Supplement

Table S1

	Left	Right	Bi-Hemispheric	Not Described
IPH	9	15	23	1
SAH	7	6	12	1
SDH		3	2	1
Chronic SDH		2		

Table S1 shows detected intracranial bleeding localizations. Most patients had more than one intracranial bleeding localization. 16 of 23 bi-hemispheric ICBs were diffuse microbleedings. Abbreviations: IPH: intraparenchymal hemorrhage; SAB: subarachnoidal hemorrhage; SDH: subdural hemorrhage.

Complete Baseline Information

Variable	All N=556	ICB N=61	No ICB N=495	P-value
General Data				
Age	52.9 (41.3-62.1)	55.4 (46.1-66.2)	52.7 (40.7-61.8)	0.071
Male Sex	368 (66%)	41 (67%)	327 (66%)	0.85
Survival to Hospital Discharge (%)	354 (64%)	18 (30%)	336 (68%)	**<0.001**
ECMO Duration (days)	9 (6-15)	9 (6-16)	9 (6-15)	0.856
SOFA Score	13 (10-16)	16 (13-18)	13 (10-16)	**<0.001**
ECMO Indication				0.155
Bacterial Pneumonia	271 (49)	32 (52)	239 (48)	
Viral Pneumonia	75 (13)	8 (13)	67 (14)	
ALF After Trauma	34 (6)	1 (2)	33 (7)	
ALF After Surgery	96 (17)	9 (15)	87 (18)	
ALF After Chemotherapy	13 (2)	4 (7)	9 (2)	
Other	67 (12)	7 (11)	60 (12)	
Laboratory Testing				
Creatinine (mg/dl)	1.2 (0.8-2.1)	1.7 (1.1-2.7)	1.2 (0.8-2.1)	**0.006**
Impaired Kidney Function (creatinine >1.5mg/dl) Before ECMO	341 (63%)	47 (77%)	294 (61%)	**0.013**
aPTT (s)	42 (35-55)	46 (39.5-61.5)	42 (35-55)	**0.024**
Prothrombin Time (%)	76 (58-92)	71 (50-89)	76 (60-92)	0.141
Fibrinogen (mg/dl)	500 (342-644)	515 (352-646)	500 (339-644.5)	0.753
Platelets (/nl)	173 (100-269)	98 (47-212)	182.5 (113-275)	**<0.001**
Blood-Urea (mg/dl)	58 (38-98)	65 (47-130)	57 (36-95)	**0.006**
Bilirubin (mg/dl)	0.8 (0.5-1.9)	0.8 (0.6-2.4)	0.8 (0.5-1.9)	0.244
ASAT (U/L)	689 (36-152)	103 (43-208)	66 (34-14)	**0.036**
ALAT (U/L)	43 (24-82)	47 (27-77)	42 (24-84)	0.470
LDH (U/L)	418 (274-676)	550 (324-900)	408 (270-651)	**0.002**
CRP (mg/dl)	146 (44-251)	163 (75-210)	1423(44-249)	0.126
AT3 (%)	61 (47-78)	59 (43-70)	61 (47-79)	0.135
White Blood Cells (/nl)	12.8 (7.9-19.1)	11.8 (7.0-20.0)	12.8 (8.1-19.0)	0.368
Cholinesterasis (U/L)	4,248 (2,664-6,887)	N=21 3,503 (1,967.5-5,831.5)	4,412 (2,763-7,019)	0.175
CK (U/L)	204 (76-705)	325 (98-841)	200 (74-684)	0.253
Albumin (g/L)	22 (17-26)	20 (14-26)	22 (18-26)	**0.043**

Alkaline Phosphatasis (U/L)	95 (63-152)	120 (67-217)	94 (63-147)	0.241
Ventilator Settings and Blood Gas Analysis				
PEEP (mbar)	15 (12-17)	15 (13-18)	15 (12-17)	0.475
$PaCO_2$ (mmHg)	64 (51-78)	71 (57-88)	62 (50-77)	**0.009**
Delta $paCO_2$ (pre- (2hrs)) (mmHg)	26 (15-41)	37 (19-49)	26 (14-40)	**0.007**
PaO_2 (mmHg)	67 (56-81)	68 (58-77)	66 (56-82)	0.901
pH	7.22 (7.15-7.3)	7.2 (7.11-7.28)	7.23 (7.15-7.31)	0.094
Delta pH (pre- (2hrs))	-0.19 (-0.28 - -0.12)	-0.21 (-0.31 - -0.14)	-0.18 (-0.27 - -0.11)	0.07
pAW mean (mbar)	22 (20-25)	22 (19.5-27)	22 (20-25)	0.482
pMax (mbar)	35 (30-38)	35 (30-38)	34 (30-38)	0.315
Norepinephrine (mg/h)	1.6 (0.6-3)	2.5 (0.8-4.9)	1.5 (0.6-3)	**0.001**
Delta Norepinephrine (pre- (2hrs))	0.4 (0 -1.1)	1 (0.1-2.3)	0.4 (0-1)	**0.005**
MAP (mmHg)	68 (61-76)	67 (61-79)	68 (61-76)	0.663
Delta MAP (pre- (2hrs)) (mmHg)	-7 (-18-3)	-10.5 (-24-3.5)	-7 (-17-3)	0.173
Factor XIII (n=97)	63 (48-90.5)	(n=8) 51.5 (35.2-64.5)	(n=89) 63 (49-93.5)	0.057

Table S2 shows the patient characteristics before starting V-V ECMO. For $paCO_2$ and norepinephrine, the change from pre-cannulation to 2 hours after starting V-V ECMO (Delta-values) is presented. Data are shown as median and IQR (25^{th}-75^{th}). SOFA: Sequential Organ Failure Assesment; aPTT: activated partial Thromboplastin-Tim; PT: Prothrombin Time; ASAT: Aspartat-Aminotransferasis; ALAT: Alanine Aminotransferasis; LDH: Lactate-Dehydrogenasis; CRP: C-reactive Protein. AT3: Anti-Thrombine 3; WBC: White Blood Cells; CK: Creatin-Kinasis; AP: Alkaline Phosphatasis; PEEP: Positive End-Expiratory Pressure; pAW: Mean Airway Pressure; MAP: Mean Arterial Pressure.

Variables During V-V ECMO Treatment

Corresponding to the variables before starting V-V ECMO shown in Table 1, the same variables were analyzed during V-V ECMO treatment. Results are shown as median and IQR (25^{th}-75^{th}) in the Supplement Table S3.

Variable (Median During V-V ECMO)	All (Median IQR 25-75) N=556	ICB N=61	No ICB N=495	P-value
Creatinine (mg/dl)	1.1 (0.7-1.7)	1.3 (0.8-1.9)	1.1 (0.7-1.6)	0.125
aPTT (s)	50 (44-56)	47 (42-52)	50 (44-57)	0.01
aPT (%)	73 (58-86)	68 (59-87)	74 (58-86)	0.762
Fibrinogen (mg/dl)	418 (307-553)	439 (268-602)	417 (307-546)	0.682
Platelets (/nl)	1,201 (71-176)	80 (34-139)	124 (76-179)	<0.001
Blood-Urea (mg/dl)	71 (46-103)	99 (59-125)	68 (48-98)	0.001
Bilirubin (mg/dl)	1.1 (0.6-3)	2.2 (0.9-5.4)	1 (0.5-2.7)	<0.001
ASAT (U/L)	70 (39-143)	82 (51-289)	66 (34-148)	0.026
ALAT (U/L)	55 (31-106)	60 (34-159)	53 (18-103)	0.113
LDH (U/L)	442 (319-630)	534 (324-900)	435 (312-615)	0.012
CRP (mg/dl)	125 (61-183)	165 (61-208)	121 (61-178)	0.0037
AT3 (%)	74 (55-93)	69 (47-87)	61 (47-79)	0.043
WBC (/nl)	12.8 (9-17.7)	12.9 (8.4-19)	12.7 (9.2-17.5)	0.676
Cholinesterasis (U/L)	N=163 3,867 (2,669-5,967)	N=15 3,189 (1,987-4,642)	N=148 3,895 (2,762-6,119)	0.069
CK (U/L)	166 (623-610)	233 (91-952)	158 (62-582)	0.19
Albumin (g/L)	22 (20-25)	21 (19-25)	22 (20-26)	0.301
AP (U/L)	1,134 (69-186)	184 (75-274)	110 (69-179)	0.001
PEEP (mbar)	14 (11-16)	15 (12-17)	13 (10-16)	0.015
$PaCO_2$ (mmHg)	40 (37-43)	39 (37-43)	40 (37-43)	0.752

PaO_2 (mmHg)	76 (69-83)	73 (67-81)	66 (56-82)	0.118
pH	7.43 (7.39-7.45)	7.42 (7.37-7.5)	7.43 (7.4-7.45)	0.447
pAW mean (mbar)	18 (15-21)	19 (17-22)	18 (15-21)	0.009
pMax (mbar)	35 (23-28)	27 (24-29)	25 (23-28)	0.015
Norepinephrine (mg/h)	0.2 (0-0.5)	0.3 (0-0.6)	0.1 (0-0.4)	0.015
MAP (mmHg)	75 (71-80)	75 (70-80)	75 (71-80)	0.929
Factor XIII (n=139)	53 (41-77)	N=13 38 (27-49)	N=126 56 (42-79)	0.001

Table S3 shows the variables as median and IQR during the ECMO treatment. aPTT: activated partial Thromboplastin-Time; PT: Prothrombin Time; ASAT: Aspartat-Aminotransferasis; ALAT: Alanine Aminotransferasis; LDH: Lactate-Dehydrogenasis; CRP: C-reactive Protein; AT3: Anti-Thrombine 3; WBC: White Blood Cells; CK: Creatin-Kinasis; AP: Alkaline Phosphatasis; PEEP: Positive End-Expiratory Pressure; pAW: Mean Airway Pressure; MAP: Mean Arterial Pressure.

Extreme Values of Laboratory Testing During V-V ECMO Treatment

Variable	All (Median IQR 25-75) N=556	ICB N=61	No ICB N=495	P-value
Maximal Creatinine (mg/dl)	1.6 (1.0-2.7)	2.1 (1.3-3.6)	1.5 (1.0-2.6)	0.008
Maximal aPTT (s)	78 (63-108)	68 (567-115)	79 (64 -108)	0.162
Minimal PT (%)	51 (39-67)	50 (40-62.5)	51 (39-67)	0.424
Minimal Fibrinogen (mg/dl)	257 (164-373)	247 (131-377)	257 (168-373)	0.672
Minimal Platelets (/nl)	73 (40-128)	45 (22-87)	76 (42-132)	<0.001
Maximal Blood-Urea (mg/dl)	111 (75-171)	142 (89-218)	107 (74-167)	0.002
Maximal Bilirubine (mg/dl)	2 (1.0-5.2)	3.8 (1.5-9.2)	1.9 (0.9-4.9)	0.001

Maximal ASAT (U/L)	161 (79-399)	245 (122-831)	152 (77-371)	0.005
Maximal ALAT (U/L)	93 (46-228)	113 (67-403)	92 (44-223)	0.057
Maximal LDH (U/L)	651 (433-1,052)	1,004 (516-2106)	637 (410-969)	<0.001
Maximal CRP (mg/dl)	237 (156-312)	251 (178-349)	234 (153-309)	0.089
Maximal AT3 (%)	93 (68-114)	92 (62-111)	93 (70-116)	0.079
Maximal WBC (/nl)	19.7 (14.4-27.5)	21.1 (15-31)	19.4 (14.4-26.8)	0.238
Minimal Cholinesterase (U/L)	N=233 3,400 (2,063-5,142)	N=25 2,150 (1,444-3,882)	N=208 3,539 (2,153-5,324)	0.01
Maximal CK (U/L)	588 (200-2089)	872 (271-3037)	576 (198-1961)	0.137
Maximal AP (U/L)	156 (92-301)	252 (77-472)	152 (93-285)	0.031
Minimal Factor XIII (n=148)	45 (33-62)	N=13 34 (21-44)	N=135 46 (34-64)	0.009

Table S4 shows extreme values of laboratory testing during V-V ECMO treatment. Variables as median and IQR (25^{th} -75^{th}) during V-V ECMO treatment. aPTT: activated partial Thromboplastin-Time; PT: Prothrombin Time; ASAT: Aspartat-Aminotransferasis; ALAT: Alanine Aminotransferasis; LDH: Lactate-Dehydrogenasis; CRP: C-reactive Protein; AT3: Anti-Thrombine 3; WBC: White Blood Cells; CK: Creatin-Kinasi; AP: Alkaline Phosphatasis.

		Number of ICBs	Frequency (%)
Day	0	13	21.3
	1	10	16.4
	2	2	3.3
	3	4	6.6
	4	2	3.3
	5	4	6.6

	6	1	1.6
	9	2	3.3
	10	2	3.3
	11	2	3.3
	12	2	3.3
	13	1	1.6
	14	2	3.3
	15	2	3.3
	17	1	1.6
	20	1	1.6
	21	1	1.6
	22	1	1.6
	24	1	1.6
	27	1	1.6
	30	2	3.3
	32	1	1.6
	33	1	1.6
	36	1	1.6
	55	1	1.6
	Total	61	100.0

Table S5: Exact timing of intracranial bleeding.

Table S6

	Number of Patients		**Univariable Analysis**			**Multivariable Regression Analysis Model 1 $paCO_2$, Norepinephrine, Platelets <100/nl AIC 334.405**			**Multivariable Regression Analysis Model 2 $paCO_2$, Norepinephrine, Platelets <50/nl AIC 338.688**		
	ICB (n=61) n(%)	No ICB (n=495) n(%)	Odds Ratio	CI95%	P-value	Odds Ratio	CI95%	P-value	Odds Ratio	CI95%	P-value
Creatinine >1.5mg/dl Before ECMO Treatment	33 (54.1)	185 (37.4)	1.98	1.15-3.40	**0.013**	0.89	0.44-1.80	0.738	0.94	0.46-1.94	0.876
aPTT >45s Before ECMO Treatment	33 (54.1)	192 (38.8)	1.80	1.05-3.08	**0.031**	1.12	0.59-2.14	0.728	1.16	0.61-2.21	0.643
Platelets <100/nl Before ECMO Treatment	31 (50.8)	104 (21.0)	3.82	2.21-6.60	**<0.001**	2.51	1.20-5.23	**0.014**			
Platelets <50/nl Before ECMO Treatment	17 (27.9)	41 (8.2)	4.21	2.21-8.03	**<0.001**				3.55	1.65 - 7.62	**0.001**
Blood-Urea > 100 mg/dl Before ECMO Treatment	20 (32.8)	105 (21.2)	1.81	1.01-3.24	**0.045**	1.34	0.69-2.78	0.357	1.25	0.62-2.53	0.533
LDH >550 U/L Before ECMO Treatment	29 (47.5)	151 (30.5)	2.07	1.20-3.57	**0.009**	1.71	0.88-3.27	0.111	1.74	0.90-3.37	0.103
$paCO_2$ >70mmHg Before ECMO Treatment	31 (50.8)	171 (34.5)	1.96	1.15-3.34	**0.014**	3.63	1.68-7.83	**0.001**	3.55	1.65-7.62	**0.001**
Delta $paCO_2$ >35mmHg	33 (54.1)	156 (31.5)	2.56	1.50-4.39	**0.001**	*					
Norepinephrine >2.5mg/h Before ECMO Treatment	30 (49.1)	138 (27.9)	2.5	1.46-4.29	**0.001**	1.67	0.86-3.21	0.128	1.64	0.85-3.15	0.140
Delta Norepinephrine >1mg/h	27 (44.2)	118 (23.8)	2.53	1.47-4.37	**0.001**	*					
ASAT >80U/L Before ECMO Treatment	35 (57.3)	200 (40.4)	1.86	1.08-3.21	**0.025**	0.83	0.41 – 1.68	0.596	0.92	0.46 – 1.84	0.803
SOFA Score						0.91	0.82-1.02	0.091	0.89	0.80-0.99	0.036
pH Before ECMO Treatment						0.08	0.004-1.62	0.101	0.06	0.003-1.17	0.064

Table S6 continued

	Multivariable Regression Analysis Model 4 Delta $paCO_2$, Delta Norepinephrine, Platelets <50/nl AIC330.327		
	Odds Ratio	CI95%	P-value
Creatinine >1.5mg/dl Before ECMO Treatment	1.23	0.59-2.57	0.589
aPTT >45s Before ECMO Treatment	1.11	0.59-2.12	0.741
Platelets <100/nl Before ECMO Treatment			
Platelets <50/nl Before ECMO Treatment	2.90	1.24-6.77	**0.014**
Platelets <20/nl Before ECMO Treatment			
Blood-Urea > 100 mg/dl Before ECMO Treatment	1.18	0.58-2.40	0.654
LDH >550 U/L Before ECMO Treatment	1.64	0.84-3.21	0.150
$paCO_2$ >70mmHg Before ECMO Treatment			
Delta $paCO_2$ >35mmHg	5.34	2.36-12.09	**<0.001**
Norepinephrine >2.5mg/h Before ECMO Treatment			
Delta Norepinephrine >1mg/h	1.69	0.90-3.19	0.104
ASAT >80U/L Before ECMO Treatment	0.87	0.43-1.77	0.696
SOFA Score	0.91	0.82-1.01	0.07
pH Before ECMO Treatment	0.02	0.001-0.42	**0.013**

Table S6 shows calculated Odds Ratios for developing ICB during V-V ECMO. The tested variables were different between the groups before starting V-V ECMO, or additionally became different during ECMO treatment. Odds Ratios (OR) were calculated after dichotomizing the variables. The ICB group's median was used as a

cut-off value. Delta values represent the difference between pre-cannulation values and values 2 hours after starting V-V ECMO. In the multivariable analysis, all of these parameters were included, and platelets were calculated continuously to avoid overfitting. In Model 1 $paCO_2$ and norepinephrine were used, in Model 2 delta $paCO_2$ and delta norepinephrine. CI95%: 95% confidence interval. Model 3 showed the lowest AIC value (AIC 328.137) and is shown in the main manuscript. SOFA: Sequential organ failure assessment; aPTT: activated partial Thromboplastin-Time; ASAT: Aspartat-Aminotransferasis; LDH: Lactate-Dehydrogenasis.

110 patients had dual-lumen cannula. 12 patients had femoro-femoral cannulation.

All other patients had femoral drainage and jugular or subclavian return site.

Devices used, Pumps

Cardiohelp	140 (25)
Deltastream	18 (3)
DP 3	139 (25)
HemoLung	3 (1)
Rotaflow	159 (29)
Sorin	97 (17)

Devices used, Oxygenators

Cardiohelp 5.0	14 (3)
Cardiohelp 7.0	82 (15)
Cardiohelp IR	41 (7)
ECC.O 5	97 (17)
ELS	23 (4)
HemoLung	3 (0.5)

Hilite LT	149 (27)
Hilite LT800	1 (0.2)
ILA MV	4 (0.7)
ILA-active	8 (1)
MECC Quadrox-D BE	7 (1)
MECC Softline	5 (1)
PALP	2 (0.4)

ICB and Cannula Diameter

Cannula Diamter (French)		Cannula Diameter												Total
		15.5	16	19	20	21	22	23	24	25	27	29	31	
ICB	no	2	2	4	3	233	26	158	17	2	46	1	1	495
	yes	0	0	0	0	25	2	26	4	0	3	0	1	61
Sum		2	2	4	3	258	28	184	21	2	49	1	2	556