*. 2016;73:934–943. doi: 10.1001/jamaneurol.2016.1017
6. Topiwala K, Hussein H, Masood K, Zhang A, Kashyap B, Bartos J, Tore H, Mistry E, Oladi B, Jagadeesan B, et al. Patterns and predictors of extra-corporeal membrane oxygenation related cerebral microbleeds. *J Stroke Cerebrovasc Dis*. 2022;31:106170. doi: 10.1016/j.jstrokecerebrovasdis.2021.106170
7. Arachchillage DRJ, Passariello M, Laffan M, Aw TC, Owen L, Banya W, Trimlett R, Morgan C, Patel BV, Pepper J, et al. Intracranial hemorrhage and early mortality in patients receiving extracorporeal membrane oxygenation for severe respiratory failure. *Semin Thromb Hemost*. 2018;44:276–286. doi: 10.1055/s-0038-1636840
8. Fletcher-Sandersjoo A, Bartek J Jr, Thelin EP, Eriksson A, Elmi-Terander A, Broman M, Bellander BM. Predictors of intracranial hemorrhage in adult patients on extracorporeal membrane oxygenation: an observational cohort study. *J Intensive Care*. 2017;5:27. doi: 10.1186/s40560-017-0223-2
9. Zhang Y, Zhang L, Huang X, Ma N, Wang P, Li L, Chen X, Ji X. Ecmo in adult patients with severe trauma: a systematic review and meta-analysis. *Eur J Med Res*. 2023;28:412. doi: 10.1186/s40001-023-01390-2
10. Moyon Q, Triboulet F, Reuter J, Lebreton G, Dorget A, Para M, Chommeloux J, Stern J, Pineton de Chambrun M, Hekimian G, et al. Venoarterial extracorporeal membrane oxygenation in immunocompromised patients with cardiogenic shock: a cohort study and propensity-weighted analysis. *Intensive Care Med*. 2024;50:406–417. doi: 10.1007/s00134-024-07354-2
11. Hou L, Liang H, Zeng S, Li J, Chen Z, Liao X, Liu S, Li M, Li B, Yuan Y. Optimising the ecmo treatment regimen increases the survival rate for adult patients with acute fulminant myocarditis: a single-centre retrospective cohort study. *Front Med (Lausanne)*. 2023;10:1146570. doi: 10.3389/fmed.2023.1146570
12. Puy L, Pasi M, Rodrigues M, van Veluw SJ, Tsivgoulis G, Shoamanesh A, Cordonnier C. Cerebral microbleeds: from depiction to interpretation. *J Neurol Neurosurg Psychiatry*. 2021;92:598–607. doi: 10.1136/jnnp-2020-323951
13. Schmidt M, Tachon G, Devilliers C, Muller G, Hekimian G, Brechot N, Merceron S, Luyt CE, Trouillet JL, Chastre J, et al. Blood oxygenation and decarboxylation determinants during venovenous ecmo for respiratory failure in adults. *Intensive Care Med*. 2013;39:838–846. doi: 10.1007/s00134-012-2785-8
14. Heilmann C, Geisen U, Beyersdorf F, Nakamura L, Benk C, Trummer G, Berchtold-Herz M, Schlensak C, Zieger B. Acquired von willebrand syndrome in patients with extracorporeal life support (ECLS). *Intensive Care Med*. 2012;38:62–68. doi: 10.1007/s00134-011-2370-6
15. Muellenbach RM, Kilgenstein C, Kranke P, Kustermann J, Kredel M, Roewer N, Ernestus RI, Westermaier T. Effects of venovenous extracorporeal membrane oxygenation on cerebral oxygenation in hypercapnic ards. *Perfusion*. 2014;29:139–141. doi: 10.1177/0267659113497073
16. Cho SM, Farrokh S, Whitman G, Bleck TP, Geocadin RG. Neurocritical care for extracorporeal membrane oxygenation patients. *Crit Care Med*. 2019;47:1773–1781. doi: 10.1097/CCM.0000000000004060
17. Taylor D, Wyncoll D. Intracranial hemorrhage occurs early in patients with severe respiratory failure requiring venovenous extracorporeal membrane oxygenation. *Crit Care Med*. 2020;48:e339–e340. doi: 10.1097/CCM.0000000000004214
18. Liebeskind DS, Sanossian N, Sapo ML, Saver JL. Cerebral microbleeds after use of extracorporeal membrane oxygenation in children. *J Neuroimaging*. 2013;23:75–78. doi: 10.1111/j.1552-6569.2012.00723.x
19. Zhang H, Xu J, Yang X, Zou X, Shu H, Liu Z, Shang Y. Narrative review of neurologic complications in adults on ecmo: prevalence, risks, outcomes, and prevention strategies. *Front Med (Lausanne)*. 2021;8:713333. doi: 10.3389/fmed.2021.713333
20. Illum B, Odish M, Minokadeh A, Yi C, Owens RL, Pollema T, LaBuzetta JN. Evaluation, treatment, and impact of neurologic injury in adult patients on extracorporeal membrane oxygenation: a review. *Curr Treat Options Neurol*. 2021;23:15. doi: 10.1007/s11940-021-00671-7
21. Doyle AJ, Hunt BJ. Current understanding of how extracorporeal membrane oxygenators activate haemostasis and other blood components. *Front Med (Lausanne)*. 2018;5:352. doi: 10.3389/fmed.2018.00352
22. Malfertheiner MV, Broman LM, Belliato M, Venti A, Bader A, Taccone FS, Di Nardo M, Maj G, Pappalardo F. Management strategies in venovenous extracorporeal membrane oxygenation: a retrospective comparison from five european centres. *Crit Care Resusc*. 2017;19:76–81.
23. Rajsic S, Breitkopf R, Jadzic D, Popovic Krneta M, Tauber H, Treml B. Anticoagulation strategies during extracorporeal membrane oxygenation: a narrative review. *J Clin Med*. 2022;11:5147. doi: 10.3390/jcm11175147
24. Hwang J, Caturegli G, White B, Chen L, Cho SM. Cerebral microbleeds and intracranial hemorrhages in adult patients on extracorporeal membrane oxygenation-autopsy study. *Crit Care Explor*. 2021;3:e0358. doi: 10.1097/CCE.0000000000000358

25. Saeed O, Jakobleff WA, Forest SJ, Chinnadurai T, Mellas N, Rangasamy S, Xia Y, Madan S, Acharya P, Algodi M, et al. Hemolysis and non-hemorrhagic stroke during venoarterial extracorporeal membrane oxygenation. *Ann Thorac Surg*. 2019;108:756–763. doi: 10.1016/j.athoracsur.2019.03.030
26. Kuipers S, Overmars LM, van Es B, de Bresser J, Bron EE, Hoefer IE, Kappelle LJ, Teunissen CE, Biessels GJ, Haitjema S. A cluster of blood-based protein biomarkers reflecting coagulation relates to the burden of cerebral small vessel disease. *J Cereb Blood Flow Metab*. 2022;42:1282–1293. doi: 10.1177/0271678X221077339
27. Berry C, Sidik N, Pereira AC, Ford TJ, Touyz RM, Kaski JC, Hainsworth AH. Small-vessel disease in the heart and brain: current knowledge, unmet therapeutic need, and future directions. *J Am Heart Assoc*. 2019;8:e011104. doi: 10.1161/JAHA.118.011104
28. Li CMF, Densy Deng X, Ma YF, Dawson E, Li C, Wang DY, Huong L, Gofton T, Nagpal AD, Slessarev M. Neurologic complications of patients with covid-19 requiring extracorporeal membrane oxygenation: a systematic review and meta-analysis. *Crit Care Explor*. 2023;5:e0887. doi: 10.1097/CCE.0000000000000887
29. Lorusso R, Gelsomino S, Parise O, Di Mauro M, Barili F, Geskes G, Vizzardi E, Rycus PT, Muellenbach R, Mueller T, et al. Neurologic injury in adults supported with veno-venous extracorporeal membrane oxygenation for respiratory failure: findings from the extracorporeal life support organization database. *Crit Care Med*. 2017;45:1389–1397. doi: 10.1097/CCM.0000000000002502
30. Nasr DM, Rabinstein AA. Neurologic complications of extracorporeal membrane oxygenation. *J Clin Neurol*. 2015;11:383–389. doi: 10.3988/jcn.2015.11.4.383