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Intracranial Hemorrhages on Extracorporeal Membrane Oxygenation: Differences Between COVID-19 and Other Viral Acute Respiratory Distress Syndrome

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OBJECTIVES: Extracorporeal membrane oxygenation (ECMO) is a potentially lifesaving procedure in acute respiratory distress syndrome (ARDS) due to COVID-19. Previous studies have shown a high prevalence of clinically silent cerebral microbleeds in patients with COVID-19. Based on this fact, together with the hemotrauma and the requirement of therapeutic anticoagulation on ECMO support, we hypothesized an increased risk of intracranial hemorrhages (ICHs). We analyzed ICH occurrence rate, circumstances and clinical outcome in patients that received ECMO support due to COVID-19–induced ARDS in comparison to viral non-COVID-19–induced ARDS intracerebral hemorrhage.

DESIGN: Multicenter, retrospective analysis between January 2010 and May 2021.

SETTING: Three tertiary care ECMO centers in Germany and Switzerland.

PATIENTS: Two-hundred ten ARDS patients on ECMO support (COVID-19, $n = 142$ vs viral non-COVID, $n = 68$).

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Evaluation of ICH occurrence rate, parameters of coagulation and anticoagulation strategies, inflammation, and ICU survival. COVID-19 and non-COVID-19 ARDS patients showed comparable disease severity regarding Sequential Organ Failure Assessment score, while the oxygenation index before ECMO cannulation was higher in the COVID group (82 vs 65 mm Hg). Overall, ICH of any severity occurred in 29 of 142 COVID-19 patients (20%) versus four of 68 patients in the control ECMO group (6%). Fifteen of those 29 ICH events in the COVID-19 group were classified as major (52%) including nine fatal cases (9/29, 31%). In the control group, there was only one major ICH event (1/4, 25%). The adjusted subhazard ratio for the occurrence of an ICH in the COVID-19 group was 5.82 (97.5% CI, 1.9–17.8; $p = 0.002$). The overall ICU mortality in the presence of ICH of any severity was 88%.

CONCLUSIONS: This retrospective multicenter analysis showed a six-fold increased adjusted risk for ICH and a 3.5-fold increased incidence of ICH in COVID-19 patients on ECMO. Prospective studies are needed to confirm this observation and to determine whether the bleeding risk can be reduced by adjusting anticoagulation strategies.

KEY WORDS: acute respiratory distress syndrome; bleeding hemorrhage; COVID-19; endothelium; extracorporeal membrane oxygenation; vascular

In critically ill COVID-19 patients, the occurrence of the acute respiratory distress syndrome (ARDS) is associated with a high mortality (1, 2). Particularly with limited resources during a pandemic, the usefulness of extracorporeal membrane oxygenation (ECMO) in COVID-19–induced ARDS

DOI: 10.1097/CCM.0000000000005441

has been debated. While some experts including the Extracorporeal Life Support Organization (ELSO) have argued for a potential beneficial role of venovenous ECMO (3), there have been reports highlighting important concerns and adverse events such as an increased bleeding risk (4). The largest cohort so far consists of 1,035 COVID-19 ARDS patients on venovenous ECMO support reporting a 90-day inhospital mortality of 39%, which is comparable to outcomes of venovenous ECMO support in other etiologies of ARDS (5, 6).

Aside from ARDS, several studies have demonstrated that COVID-19 is a multisystem disease associated with systemic endothelialitis (7), thereby triggering a rather unique type of coagulopathy (8). In this context, both microvascular clotting and macrovascular complications such as pulmonary embolism have been reported (9). These observations led to implementation of intensified anticoagulation for critically ill COVID-19 patients. The ELSO recommends following existing institutional anticoagulation guidelines but to consider anticoagulation intensity at the higher end of the usual targets (3).

On the one hand, one might speculate that for COVID-19 patients on venovenous ECMO, an activated coagulation system might facilitate oxygenator clotting rendering these anticoagulation targets even too low. On the other hand, intensifying the anticoagulation increases the risk of bleeding complications (10, 11). In a recent study (4), around a fifth of COVID-19 patients experienced an intracerebral hemorrhage (ICH) during venovenous ECMO support. In another multicenter study, 12% of COVID-19 patients on venovenous ECMO suffered from any ICH (12). The recent (pre-COVID) Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) trial only reported an ICH incidence of 2% in ARDS patients, mostly due to bacterial and viral pneumonia (6). Possible contributing factors that could lead to an enhanced bleeding risk have not been reported in these studies but might include severity of hypoxia, hypercapnia, thrombocytopenia, and renal failure prior to commencing venovenous ECMO (13, 14). From a pathophysiological perspective, the COVID-associated endotheliopathy might also involve the cerebral microvasculature, thereby increasing susceptibility to ICH (6, 11, 15). ICH during venovenous ECMO support is a severe and well-known complication (16, 17) and its presumed occurrence in COVID-19 on venovenous ECMO is not understood and requires further elucidation to individualize anticoagulation targets.

In this multicenter study, we retrospectively assessed intracranial bleeding complications of COVID-19 ARDS patients undergoing venovenous ECMO support compared with non-COVID-19 viral controls in three tertiary ECMO referral centers.

METHODS

Study Design and Study Subjects

This study was a retrospective, multicenter observational study conducted at Hannover Medical School (Germany), University Hospital Bonn (Germany), and University Hospital Zurich (Switzerland). The study protocol was registered at ClinicalTrials.gov (identifier: NCT04853953) and independently approved by the responsible local ethics committees (Ethikkommission Hannover Medical School, number 9723_BO_K_2021; Kantonale Ethikkommission Zürich, BASEC 2021-00825; Ethikkommission University Hospital Bonn number 196/21).

All greater than or equal to 18 years with COVID-19 ARDS requiring venovenous ECMO support were assessed for eligibility between March 1, 2020, and March 31, 2021. COVID-19 infection was determined by real-time reverse transcriptase-polymerase chain reaction positivity of nasopharyngeal swabs and tracheobronchial secretions. For comparison, cohorts of critically ill patients with viral (non-COVID-19) ARDS on venovenous ECMO were assessed for inclusion between January 1, 2010, and May 1, 2021.

Baseline Data Collection

Clinical data including demographics, comorbidities, immunosuppression (18), and mortality were collected using the inhospital patient data management systems. At time of venovenous ECMO initiation, the Sequential Organ Failure Assessment (SOFA) score (19), vasopressors, and renal replacement therapy were analyzed. Further, the invasiveness of the mechanical ventilation, ventilator and blood gas parameters, and relative delta $Paco_2$ within 24 hours after cannulation (20) were collected at venovenous ECMO initiation (last available blood gases and respirator settings before implantation of the ECMO cannulas). In addition, routine laboratory parameters of inflammation and coagulation at venovenous ECMO initiation were recorded.

Anticoagulation Strategy and Critical Care Related Parameters During ECMO Support

The duration of venovenous ECMO support (d), primary anticoagulant (unfractionated heparin [UFH], argatroban), as well as the initially targeted anticoagulation strategy (i.e., at venovenous ECMO initiation) and levels were compared. The latter were based on distinct, targeted laboratory parameter ranges to guide the patients' anticoagulation. These ranges were targeted at venovenous ECMO initiation by the clinicians in charge and were one of the following: activated partial thromboplastin time (aPTT) 35–40 seconds, aPTT 40–60 seconds, activated clotting time (ACT) 140–170 seconds, anti-factor Xa activity 0.3–0.4 U/mL, and anti-factor Xa activity 0.4–0.6 U/mL. The cumulative and mean dose of UFH or argatroban per kg bodyweight during the first 7 days of venovenous ECMO support was recorded.

Intracranial Hemorrhage (Primary Endpoint) and Other Bleeding and Thromboembolic Events (Secondary Endpoint)

Patients were monitored by clinical examination for abnormalities suggestive of ICH events including seizures, focal neural deficits, pupil size differences, lack of improvement in consciousness, and bradycardia. Unclear clinical signs were evaluated by neurology consult. Where ICH events were suspected, cranial imaging (CT or MRI) was immediately performed. Asymptomatic patients did not receive cranial imaging screening for ICH events. The individual center's standard operating procedures for ICH screening were equal in controls and COVID-19 patients. All bleeding complications during the venovenous ECMO support were analyzed. ICH were categorized as major if fulfilling one of the following criteria: 1) requiring neurosurgical intervention, 2) imaging was ordered due to clinical neurologic deficit, 3) imaging demonstrated a clinically relevant bleeding excluding microhemorrhage or minor subarachnoid hemorrhage without midline shifts, or 4) the bleeding was fatal and/or led to withdrawal of therapy. For all ICH events, laboratory parameters concerning anticoagulation at diagnosis of ICH were analyzed. In addition, surrogates of the intensity of the venovenous ECMO treatment at diagnosis of ICH were obtained.

Noncerebral bleedings were divided similarly into major and minor bleedings. A noncerebral bleeding was major if: 1) requiring a surgical intervention (e.g., drainage, operation, tamponade, coiling) or 2) requiring the administration of greater than or equal to erythrocyte concentrates per day.

Thromboembolic events were recorded if reported on CT scans or ultrasound examinations.

Outcome Parameters

The primary outcome was the occurrence of ICH in critically ill COVID-19 patients requiring venovenous ECMO support compared with controls. Secondary outcomes were 90-day ICU survival, clinical and laboratory parameters at ICH, extracranial bleeding events, and mean doses of UFH/argatroban over the first 7 days of venovenous ECMO support.

Statistical Analysis

Overall, 90-day ICU survival was compared using Kaplan-Meier curves and hazard ratios (HRs) were calculated via Cox proportional hazard modeling (21). In the multivariable model, sex, SOFA score at venovenous ECMO implantation, leucocyte count, Pao_2/Fio_2 index at venovenous ECMO implantation, obesity (BMI > 30 kg/m^2), presence of ICH, and disease-group (COVID-19 vs controls were selected as fixed covariables while the study site was used as a random-effects frailty term [22]). To evaluate risk factors for the occurrence of ICH, a competing risk regression model was used treating ICU mortality without ICH as a competing event. Due to the limited number of ICH events, a narrowed set of covariables was used: age, SOFA score at venovenous ECMO implantation, sex, obesity, disease-group, major extracranial bleeding, relative change of $Paco_2$ during first 24 hours of ECMO (20), and mean UFH dose per kg during first 7 venovenous ECMO days, while handling the study site as a random-effect frailty term (23). The HR for ICH between COVID-19 and controls is stated as the subdistribution HR (subhazard ratio [SHR]), which is similar to the HR in Cox proportional hazard models, except it accounts for all events including the competing risk (i.e., death without ICH) (24). For multivariable models, missing data were imputed using overall means. All analyses were performed using the R environment for statistical computing version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Population and Baseline Characteristics

We identified 142 COVID-19 patients suffering from severe ARDS requiring venovenous ECMO support. As a control group, we included 68 non-COVID-19 viral ARDS patients on venovenous ECMO (influenza [n = 40], respiratory syncytial virus [n = 3], cytomegalovirus, human metapneumovirus, non-COVID-19 coronavirus [each n = 1], and parainfluenza virus [n = 2]). COVID-19 patients were older compared with controls, more often male and had a higher prevalence of preexisting hypertension and diabetes mellitus and were less commonly chronically immunosuppressed (11% vs 22%) (**Table 1**).

At venovenous ECMO cannulation, disease severity determined by overall SOFA score and vasopressor dose were comparable in both groups, while the oxygenation index was higher in the COVID-19 group. Ventilation settings were similar except for a lower plateau pressure in the COVID-19 group. Median venovenous ECMO support duration was 14 days (interquartile range [IQR], 7–23 d) in the COVID-19 group versus 12 days (IQR, 8–20 d) in the control group (p = 0.691).

Laboratory markers of inflammation and coagulopathy indicated by C-reactive protein, ferritin, and D-dimers were similar. In the COVID-19 group, there was an increased peripheral leucocyte count and lower levels of lactate dehydrogenase (Table 1).

Primary Endpoint—Occurrence of Intracranial Hemorrhage and Cranial Imaging

Overall, ICH of any severity occurred in 29 of 142 COVID-19 patients (20%) versus four of 68 patients in the control group (6%) with further characterization provided in the **Supplemental Table 1** (http://links.lww.com/CCM/G967). Fifteen of those 29 ICH events in the COVID-19 group were classified as major (52%) including nine fatal cases directly attributable to the ICH event (9/29, 31%). In the control group, there was only one major (fatal) ICH event (1/4, 25%). The median

TABLE 1.

Demographics and Baseline Characteristics of Patients With COVID-19 Pneumonia on Venovenous Extracorporeal Membrane Oxygenation With and Without Intracranial Hemorrhage Versus Non-COVID Viral Acute Respiratory Distress Syndrome Controls

	COVID-19				Viral Non-COVID	
Characteristic[a]	All (142)	No ICH (113)	ICH (29)	p[b]	All (68)	p[c]
Age, yr	59 (52–65)	59 (51–65)	60 (54–66)	0.222	51 (44–60)	< 0.001
Sex (female)	27 (19)	24 (21.2)	3 (10.3)	0.182	22 (32)	0.032
Body mass index, kg/m^2	30 (26.3–35.6)	30.5 (26.3–37.1)	27.8 (25.7–34.5)	0.362	28.9 (26.1–31.1)	0.102
Comorbidities, *n* (%)						
Obesity	73 (51.4)	64 (56.6)	9 (31)	0.014	27 (39.7)	0.112
Chronic obstructive pulmonary disease	10 (7)	7 (6.2)	3 (10.3)	0.436	9 (13)	0.143
Hypertension	89 (62.7)	67 (59.3)	22 (75.9)	0.1	27 (40)	0.002
Coronary artery disease	16 (11.3)	10 (8.8)	6 (20.7)	0.072	9 (13)	0.680
Congestive heart failure	12 (8.5)	9 (8)	3 (10.3)	0.681	NA	NA
Diabetes mellitus	45 (31.7)	34 (30.1)	11 (37.9)	0.418	9 (13)	0.004
Chronic kidney disease	11 (7.7)	8 (7.1)	3 (10.3)	0.567	5 (7)	0.920
Previous stroke	10 (7)	5 (4.4)	5 (17.2)	0.016	5 (7)	0.912
Previous ICH	3 (2.1)	1 (0.9)	2 (6.9)	0.045	3 (4)	0.339
Immunosuppression	15 (10.6)	11 (9.7)	4 (13.8)	0.526	15 (22)	0.026
Solid organ transplant	8 (5.6)	8 (7.1)	0 (0)	0.14	5 (7)	0.629

(*Continued*)

TABLE 1. (*Continued*).

Demographics and Baseline Characteristics of Patients With COVID-19 Pneumonia on Venovenous Extracorporeal Membrane Oxygenation With and Without Intracranial Hemorrhage Versus Non-COVID Viral Acute Respiratory Distress Syndrome Controls

	COVID-19				Viral Non-COVID	
Characteristic[a]	All (142)	No ICH (113)	ICH (29)	*p*[b]	All (68)	*p*[c]
Respiratory and organ dysfunction parameters at ECMO initiation						
FIO_2, %	100 (84–100)	100 (80–100)	100 (100–100)	0.131	100 (100–100)	0.015
Positive end-expiratory pressure, mbar	15 (12–16)	15 (13–16)	15 (12–16)	0.801	16 (12–18)	0.128
Minute volume, L/min	9.3 (7.4–11.5)	9.3 (7.1–11.1)	9.2 (7.7–12)	0.493	9.4 (7.7–12.4)	0.541
Plateau pressure, mbar	30 (28–34)	30 (28–34)	31 (28–33)	0.954	33 (30–35)	0.018
Oxygenation index (PaO_2/FIO_2)	82 (64–108)	83 (64–113)	81 (66–103)	0.613	65 (57–85)	< 0.001
$PaCO_2$, mm Hg	53 (39–69)	50 (38–66)	62 (50–78)	0.105	59.5 (48.8–70.1)	0.93
Relative $PaCO_2$ delta first 24 hr, %	−40 (−49 to −30)	−38 (−52 to −16)	−45 (−51 to −34)	0.134	−40 (−51 to −37)	0.585
pH	7.27 (7.2–7.34)	7.28 (7.2–7.36)	7.26 (7.19–7.29)	0.07	7.26 (7.2–7.35)	0.770
Lactate, mmol/L	1.6 (1–2.6)	1.5 (1–2.8)	1.6 (1–2.3)	0.283	1.6 (1.1–2.4)	0.780
Vasopressor, *n* (%)	124 (87.3)	100 (88.5)	24 (82.8)	0.407	58 (85)	0.686
Norepinephrine dose, µg/kg/min	0.15 (0.039–0.33)	0.133 (0.043–0.33)	0.15 (0.02–0.335)	0.395	0.18 (0.07–0.3)	0.76
Renal replacement therapy, *n* (%)	37 (26.1)	33 (29.2)	4 (13.8)	0.092	13 (19)	0.269
Sequential Organ Failure Assessment score (points)	13 (11–15)	13 (11–15)	13 (12–15)	0.74	14 (12–16)	0.055
Laboratory parameters at ECMO initiation						
C-reactive protein, mg/L	230 (128–305)	226 (131–299)	254 (119–327)	0.802	245 (140–339)	0.492
Ferritin, µg/L	1,309 (836–3,104)	1,255 (817–3,075)	1,849 (888–3,870)	0.940	1,581 (964–1,820)	0.741
Interleukin-6, ng/L	164 (56–594)	217 (71–750)	97 (44–523)	0.445	NA	NA
Leucocyte count, 10^3/µL	13.7 (9.4–16.9)	13.6 (9.3–16.9)	14.1 (9.5–17.4)	0.718	8.7 (4.6–15.4)	< 0.001
D-dimer, mg/L	5.4 (2.3–13.3)	5.3 (2.3–13.4)	5.6 (2.6–10.4)	0.933	7.2 (3.6–17.8)	0.070
Lactate dehydrogenase, U/L	524 (424–677)	524 (426–672)	532 (410–715)	0.598	632 (424–988)	0.040

ECMO = extracorporeal membrane oxygenation, ICH = intracerebral hemorrhage, NA = not available.

[a]Values are given as *n* (%) for categorical data or median (interquartile range) for continuous data.

[b]COVID-19 with vs without intracranial hemorrhage using rank-sum test or χ^2 test, as appropriate.

[c]Complete COVID-19 group vs non-COVID viral acute respiratory distress syndrome group.

time from venovenous ECMO cannulation to ICH was 9 days (IQR, 5–21 d; range, 0–35 d). The adjusted SHR for the occurrence of an ICH event in the COVID-19 group was 5.82 (97.5% CI, 1.9–17.8; p = 0.002) (**Fig. 1**, *A* and *B*). Presence of obesity was associated with reduced risk of ICH (SHR, 0.39; 97.5% CI, 0.2–0.8; p = 0.017), while a prior major extracranial bleeding event was associated with an increased risk for ICH (SHR, 2.28; 97.5% CI, 1.0–5.1; p = 0.044) (**Fig. 1***C*).

The total number of cranial CT or MRI examinations was 227 (1.1 per ECMO run). In 109 of 210 patients (51.9%), cranial imaging was performed at least once during ECMO support with similar rates between COVID-19 and the control group (55 vs 46%, respectively; p = 0.205). The median time to first cranial imaging was 2 days (IQR, 0–7 d) and 50% of first cranial imaging was performed within 24 hours of cannulation.

The ICH rate was higher in patients who had anticoagulation strategies aiming at an aPTT of 40–60 seconds or anti-Xa 0.4–0.7 U/mL (both 31%) compared with ACT 140–170 seconds (4%) and anti-Xa 0.3–0.4 U/mL (18%).

Overall Survival and Effect of ICH on Survival

Ninety-day survival in the COVID-19 group was 38.7% versus 55.9% in the control group (unadjusted HR, 1.44; 95% CI, 0.9–2.2; adjusted HR, 1.03; 95% CI, 0.6–1.7; p = 0.908). The presence of ICH (any severity)

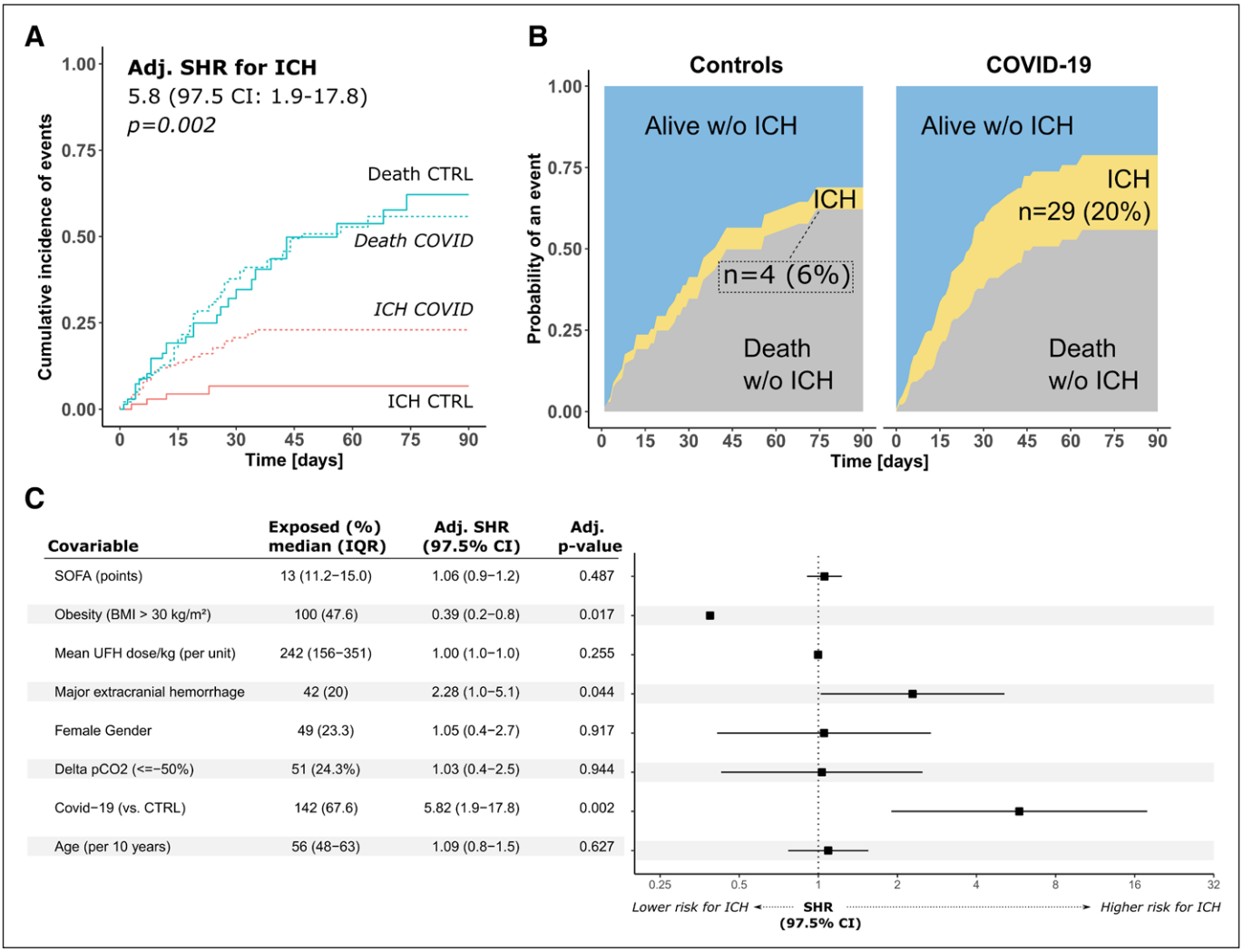

Figure 1. Primary endpoint of intracranial hemorrhage (ICH) in COVID-19 and other viral acute respiratory distress syndromes. Cumulative incidence function for ICH and death from other causes (competing event) in venovenous extracorporeal membrane oxygenation patients with COVID-19 versus controls (CTRL) (**A**). Cumulative incidence of ICH and death as multistate comparison is shown in (**B**) demonstrating increased incidence of ICH in COVID-19 patients. Multivariable competing risk regression model using study site as a random-effect term with subhazard ratios (SHRs) and 97.5% CIs (**C**). BMI = body mass index, IQR = interquartile range, SOFA = Sequential Organ Failure Assessment, UFH = unfractionated heparin.

was an independent risk factor for mortality in the entire cohort (adjusted HR, 2.37; 95% CI, 1.4–4.0; p = 0.001) (**Fig. 2*A***). Importantly, 29 of 33 patients (88%) with an ICH event died on ICU (Supplemental Table 1, http://links.lww.com/CCM/G967). Likewise, SOFA score was independently associated with mortality (adjusted HR, 1.1; p = 0.013). After multivariable adjustment, COVID-19 was not an independent risk factor for mortality (**Fig. 2*B***). Importantly, overall survival in the COVID-19 group was similar between all study sites (log-rank test p = 0.591). The cranial imaging timing (none; within 24 hr of cannulation; > 24 hr after cannulation) had no impact on overall survival (log-rank p = 0.294).

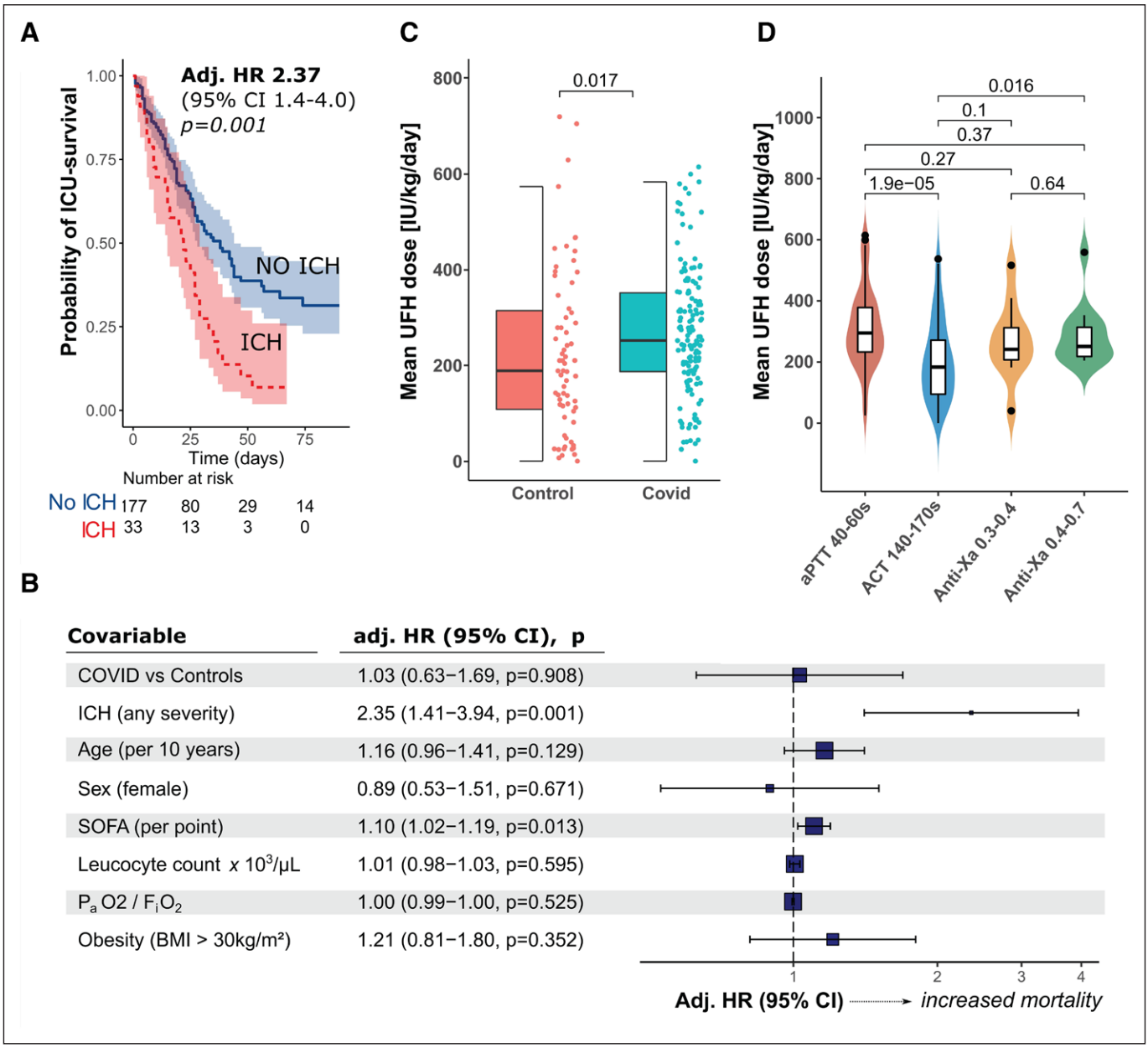

Figure 2. Impact of intracranial hemorrhage (ICH) on mortality and anticoagulation regimens. Kaplan-Meier survival curve stratified by presence of intracranial hemorrhage ICH for the entire cohort (COVID-19 and controls) demonstrating ICH as a risk factor for mortality (**A**) and multivariable Cox regression model for 90-d ICU mortality using study site as a random-effect term (**B**). Comparison of mean unfractionated heparin (UFH) dose per kg bodyweight over the first 7 d of extracorporeal membrane oxygenation (ECMO) between COVID-19 and controls (**C**). Comparison of UFH dose per kg bodyweight over the first 7 d of ECMO stratified by anticoagulation strategy in the COVID-19 cohort (**D**). ACT = activated clotting time, aPTT = activated partial thromboplastin time, BMI = body mass index, HR = hazard ratio, IU = international units, SOFA = Sequential Organ Failure Assessment.

Thromboembolic Events

Overall, thromboembolic events detected during ICU stay were more common in the COVID-19 group (30/142 [21.1%] vs 4/68 [6%]) in the control group (p = 0.007). Thromboembolic events that occurred after implementation of venovenous ECMO were less common and occurred in 14 of 142 (10%) in the COVID-19 group versus four of 68 (6%) in the control group (p = 0.335). The mean daily heparin dose per kg bodyweight during the first 7 days of ECMO was similar between patients without and with thromboembolic events (238 vs 252 international units [IU]/kg, respectively; p = 0.311). The rate or SHR of ICH was similar between patients with and without thromboembolic events (SHR, 0.39; 97.5 CI, 0.1–1.8; p = 0.227).

Anticoagulation Strategies

Between the centers, different heparinization monitoring strategies were implemented with one center primarily adjusting UFH dosing by aPTT, one center by ACT, and one center by anti-Xa activity. The distribution of primary test was similar between the COVID-19 and the control group (**Table 2**). The primary anticoagulant used was UFH in almost all (except five) COVID-19 patients; otherwise, argatroban was used initially. In 17.6% and 7%, respectively, UFH was switched to argatroban during venovenous ECMO support for suspected or confirmed heparin-induced thrombocytopenia. The mean daily UFH dose over the first 7 days per kg bodyweight was higher in the COVID-19-group compared with controls (252 IU/kg [IQR, 186.7–351.9 IU/kg] vs 196.5 IU/kg [IQR, 108.4–332.4 IU/kg]; fold-change, 1.28) (p = 0.017) (**Fig. 2***C*). Stratified by anticoagulation strategy in the COVID-19 group, the mean UFH dose was highest in the aPTT 40–60 seconds group (295 IU/kg/d [IQR, 232–380 IU/kg/d]), followed by anti-Xa 0.4–0.7 U/mL (251 U/mL [IQR, 218–313 U/mL]), anti-Xa 0.3–0.4 U/mL (242 U/mL [IQR, 188–316 U/mL]), and ACT 140–170 seconds (183 s [IQR, 89–272 s]) (**Fig. 2***D*). There was no influence of the anticoagulation strategy on mortality (log-rank p = 0.724). Coagulation and venovenous ECMO parameters at the day of ICH occurrence are summarized in **Table 3**. Besides a mild thrombocytopenia, all measured coagulation parameters were within the

TABLE 2.
Anticoagulation Strategies and Heparin Dosing

	COVID-19				Controls	
Parameter	**All (144)**	**No ICH (113)**	**ICH (29)**	**p[a]**	**All (68)**	**p[b]**
Anticoagulation strategy, *n* (%)						
aPTT 35–40 s	NA	NA	NA	NA	24 (35)	NA
aPTT 40–60 s	69 (48.6)	48 (42.5)	21 (72.4)	0.004	6 (13.6)	NA
Activated clotting time 140–170 s	49 (34.5)	47 (41.6)	2 (6.9)	< 0.001	30 (44)	NA
Anti-Xa 0.3–0.4 U/mL	10 (7)	8 (7.1)	2 (6.9)	0.973	7 (16)	NA
Anti-Xa 0.4–0.6 U/mL	13 (9.2)	9 (8)	4 (13.8)	0.332	1 (2)	NA
Anticoagulative medication, *n* (%)						
Unfractionated heparin	137 (96.5)	109 (96.5)	28 (96.6)	0.981	68 (100)	0.117
Argatroban	25 (17.6)	21 (18.6)	4 (13.8)	0.546	3 (7)	0.080
Heparin dose						
Cumulative dose over 7 d, international units/kg bodyweight	252 (186.7–351.9)	251.1 (182.5–326.1)	294.4 (206.6–402.9)	0.193	196.5 (108.4–332.4)	0.017

aPTT = activated partial thromboplastin time, ICH = intracerebral hemorrhage, NA = not available.
[a]COVID-19 with vs without intracranial hemorrhage using rank-sum test or χ^2 test, as appropriate.
[b]Complete COVID-19 group vs non-COVID viral acute respiratory distress syndrome group.

TABLE 3.
Coagulation Parameters and Extracorporeal Membrane Oxygenation Settings at Time of Intracranial Hemorrhage in 33 Patients

Characteristic	Median or *n*	(Interquartile Range) or (%)	Normal Range
Coagulation parameters			
Platelet count, × 1,000/μL	97	(64–164)	160–370
Activated partial thromboplastin time, s	42	(32–48)	26–36
International normalized ratio	1.1	(1.1–1.4)	0.9–1.25
Activated clotting time, s	154	(148–156)	70–120
Fibrinogen, g/L	5.0	(4.1–6.3)	1.8–3.5
Hypofibrinogenemia, *n* (%)	2	(7)	
D-dimers, mg/L	11.4	(5.4–35.2)	0–0.5
Hyperfibrinolysis, *n* (%)[a]	2	(7)	
Von Willebrand factor:antigen, %	535	(368–600)	58–174
ECMO support parameters			
ECMO blood flow, L/min	4.6	(3.9–5.4)	
Fraction of sweep gas oxygen, %	80	(70–100)	
Sweep gas flow, L/min	5.5	(4–7)	

ECMO = extracorporeal membrane oxygenation.
[a]Fibrinogen < 1.8 g/L and D-dimers > 0.5 mg/L.

targeted range. ECMO-related parameters at ICH onset demonstrated high dependence on venovenous ECMO support both considering oxygenation and decarboxylation (Table 3).

DISCUSSION

In this retrospective multicenter analysis, we found that COVID-19 patients requiring venovenous ECMO support for severe ARDS had a six-fold increased adjusted risk of ICH compared with a control venovenous ECMO cohort of viral non-COVID-19 ARDS patients. Also, ICHs were more common in COVID-19 and their incidence was independently associated with increased mortality.

Despite the known lack of clear evidence of an outcome benefit, venovenous ECMO has been widely used in specialized centers as a rescue strategy in severe ARDS. The recent EOLIA trial did not show survival advantage but its interpretation is complicated by a high number of rescue crossovers from the standard to the ECMO group (6). Most intensivists agree that venovenous ECMO can acutely reverse life-threatening hypoxemia or hypercapnia, thereby protecting the patient from ischemia and facilitating the adherence to lung-protective ventilation strategies.

Nevertheless, venovenous ECMO support represents an invasive approach that predisposes to numerous potential complications. Besides the cannulation process per se, relevant complications are often related to the so-called hemotrauma that plays a critical role in the balance between inflammation and coagulation (25, 26). In general, the term hemotrauma summarizes effects of an injury to the blood compartment by the physical shear stress in the centrifugal pump triggering hemolysis, microinflammation, endothelial cell damage, and coagulopathy often characterized by hyperfibrinolysis (27).

Together with the need for a systemic anticoagulation, these device-associated effects on coagulation can both trigger and maintain (major) bleeding events. In the most recent EOLIA trial, the ICH incidence was similar in the non-ECMO group (4%) and the venovenous ECMO group (2%) (6). Of note, the control group in our study had a comparable rate of ICH (major 1.4%).

The primary intention of this present study was based on the clinical observation of increased ICH events at three high-volume ECMO centers during the early pandemic. Acknowledging the available literature, the range of reported ICHs in COVID-19 patients on ECMO is relatively wide but alarmingly

high (5–42%) (5, 28–30). A recent single-center study reported a 16% ICH rate in 50 COVID-19 patients on ECMO support (4). These reports are generally in line with our current multicenter evaluation (n = 210), where we observed an overall incidence of ICHs of 20%. Overall, incidence of directly fatal ICH in COVID-19 was 6.3% versus 1.4% in the control group, while 88% of all patients with ICH eventually died on ICU.

The fact that COVID-19–associated coagulopathy has been acknowledged as a risk factor of thromboembolism in both the macrocirculatory and microcirculatory vascular beds (4, 14, 31) raises the question why these patients at the same time should present with a higher (intracranial) bleeding risk. The high incidence of hemorrhage may be triggered by severe acute respiratory syndrome coronavirus 2 effects or by iatrogenic factors associated with strict anticoagulation strategies to prevent thromboembolic events. Spontaneous ICH in COVID-19 patients with ARDS not receiving ECMO support are not uncommon (10%) but was similar to non-COVID-19 ARDS (32). Of note, in our cohort, the overall rate of thromboembolic events was increased in COVID-19, in line with the existing literature, but were not a risk factor for the occurrence of ICH.

It is possible that the COVID-19–associated endotheliopathy involving intracranial vessels (33) might increase the susceptibility of the cerebral microvasculature to hemorrhage, similarly to cases of immune diffuse alveolar hemorrhage (34). Overall, higher age and comorbidity, an increased vulnerability together with stricter anticoagulation regimen and ECMO hemotrauma might explain an increased bleeding risk. Contrarily to a general COVID-19 population (35–37), in this population entirely on ECMO support, D-dimers were not predictive of adverse outcomes.

In this study, we found a significantly higher UFH dose in COVID-19 patients. Of note, a recent randomized controlled trial in 562 COVID-19 patients (not receiving ECMO support) investigating two prophylactic heparin doses did not show a difference in the prevention of thromboembolic events but the higher heparin dose group had more intracranial bleedings (38). Importantly, the recent ELSO recommendations regarding increased anticoagulation were a major driver for the observed increased UFH doses in the present study (3). In further exploratory analyses, we found that most ICH events occurred within the aPTT 40–60 seconds and anti-Xa 0.4–0.7 U/mL groups, which also had the highest UFH doses (Fig. 2*D*). This study was not designed to compare different anticoagulation monitor strategies and UFH doses alone are insufficient to determine anticoagulation intensity (39, 40), but these data suggest different anticoagulation strategies and monitoring may influence the risk for ICH events. This is in keeping with the most recent results of the Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP), the Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC) trial and the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV-4) trials data demonstrating increased bleeding risk with higher anticoagulation targets without reducing mortality (41). Hence, anticoagulation strategies in COVID-19 patients receiving venovenous ECMO support should be revisited and need to be prospectively analyzed.

There was no difference in survival with regards to timing of cranial imaging and there were only two ICH events (one major) detected on cranial imaging performed within the first 24 hours after cannulation. Our rate of 52% patients who had any cranial imaging is comparable to standard of care in other centers (42). To our knowledge, no studies comparing different cranial imaging strategies to detect cerebral insults in venovenous ECMO have been reported so far. Thus, prospective trials are needed to provide appropriate recommendations regarding the ideal screening strategy.

Our study has limitations. Despite its multicentric nature, this study was retrospective and hampered by the different anticoagulation strategies between the participating centers. We acknowledge the fact that all presented findings are primarily clinical observations. In addition, the data were collected during different time periods as most COVID-19 patients were treated more recently than controls. ACT and aPTT can be confounded by acute phase proteins (43), and while all patients were monitored for antithrombin-III levels, future research in hemostatic mechanisms are needed. Also, anticoagulation strategies before implementation of ECMO may have influenced occurrence of ICH events, as recently described (41) but were not part of the present analysis. Last, 48% of patients without neurologic symptoms did not undergo cranial imaging, which may represent under-reporting of minor ICH events.

The central unsolved question arising from the here presented retrospective data certainly lies in the

explanation for the higher incidence of ICH in COVID-19 associated ARDS. Whether the unique pathophysiology of COVID-19 ARDS or the clinical application of ECMO support (including anticoagulation strategies) or both predominate needs to be answered in prospective investigations. Nevertheless, we believe that our observation might be clinically relevant and should lead to consider adjustments of the anticoagulation strategy during venovenous ECMO support in patients with COVID-19–associated ARDS, especially since therapeutic anticoagulation has not been shown to reduce mortality risk whilst increasing major bleeding events in critically ill COVID patients (41). Given mortality and morbidity burden of ICH, use of ECMO should be judiciously weighted in COVID-19.

CONCLUSIONS

In summary, our retrospective multicenter analysis shows a six-fold increased adjusted risk for intracranial hemorrhages and a 3.5-fold increased total incidence of any ICH in COVID-19 patients compared with a control group with other respiratory viral infections' on venovenous ECMO support. We demonstrated higher anticoagulation dosing and strategies in COVID-19 compared with controls. Both groups demonstrated high-mortality rates (88%) if ICH developed. Our results suggest local anticoagulation strategies be more considered during ECMO until further studies are available.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

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Dr. Seeliger is supported by Program of Hannover Medical School for Clinician Scientists (PRACTIS), funded by the Deutsche Forschungsgemeinschaft (DFG, ME 3696/3-1) and the German Center for Lung Research (DZL). Dr. David received funding from the German Centre for Lung Research. Dr. Hoeper received funding from Acceleron, Actelion, Bayer, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, and Pfizer. Dr. Putensen's institution received funding from the DFG (PU 219/2-3); he received funding from Pluristem Ltd and Dräger Medical. Dr. Bode is supported by the DFG (BO 3640/2-1) and the Federal Ministry of Education and Research (01KI20343). Dr. David's institution received funding from the German Research Foundation (DA1209/4-3), DFG, DZL, Cytobsorbents, Octapharma, and Terumo; he received funding from Terumo, Octapharma, and Cytosorbents. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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REFERENCES

1. Wu C, Chen X, Cai Y, et al: Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020; 180:934–943
2. Wendel Garcia PD, Fumeaux T, Guerci P, et al; RISC-19-ICU Investigators: Prognostic factors associated with mortality risk and disease progression in 639 critically ill patients with COVID-19 in Europe: Initial report of the international RISC-19-ICU prospective observational cohort. *EClinicalMedicine* 2020; 25:100449
3. Shekar K, Badulak J, Peek G, et al; ELSO Guideline Working Group: Extracorporeal life support organization coronavirus disease 2019 interim guidelines: A consensus document from an International Group of Interdisciplinary Extracorporeal Membrane Oxygenation Providers. *ASAIO J* 2020; 66:707–721
4. Doyle AJ, Hunt BJ, Sanderson B, et al: A comparison of thrombosis and hemorrhage rates in patients with severe respiratory failure due to coronavirus disease 2019 and influenza requiring extracorporeal membrane oxygenation. *Crit Care Med* 2021; 49:e663–e672
5. Barbaro RP, MacLaren G, Boonstra PS, et al; Extracorporeal Life Support Organization: Extracorporeal membrane oxygenation support in COVID-19: An international cohort study of the Extracorporeal Life Support Organization registry. *Lancet* 2020; 396:1071–1078
6. Combes A, Hajage D, Capellier G, et al; EOLIA Trial Group, REVA, and ECMONet: Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018; 378:1965–1975
7. Varga Z, Flammer AJ, Steiger P, et al: Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; 395:1417–1418

8. Goshua G, Pine AB, Meizlish ML, et al: Endotheliopathy in COVID-19-associated coagulopathy: Evidence from a single-centre, cross-sectional study. *Lancet Haematol* 2020; 7:e575–e582
9. Helms J, Tacquard C, Severac F, et al; CRICS TRIGGERSEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis): High risk of thrombosis in patients with severe SARS-CoV-2 infection: A multicenter prospective cohort study. *Intensive Care Med* 2020; 46:1089–1098
10. Stahl K, Seeliger B, Hofmaenner DA, et al: The Janus face of coronavirus disease 2019-associated coagulopathy. *Crit Care Med* 2021; 49:e1049–e1050
11. Kirschenbaum D, Imbach LL, Rushing EJ, et al: Intracerebral endotheliitis and microbleeds are neuropathological features of COVID-19. *Neuropathol Appl Neurobiol* 2021; 47:454–459
12. Lebreton G, Schmidt M, Ponnaiah M, et al; Paris ECMO-COVID-19 investigators: Extracorporeal membrane oxygenation network organisation and clinical outcomes during the COVID-19 pandemic in Greater Paris, France: A multicentre cohort study. *Lancet Respir Med* 2021; 9:851–862
13. Lockie CJA, Gillon SA, Barrett NA, et al: Severe respiratory failure, extracorporeal membrane oxygenation, and intracranial hemorrhage. *Crit Care Med* 2017; 45:1642–1649
14. Ackermann M, Verleden SE, Kuehnel M, et al: Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med* 2020; 383:120–128
15. Lee MH, Perl DP, Nair G, et al: Microvascular injury in the brains of patients with Covid-19. *N Engl J Med* 2021; 384:481–483
16. Cavayas YA, Del Sorbo L, Fan E: Intracranial hemorrhage in adults on ECMO. *Perfusion* 2018; 33:42–50
17. Fletcher-Sandersjöö A, Thelin EP, Bartek J Jr, et al: Incidence, outcome, and predictors of intracranial hemorrhage in adult patients on extracorporeal membrane oxygenation: A systematic and narrative review. *Front Neurol* 2018; 9:548
18. Knaus WA, Draper EA, Wagner DP, et al: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13:818–829
19. Vincent JL, Moreno R, Takala J, et al: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; 22:707–710
20. Cavayas YA, Munshi L, Del Sorbo L, et al: The early change in $PaCO_2$ after extracorporeal membrane oxygenation initiation is associated with neurological complications. *Am J Respir Crit Care Med* 2020; 201:1525–1535
21. Harrison E, Drake T, Ots R: finalfit: Quickly create elegant regression results tables and plots when modelling. 2020. Available at: https://cran.r-project.org/web/packages/finalfit/index.html. Accessed July 20, 2022
22. Balan TA, Putter H: A tutorial on frailty models. *Stat Methods Med Res* 2020; 29:3424–3454
23. Ha ID, Noh M, Kim J, et al: frailtyHL: Frailty Models via Hierarchical Likelihood. 2019. Available at: https://cran.r-project.org/web/packages/frailtyHL. Accessed July 20, 2022
24. Fine JP, Gray RJ: A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; 94:496
25. Sniderman J, Monagle P, Annich GM, et al: Hematologic concerns in extracorporeal membrane oxygenation. *Res Pract Thromb Haemost* 2020; 4:455–468
26. Murphy DA, Hockings LE, Andrews RK, et al: Extracorporeal membrane oxygenation-hemostatic complications. *Transfus Med Rev* 2015; 29:90–101
27. Granja T, Hohenstein K, Schüssel P, et al: Multi-modal characterization of the coagulopathy associated with extracorporeal membrane oxygenation. *Crit Care Med* 2020; 48:e400–e408
28. Schmidt M, Hajage D, Lebreton G, et al; Groupe de Recherche Clinique en REanimation et Soins intensifs du Patient en Insuffisance Respiratoire aiguE (GRC-RESPIRE) Sorbonne Université; Paris-Sorbonne ECMO-COVID investigators: Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: A retrospective cohort study. *Lancet Respir Med* 2020; 8:1121–1131
29. Ramanathan K, Shekar K, Ling RR, et al: Extracorporeal membrane oxygenation for COVID-19: A systematic review and meta-analysis. *Crit Care* 2021; 25:211
30. Ripoll B, Rubino A, Besser M, et al: Observational study of thrombosis and bleeding in COVID-19 VV ECMO patients. *Int J Artif Organs* 2021 Jan 28. [online ahead of print]
31. Malas MB, Naazie IN, Elsayed N, et al: Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. *EClinicalMedicine* 2020; 29:100639
32. Lang CN, Dettinger JS, Berchtold-Herz M, et al: Intracerebral hemorrhage in COVID-19 patients with pulmonary failure: A propensity score-matched registry study. *Neurocrit Care* 2021; 34:739–747
33. McAlpine LS, Zubair AS, Maran I, et al: Ischemic stroke, inflammation, and endotheliopathy in COVID-19 patients. *Stroke* 2021; 52:e233–e238
34. Seeliger B, Stahl K, Schenk H, et al: Extracorporeal membrane oxygenation for severe ARDS due to immune diffuse alveolar hemorrhage: A retrospective observational study. *Chest* 2020; 157:744–747
35. He X, Yao F, Chen J, et al: The poor prognosis and influencing factors of high D-dimer levels for COVID-19 patients. *Sci Rep* 2021; 11:1830
36. Rostami M, Mansouritorghabeh H: D-dimer level in COVID-19 infection: A systematic review. *Expert Rev Hematol* 2020; 13:1265–1275
37. Poudel A, Poudel Y, Adhikari A, et al: D-dimer as a biomarker for assessment of COVID-19 prognosis: D-dimer levels on admission and its role in predicting disease outcome in hospitalized patients with COVID-19. *PLoS One* 2021; 16:e0256744
38. Sadeghipour P, Talasaz AH, Rashidi F, et al: Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: The INSPIRATION randomized clinical trial. *JAMA* 2021; 325:1620–1630
39. Chlebowski MM, Baltagi S, Carlson M, et al: Clinical controversies in anticoagulation monitoring and antithrombin supplementation for ECMO. *Crit Care* 2020; 24:19

40. Ranucci M, Cotza M, Isgrò G, et al; Surgical Clinical Outcome REsearch (SCORE) Group: Anti-factor Xa-based anticoagulation during extracorporeal membrane oxygenation: Potential problems and possible solutions. *Semin Thromb Hemost* 2020; 46:419–427
41. Goligher EC, Bradbury CA, McVerry BJ, et al: Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. *N Engl J Med* 2021; 385:777–789
42. Iacobelli R, Fletcher-Sandersjöö A, Lindblad C, et al: Predictors of brain infarction in adult patients on extracorporeal membrane oxygenation: An observational cohort study. *Sci Rep* 2021; 11:3809
43. Streng AS, Delnoij TSR, Mulder MMG, et al: Monitoring of unfractionated heparin in severe COVID-19: An observational study of patients on CRRT and ECMO. *TH Open* 2020; 4:e365–e375