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MAIN TEXT

Coagulation abnormalities in patients with COVID-19 on venovenous ECLS increased risk for technical complications and support times but had no impact on survival

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Abstract

Background: Patients with severe coronavirus disease-19 (COVID-19)-associated acute respiratory distress on venovenous extracorporeal lung support (V-V ECLS) showed a high incidence of vascular as well as ECLS-related thrombotic complications. The latter may influence the outcome of the patients.

Methods: This is a retrospective monocentric study on prospectively collected data of technical complications including 69 adult COVID-19 patients on V-V ECLS (ECLS Registry, March 2020 until April 2021) without and with system exchanges. Alterations in ECLS-specific data, hemolysis, coagulation, and hemostasis parameters were analyzed.

Results: Every second COVID-19 patient on V-V ECLS developed technical complications. Optimized ECLS management at our ECLS center reduced cases of acute clot formation (pump head thrombosis, acute oxygenator thrombosis) (17%), and allowed early identification of progressive clotting processes (worsened gas transfer, coagulation disorder) (14%, 54%) with a significant overhang of hyperfibrinolysis (37%). Although COVID-19 disease and technical complications caused the prolonged length of stay at the intensive care unit and ECLS support times, the proportion of successful weaning and survival rates were comparable with patients without system exchange.

Conclusion: The survival of ECLS patients with COVID-19 was independent of the requirement for system exchange due to technical-induced coagulation disorders. Close monitoring for circuit clotting is mandatory in COVID-19 patients and is one prerequisite for successful organ support in these difficult patients.

KEYWORDS

ECMO, hyperfibrinolysis, outcome, SARS-CoV-2, thrombosis

1 | INTRODUCTION

Almost all patients infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have an asymptomatic or mild course of coronavirus disease 2019 (COVID-19), a considerable number of patients required hospitalization.[1] Among these critically ill patients, up to 20% will require mechanical ventilation and 1%–4% will receive venovenous ECLS (V-V ECLS).[1–3] ECLS could offer life-saving rescue organ support when maximal conventional treatment fails to maintain adequate oxygenation and ventilation in COVID-19 patients.[4–7]

However, there are only limited data describing ECLS support for COVID-19 patients with a special focus on the coagulation characteristics of these patients[8,9] and the risk of thrombotic complications during ECLS organ support.[10,11] These studies reported about experiences within the early period of the COVID-19 pandemics (March 2020 to July 2020), and included only low patient numbers (6 to 43 patients) with a complication rate of 0% to 88%.[8–16]

The aim of the present single-center study was to investigate the rate of technical-induced complications during V-V ECLS within the first year of COVID-19 pandemics including 69 patients with severe ARDS.

2 | MATERIALS AND METHODS

2.1 | Study design

We performed a retrospective single-center medical record review of consecutive hospitalized adult patients admitted to the University Medical Center Regensburg, Germany, between March 2020 and April 2021, with a diagnosis of COVID-19 confirmed by positive PCR testing and undergoing V-V ECLS.[17] Ethical consent was waived by the Ethics Committee of the University of Regensburg (No 21-2705-104), as all devices are approved for clinical use, no personalized data, and only routine laboratory parameters were used.

2.2 | Study population

ECLS management has been described in detail previously.[18,19] Patients with an ECLS support time less than 2 days were excluded from analysis. The cannulation technique used was drainage via the femoral vein and return via the internal jugular vein (93%) or femoral vein (7%). Single lumen return cannulas (Maquet-Getinge, Rastatt, Germany) (99%) were mainly used for anatomical reasons (3× 15Fr, 19× 17Fr, 36× 19Fr, 10× 21Fr). One patient was supported with a double-lumen cannula (24Fr NovaPort-twin, Heilbronn, Germany). On ECLS, an aPTT target value of 50–60 s was aimed according to current recommendations.[20] The type of ECLS-system ($n = 23$ Cardiohelp HLS Set, $n = 7$ PLS Set, both Maquet-Getinge; $n = 6$ Paragon, Chalice Medical Ltd., Nottinghamshire, UK; $n = 4$ Nautilus, Medtronic, MN, USA; $n = 24$ Hilite LT7000, Novalung, Heilbronn, Germany; $n = 5$ ECC.O5 Sorin, Italy) was chosen by availability and patient-specific needs. The used ECLS systems included hollow fiber polymethylpentene membrane oxygenators (PMP-MOs) and blood pumps ($n = 23$ Rotaflex, $n = 16$ Rotaflow, Maquet; $n = 24$ Deltastream DP3, Novalung; $n = 6$ Revolution, Sorin).

All patients in this study were on therapeutic anticoagulation (continuous infusion) with either unfractionated heparin (UFH), argatroban or Clexane (Enoxaparin).[21] Target activated partial thromboplastin time (aPTT) was 50–60 s and was adjusted depending on thrombus burden or bleeding events. If there was suspicion of heparin-induced thrombocytopenia or insufficient thrombus control in the circuit with UFH, the anticoagulation was switched to argatroban with an aPTT target of >60 s. In six patients, anticoagulation was switched to Enoxaparin during ECLS, monitored by anti-Factor Xa activity.

The study population included 69 patients that required either only one ECLS system ($n = 34$), or at least one system exchange due to technical complications ($n = 35$) (Figure 1).

2.3 | Data collection and analysis

Data of this study were acquired from the Regensburg ECLS database, in which patient characteristics (e.g., age, gender, SOFA score, acute renal failure), prospective physical parameters (e.g., blood flow (BF), partial pressure of O_2 and CO_2 in the blood at the outlet of the MO (pO_2 postMO, pCO_2 postMO), gas flow (GF)) and laboratory parameters (e.g., blood gases, blood counts, D-dimers (DD), fibrinogen (FG), plasma-free hemoglobin (fHb), lactate dehydrogenase (LDH)), ECLS management data (e.g., total ECLS time, run time of the 1st MO), and outcome (successful weaning, hospital discharge) of ECLS patients are collected. Transmembrane pressure drop was defined as the difference between pressure at the inlet and outlet of the MO (dpMO = pMOin – pMOout). Transfusion requirements (FFP, fresh frozen plasma; PC, platelet concentrate; RBC, red blood cells; Factor I, Factor XIII, Immunplasma), applications of tranexamic acid and early application of corticosteroids (Dexamethasone, Hydrocortisone, Prednisolone), and dosages of heparin and norepinephrine were documented.

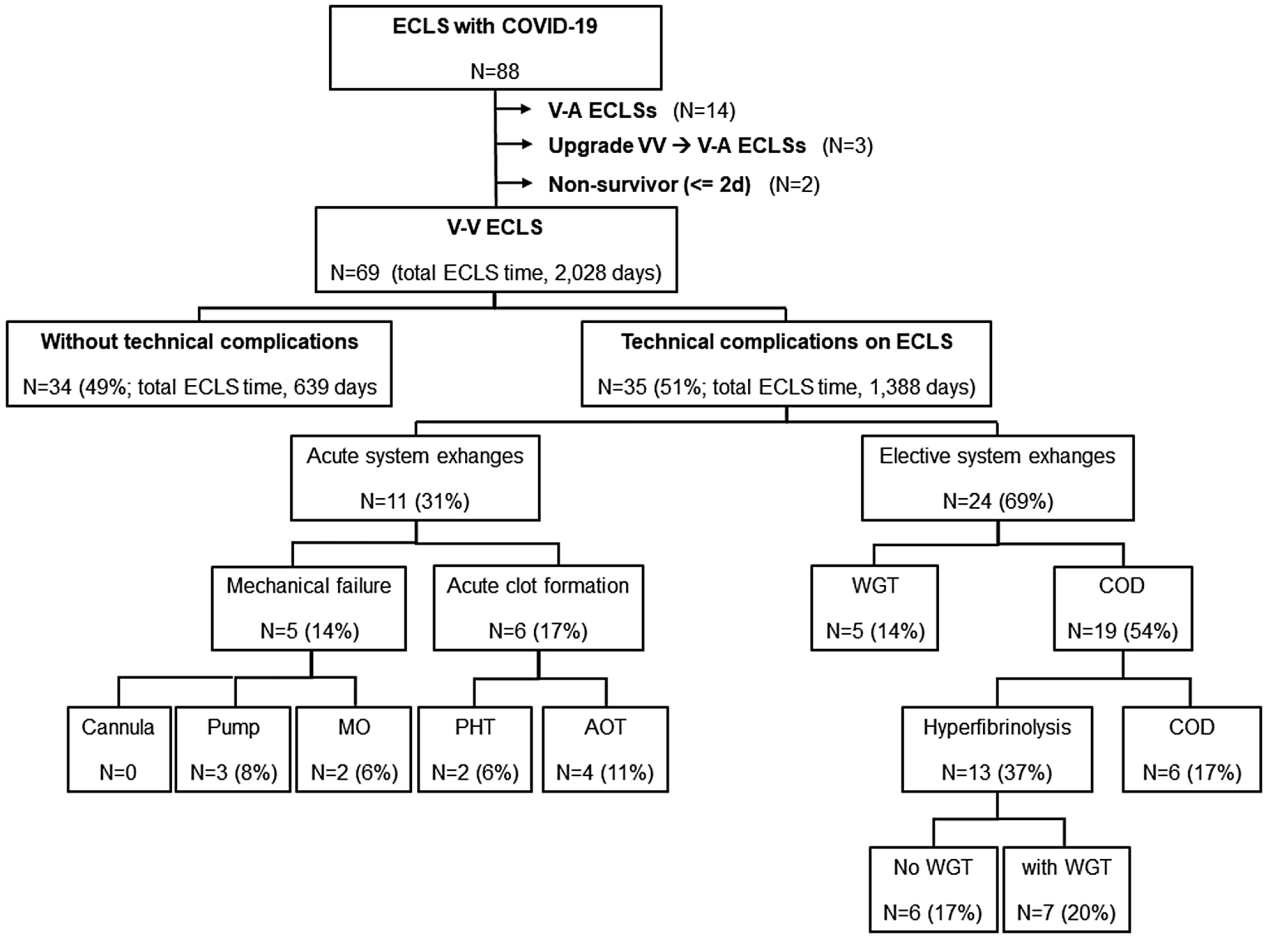

FIGURE 1 Flow chart of the retrospective observational study of the ECLS registry during 1 year of COVID-19 pandemic in Regensburg

2.4 | Identification of technical complications

Reasons for acute and elective system exchanges during V-V ECLS were identified according to Lubnow et al.[18] (Figure 1). Technical complications demanding an acute system exchange included mechanical failures (leakage at the membrane oxygenator [MO], connectors or pump head) and acute clot formation within the MO or the pump head. Extended clots within the MO (acute oxygenator thrombosis, AOT) caused an increase in the dpMO and a decrease in blood flow at the same pump speed.[22] Pump head thrombosis (PHT) was identified by a sudden sound change of the blood pump, technically induced hemolysis (with an acute increase in plasma-free hemoglobin) and/or a decrease in platelet count. Elective system exchanges included worsening of gas transfer (WGT) and device-induced coagulation disorder (COD). WGT was defined as a significant decrease in the partial pressure of O_2 in the blood at the outlet of the MO (pO_2 postMO) or more than 50% compared to the initial value and an elevation of the partial pressure of CO_2 in the blood at the outlet of the MO (pCO_2 postMO) over 40 mm Hg at high gas flow rates (≥10 L/min). Markers for a COD were an otherwise unexplainable (e.g., DIC, thrombosis, pulmonary embolism, trauma, surgery) increase in the levels of DD from <10 mg/dl to 25–35 mg/dl (fibrinolysis in the MO), or an otherwise unexplainable increase in DDs and a decrease in FG concentration (<200 mg/dl) (device-induced hyperfibrinolysis) with subsequent improvement after exchange.[18] These markers were mostly accompanied by a decrease in platelet count and a diffuse unaccountable bleeding tendency before system-exchange, which normally reversed after exchange. A reference group was identified (no system exchange, support time ≥12 days) to demonstrate an "uncomplicated ECLS run."[18] Mortality included all patients that died within 30 days after ECLS weaning.

2.5 | Statistics

Data are expressed as median (25–75 percentile) and were analyzed with the Wilcoxon-signed-rank-test (SigmaStat

3.1, Systat Software, San Jose, CA, USA). Data were analyzed for normality (Kolmogorov–Smirnov test) and homogeneity of variance (Levene). Intergroup differences were compared using the Friedman test for repeated measures analysis of variance (ANOVA) by ranks, with post hoc Dunn's Method for multiple comparison versus control (time of system-exchange). p-values ≤0.05 indicated a significant difference.

3 | RESULTS

3.1 | Study population

Within the 1-year study period 88 COVID-19 patients were supported with ECLS at our ECLS center (venoarterial, $n = 17$; venovenous, $n = 71$). Only patients requiring V-V EMCO and surviving more than 2 days were included in the present study ($n = 69$).

All patients had platelet counts >100/nl before inclusion, and there was no indication for DIC. Only three patients presented acute renal failure, defined as the need for renal replacement therapy. Before ECLS COVID-19 patients presented an aggravated acute phase response (e.g., elevated levels of vWF-Ag, -Act, FVIII, CRP, leukocytes) and worsened coagulopathy (e.g., elevated levels of D-dimers, fibrinogen). Patients were grouped by the absence ($n = 34$, 49%) and presence ($n = 35$, 51%) of technical complications that required a system exchange during ECLS support.[18,23] Patient characteristics, initial anticoagulation, and early steroid application as well as baseline coagulation, inflammatory, and ventilation data of both COVID-19 groups were comparable (Table 1, Table S1).

Patients requiring at least one system exchange had a longer ECLS support time ($p < 0.001$), total ventilation time ($p = 0.022$), and residence time in the intensive care unit (ICU) ($p = 0.007$). However, the run time of the 1st MO was significantly shorter ($p = 0.009$) compared to exchange-free ECLS runs. Despite prolonged ECLS support time and requirement of 2 to 6 MOs, there was no difference in successful weaning events (no exchange, 68%; exchange, 69%; $p = 0.860$), and 30d-mortality (no exchange, 41%; exchange, 31%; $p = 0.458$). The median survival time after end of ECLS until time of analysis (Nov 2021) for the non-exchange and exchange group was 279 (248–408) days and 338 (280–524) days ($p = 0.421$), respectively. Furthermore, patients with a system exchange required significantly more blood products per ECLS day (RBC, $p = 0.020$; Factor I, $p = 0.003$; Factor XIII, $p = 0.053$) compared to patients free of exchange. Forty-six percent of patients with a system exchange were treated with tranexamic acid ($p = 0.004$) (Table 2).

Coagulation-related exchange reasons included acute clot formation (no mechanical failure), and elective coagulation disorder (COD, WGT). Both, PHT (1× DP3, 1× Rotaflow) and AOT (3× Cardiohelp-MO, 1× Hilite7000LT-MO) summarized acute clot formation. While only five (14%) ECLS systems were exchanged due to isolated WGT, 19/35 exchanged ECLS systems (54%) presented COD (Figure 1). Patient characteristics, initial ventilation, and laboratory parameters were comparable regarding the three exchange reasons (Table 1, Table S1). Furthermore, there were no significant differences in the ECLS support, total intubation, and ventilation times. However, the run time of the 1st MO tended to be shorter in cases of acute clot formation (PHT, 8, 9 days; AOT, 2, 3, 4, 16 days) compared to WGT and COD (Table 2). Patients that required a system exchange due to COD were substituted significantly more Factor I ($p = 0.012$) (Table 2). There was no difference in successful weaning events and mortality.

3.2 | Technical complications on ECLS of COVID-19 patients

Daily analysis of gas transfer, coagulation, and hemolysis data allowed the early identification of WGT and COD. The reference group (Figure S1) presented a significant decrease in CRP, fibrinogen, and platelet count, and an increase in DD, INR, and ATIII after a comparable support time. Gas transfer, aPTT, and hemolysis data remained unchanged.

3.2.1 | Acute system exchanges

Mechanical failure was documented for three pumps (1× deltastream DP3, Fresenius; 1× DidecoRevolution, Sorin; 1× Rotaflow, Maquet) and two MOs (1× Paragon®, 1× Hilite 7000LT). Two patients (3%) developed a PHT with a sudden increase in LDH and fHb levels before and decrease after exchange (Figure 2A,B) and visible clots within the pump head after removal and blood drainage. Four patients (6%) showed AOTs with an increase in dpMO/blood flow before and a decrease after exchange (Figure 2C). For the reference group, fHb, LDH, and dpMO/blood flow remained unchanged. Except higher CRP values before exchange, there was no difference in the time line between acute exchanges and the reference group (Figure S1).

TABLE 1 Patient characteristics of different study groups before ECLS

	All	No exchange	System exchange	*p*-value	Acute	COD	WGT	*p*-value
Patients (*n*)	69	34	35		6[§]	19	5	
Age (years)	58 (52–64)	57 (53–63)	58 (51–65)	0.623	56 (49–65)	58 (54–65)	62 (49–66)	0.945
Males (*n*;%)	56; 81	26; 76	30; 86	0.500	4; 67	18; 95	5; 100	0.097
BMI ($kg * m^{-2}$)	28.7 (26.5–34.1)	29.0 (27.7–35.6)	27.8 (24.7–32.8)	0.665	39.1 (29.0–42.1)	27.8 (24.6–31.7)	32.5 (29.4–34-0.3)	0.075
MV (days)	2.0 (1.0–9.0)	2.0 (1.0–8.3)	3.0 (1.0–13.0)	0.827	3.0 (1.0–5.0)	1.0 (0.0–13.0)	5.0 (0.5–14.5)	0.879
SOFA score	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.8–10.0)	0.461	9.5 (8.0–10.3)	9.0 (9.0–11.0)	9.0 (7.0–10.0)	0.572
LIS	3.3 (3.0–3.3)	3.3 (3.3–3.4)	3.3 (3.0–3.3)	0.541	3.3 (3.3–3.3)	3.3 (3.0–3.4)	3.0 (3.0–3.5)	0.580
RRT (*n*; %)	3; 4	3; 9	0; 0	0.114	0; 0	0; 0	0; 0	–
IHT (*n*; %)	22; 32	10; 29	12; 34	0.860	1; 17	7; 37	2; 40	0.620
NE (μg/kg/min)	0.11 (0.04–0.21)	0.10 (0.02–0.21)	0.12 (0.04–0.22)	0.329	0.10 (0.05–0.23)	0.19 (0.12–0.29)	0.03 (0.0–0.17)	0.060
PaO_2/FiO_2 (mm Hg)	67 (56–89)	76 (57–95)	64 (53–71)	0.109	57 (52–67)	64 (50–70)	68 (55–91)	0.514
$PaCO_2$ (mm Hg)	60 (51–74)	65 (54–80)	58 (51–69)	0.576	58 (49–63)	55 (50–76)	66 (57–69)	0.435
apH	7.30 (7.22–7.36)	7.28 (7.18–7.36)	7.31 (7.25–7.36)	0.414	7.35 (7.28–7.39)	7.28 (7.25–7.32)	7.33 (7.24–7.41)	0.428
TV (ml)	473 (387–567)	453 (371–364)	509 (398–570)	0.490	500 (378–614)	498 (450–567)	550 (546–673)	0.465
TV/kg pred. BW (ml/kg)	7.2 (5.8–8.6)	6.9 (5.7–8.5)	7.4 (5.9–8.3)	0.612	7.6 (5.8–8.5)	7.5 (6.9–8.4)	8.3 (7.5–9.7)	0.556
Minute ventilation (L/min)	11 (9–13)	10 (8–12)	12 (9–13)	0.053	12 (10–14)	12 (10–14)	13 (11–14)	0.836
PIP (cm H_2O)	32 (29–35)	30 (28–35)	32 (30–35)	0.354	34 (29–35)	32 (30–34)	32 (28–34)	0.698
PEEP (cm H_2O)	15 (13–15)	15 (13–16)	15 (13–15)	0.394	13 (11–15)	15 (14–15)	15 (12–17)	0.180
Early CS (*n*; %)	42 (61)	25 (74)	17 (49)	0.061	2 (33)	12 (63)	3 (60)	0.432
H/A/E (*n*)	58/7/4	28/3/3	30/4/1	0.267	5/1/0	15/3/1	3/2/0	0.734

Note: Data are presented as median (IQR) or amount (*n*; %). Statistics: One way ANOVA on variance, chi-square test.

Abbreviations: apH, arterial pH; ARF, acute renal failure; BMI, body mass index; CS, early corticosteroids (Dexamethasone, Hydrocortisone, Prednisolone); H/A/C, initial anticoagulation with unfractionated heparin, Argatroban, Enoxparin; IHT, ECLS inter-hospital transport; LIS, Murray lung injury score; MV, mechanical ventilation; NE, Norepinephrine; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2/FiO_2, ratio of partial pressure of arterial oxygen and fraction of inspired oxygen; PEEP, positive end-expriatory pressure; PIP, peek inspiratory pressure; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment; TV, tidal volume.

[§]Summarized all pump head thrombosis ($n = 2$) and acute oxygenator thrombosis ($n = 4$).

TABLE 2 Patient data of different study groups during and after ECLS

	All	No exchange	System exchange	*p*-value	Acute	COD	WGT	*p*-value
Patients (*n*)	69	34	35		6[§]	19	5	
Stay in ICU (days)	41 (29–75)	34 (24–53)	59 (32–81)	0.007	53 (38–73)	75 (39–95)	32 (21–80)	0.364
Ventilation (days)	37 (26–69)	32 (21–48)	45 (29–77)	0.022	41 (29–56)	54 (31–81)	28 (18–80)	0.400
ARF (*n*; %)	11; 16	6; 18	5; 14	0.958	0; 0	3; 16	2; 40	0.205
MOs (*n*; %) [min–max]	2 (1–2) [1–6]	1 [1]	2 (2–3) [2–6]	–	3 (2–4) [2–4]	2 (2–3) [2–6]	2 (2–3) [2–3]	0.792
Cum. support time (days)	2028	640	1388	–	193	845	155	–
Run time 1st MO (days)	11 (8–20)	16 (9–26)	10 (5–17)	0.009	6 (3–11)	11 (9–17)	12 (3–24)	0.084
Total ECLS time (days)	21 (14–39)	16 (9–26)	31 (18–64)	<0.001	28 (15–44)	38 (21–65)	17 (11–59)	0.238
Successful wean (*n*; %)	47; 68	23; 68	24; 69	0.860	5; 83	12; 63	3; 60	0.620
Discharge hospital (*n*; %)	37; 54	15; 44	22; 63	0.187	5; 83	10; 53	3; 60	0.408
30d mortality (*n*; %)	25; 36	14; 41	11; 31	0.458	1; 17	7; 37	2; 40	0.620
TXA (*n*; %)	20; 29	4; 12	16; 46	0.004	1; 20	10; 53	2; 40	0.297
RBC/days ECLS	0.27 (0.13–0.39)	0.17 (0.06–0.34)	0.29 (0.20–0.42)	0.020	0.25 (0.16–0.35)	0.30 (0.23–0.48)	0.29 (0.15–0.70)	0.655
FFP/days ECLS	0.00 (0.00–0.12)	0.00 (0.00–0.05)	0.00 (0.00–0.32)	0.232	0.00 (0.00–0.01)	0.00 (0.00–0.32)	0.00 (0.00–0.50)	0.384
PC/days ECLS	0.00 (0.00–0.06)	0.00 (0.00–0.00)	0.00 (0.00–0.06)	0.102	0.00 (0.00–0.05)	0.00 (0.00–0.05)	0.00 (0.00–0.06)	0.626
FI/days ECLS	0.00 (0.00–0.11)	0.00 (0.00–0.00)	0.07 (0.00–0.22)	0.003	0.00 (0.00–0.00)[a]	0.10 (0.00–0.32)[a]	0.00 (0.00–0.21)	0.012
FXIII/days ECLS	0.00 (0.00–0.05)	0.00 (0.00–0.01)	0.03 (0.00–0.16)	0.053	0.03 (0.00–0.26)	0.04 (0.00–0.16)	0.00 (0.00–0.18)	0.613
IP/days ECLS	0.00 (0.00–0.03)	0.00 (0.00–0.01)	0.00 (0.00–0.03)	0.707	0.07 (0.00–0.09)	0.00 (0.00–0.00)	0.00 (0.0.00–0.14)	0.068

Note: Data are presented as median (IQR) or amount (*n*; %). Statistics: One way ANOVA on variance, chi-square test.

Abbreviations: ARF, acute renal failure; FFP, fresh frozen plasma (1 FFP contains 230 ml plasma); FI, coagulation factor I (20 mg/ml human fibrinogen, Hemocomplettan, CLS Behring, Frankfurt, Germany); FXIII, coagulation factor XIII (1250 IU in 20 ml human Factor XIII, Fibrogammin, CLS Behring); ICU, intensive care unit; IP (1 IP contains 200 ml immunplasma from convalescent COVID-19 patients); MO, membrane oxygenator; PC, platelet concentrate (1 PC contains 250 ml and 2–4 × 10^{11} platelets); RBC, red blood cells; TXA, tranexamic acid (number of patients with TXA treatment during ECLS; 100 mg/ml infusion, Advanz Pharma, London, UK).

[a]Comparing acute versus COD.

[§]Summarized all pump head thrombosis ($n = 2$) and acute oxygenator thrombosis ($n = 4$).

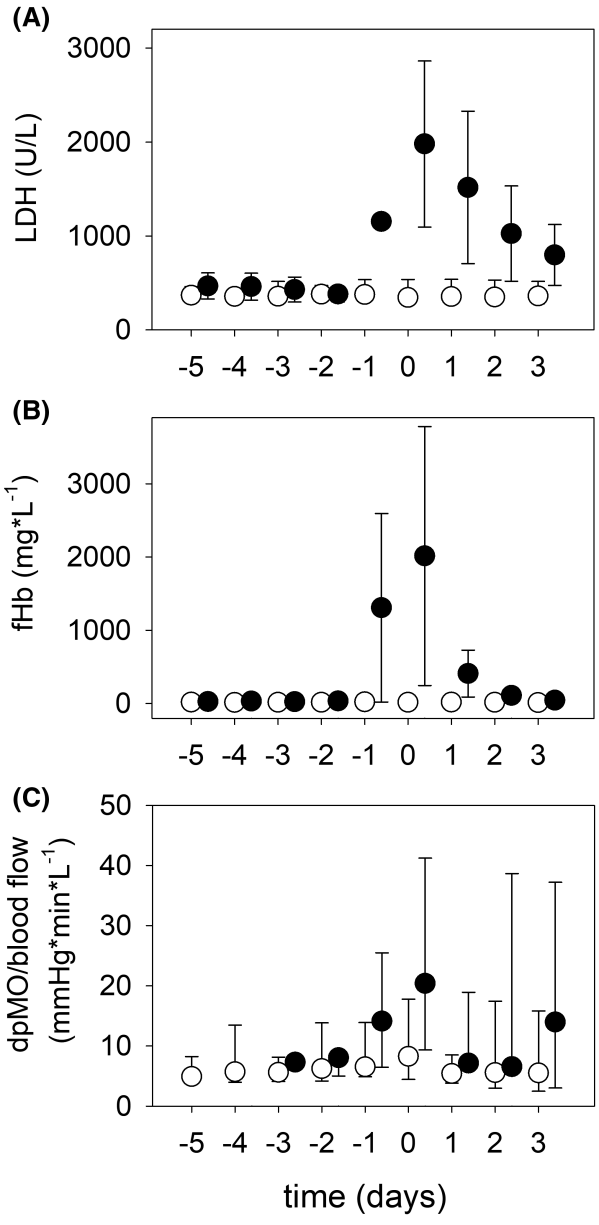

FIGURE 2 Pump head thrombosis (PHT) (A,B) and acute oxygenator thrombosis (AOT) (C). Time line of respective values (median, IQR) before and after system exchange; "day 0" = system exchange. Patients with system exchange (black dots, PHT, $n = 2$; AOT, $n = 4$). (A) Alterations in lactate dehydrogenase (LDH) and (B) plasma-free hemoglobin (fHb) with PHT and (C) alterations in pressure drop across the oxygenator (dpMO) normalized by blood flow in patients with AOT before and after exchange. White dots in all graphs presented data from patients ($n = 20$) without a system exchange and a support time ≥12 days. Values at day 9 after ECLS initiation were set as "day 0" and depicted accordingly with no significant temporal changes. Statistics failed due to low sample size of exchanged cases

3.2.2 | Elective system exchanges

Five patients (14%) required a system exchange due to isolated WGT (Figure 3). Despite an up-regulation of the gas flow rate before a system exchange ($p = 0.016$), pCO_2 postMO (> 40 mm Hg, $p = 0.062$) as well as CO_2 elimination ($p = 0.029$) worsened significantly, while pO_2 postMO and O_2 transfer remained unchanged. However, the gas transfer performance of this group was significantly limited before exchange compared to the reference group. After exchange, gas transfer data normalized and approximate to the reference group. In contrast, inflammatory, hemolysis, and coagulation data remained unchanged before and after exchange (Figure S2).

Progression of device-related COD was another reason for elective system exchange (19/35, 54%). This is a heterogeneous group that was subdivided into three subgroups:

Six patients (17%) presented a local fibrinolysis in the MO due to progressive clot formation. While fibrinogen levels and platelet counts remained unchanged, D-dimers were high before and recovered after exchange ($p = 0.005$) (Figure 4A–C). Furthermore, there was no significant alteration in the time line of gas transfer, inflammatory, coagulation and hemolysis data (Figure 4D–I, Figure S3). Only the pO_2 postMO was significantly lower within the 5 days before the exchange compared to the reference group (Figure 4H). After exchange, pO_2 postMO and DDs improved.

The majority of patients with COD developed a device-induced hyperfibrinolysis without ($n = 6$) (Figure 5) and with additional WGT ($n = 7$) (Figure 6). Main characterisics for both groups: The fibrinogen concentration decreased significantly below the normal value of 200 mg/dl, accompanied by an increase in D-dimer levels and a decrease of platelet counts within 5 days before a system exchange. After exchange, D-dimer levels decreased signifcantly and fibrinogen concentrations as well as platelet counts slowly recovered (not significant). This was in contrast to patients without system exchange after a comparable support time.

While six of 13 patients showed no effect on gas transfer data (Figure 5D–I), the remaining seven of 13 patients presented an additional WGT. This manifested in an up-regulation of the gas flow rate accompanied by a decrease in CO_2 elimination and pO_2 postMO before exchange and an improvement within 1 day after exchange (Figure 6D,F,H). This effect corresponds to the time line in the group with an isolated WGT (Figure 3).

The other parameters remained unchanged except for aPTT. Independent of the presence of WGT, aPTT decreased continuously regardless of the system exchange. aPTT was lower compared to the reference group (Figures S4 and S5).

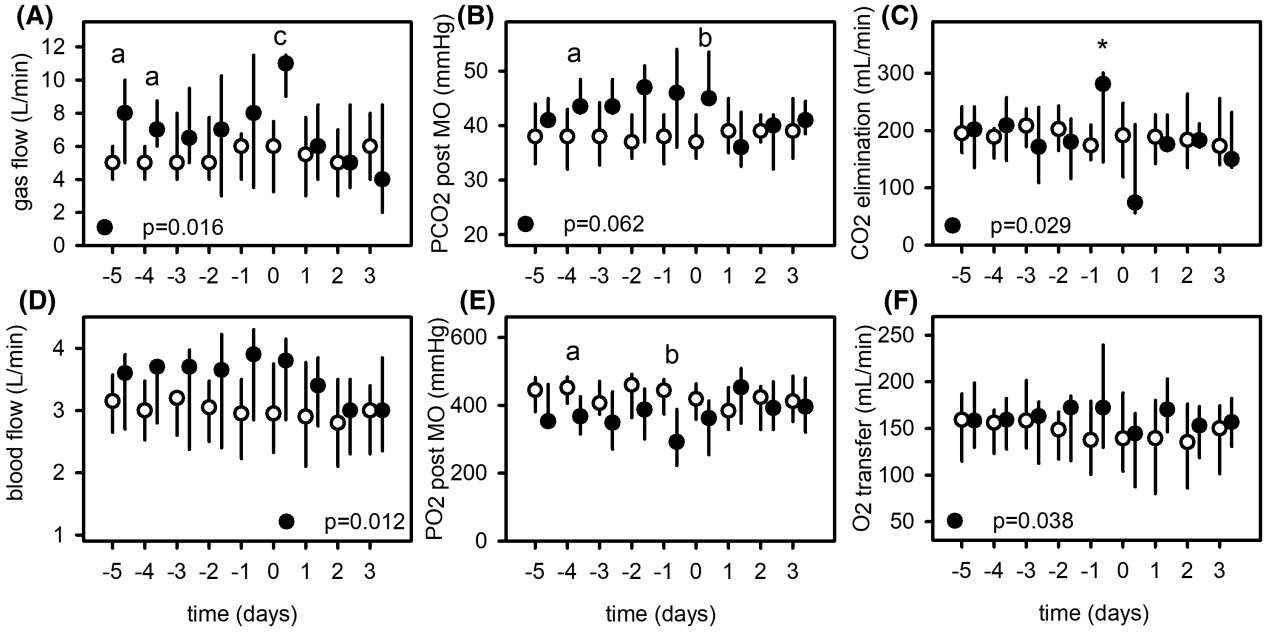

FIGURE 3 Isolated WGT as a reason for an elective system exchange. Time line of respective values (median, IQR) before and after system exchange; "day 0" = system exchange. Patients with system exchange (black dots, $n = 5$). (A) Gas flow rate increased before and decreased after exchange. (B) Partial pressure of CO_2 at the outlet of the MO tended to increase (>40 mm Hg) before and decreased after exchange. (C) CO_2 elimination significantly decreased before and improved after exchange. (D) Blood flow decreased after system exchange. (E) The oxygenation capability (PO_2 postMO) remained unchanged, while (F) O_2 transfer decreased before and normalized after exchange. White dots in all graphs presented data from patients ($n = 20$) without a system exchange and a support time ≥12 days. Values at day 9 after ECLS initiation were set as "day 0" and depicted accordingly with no significant temporal changes. Statistical differences in the time lines of patient groups are shown next to the dots within the graphics (two-way ANOVA on ranks). *$p < 0.05$ compared to day 0 (only black dots). a, $p < 0.05$; b, $p < 0.010$; c, $p < 0.001$ compared to the reference group at specified times

4 | DISCUSSION

The incidence of thrombo-embolic complications is very high in patients with COVID-19[24] which was considered to be a reason for a higher risk of device-induced technical complications with ECLS organ support.[15] The present study demonstrates that every second COVID-19 patients on V-V ECLS developed technical complications. Optimized ECLS management can reduce cases of acute clot formation (PHT, AOT) (17%), and allows early identification of progressive clotting processes (WGT, COD) (14%, 54%) with a significant overhang of hyperfibrinolysis (37%). Although COVID-19 disease and technical complications caused prolonged length of stay at the ICU and ECLS support times, the proportion of successful weaning as well as survival rates was comparable with patients free of system exchanges.

In contrast to a historical control of non-COVID patients on V-V ECLS,[18] COVID-19 patients required significantly more device-induced system exchanges (COVID-19: 35/69, 51%; non-COVID, 83/265, 31%; $p = 0.002$). Patients from both studies were treated at our ECLS center with comparable regimens. Patients from both studies were supported with PMP-MOs that are characterized by a per se low changing frequency and inconspicuous infection incidence.[25] Patient characteristics were comparable in both studies. However, the proportion of detectable clot formation/coagulation disorder was 43% (30/69) for COVID-19 and 27% (71/265) for non-COVID patients. A retrospective study from Bemtgen et al.[11] confirmed the higher rates of thrombotic events within the ECLS circuit in COVID-19 patients (COVID-19: 7/11, 64%; non-COVID: 15/55, 27%). Despite limited data in the literature, acute clot formation in the blood pumps (PHT) and oxygenators (AOT) in COVID-19 patients was observed previou sly.[5,8–12,14,15,26–28] The focus is less on the cause of the system exchange and more on the necessity of an exchange. While at our ECLS center the incidence of PHT was low and independent of COVID-19 infection (COVID-19: 2/69, 3%; non-COVID: 13/265, 5%),[18] Bemtgen et al.[11] documented twice as many PHT in COVID-19 compared to non-COVID patients (5/11, 45%; 11/55, 20%). PHT was also the solely exchange reason in small studies by Helms et al.[8] and Kalbhenn et al.[15] with a frequency of 17% (2/12) and 33% (2/6), respectively. However, the reportedly high incidence of PHT in COVID-19 patients should be judged with caution due to very small subgroups (6 to 12 patients compared to 69 in the present study). In addition,

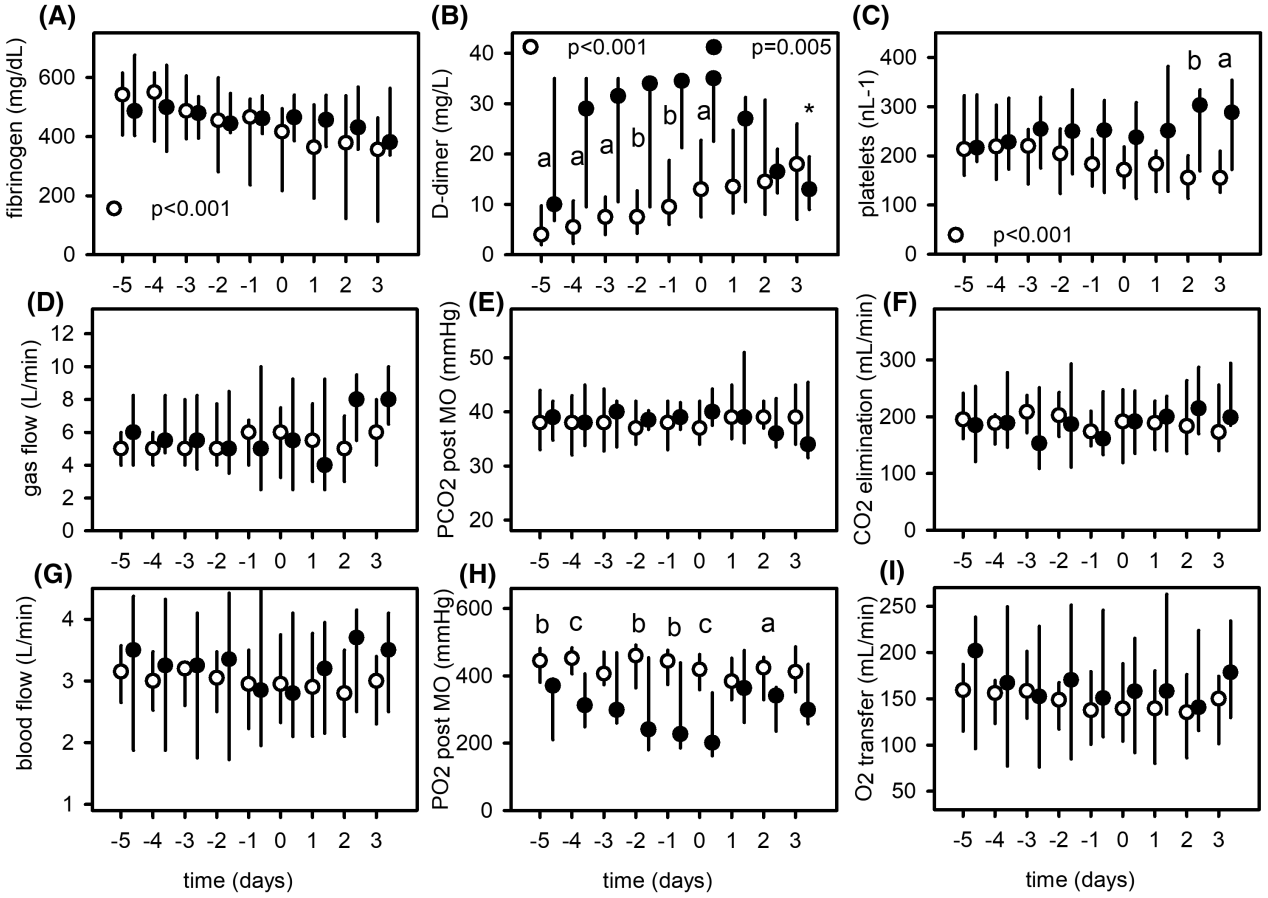

FIGURE 4 Clot formation and local fibrinolysis as a reason for an elective system exchange. Time line of respective values (median, IQR) before and after system exchange; "day 0" = system exchange. Patients with system exchange (black dots, $n = 6$). (A) Fibrinogen and (C) platelet counts remained unchanged. Only (B) D-dimer levels increased before and decreased after exchange. System exchange had no effect on (D) gas flow rate, (E) partial pressure of CO_2 at the outlet of the MO, (F) CO_2 elimination, (G) blood flow, and (I) O_2 transfer. (H) Partial pressure of O_2 at the outlet of the MO presented significantly lower levels before exchange compared to patients without system exchange. White dots in all graphs presented data from patients of the reference group ($n = 20$). Statistical differences in the time lines of patient groups are shown next to the dots within the graphics (two-way ANOVA on ranks). *$p < 0.05$ compared to day 0 (only black dots). a, $p < 0.05$; b, $p < 0.010$; c, $p < 0.001$ compared to the reference group at specified times

the incidence of acute oxygenator thrombosis (AOT) vary considerably in the literature (8%–88%).[5,9,10,12,14,26–28] As shown in the present study and by Lubnow et al.,[18] AOT appeared independent of COVID-19 infection with an incidence of 6%. Membrane thrombosis (increase in dpMO) was also identified as exchange reason by Akhtar et al.[10] and Zhang et al.[14] (5/18, 28% and 17/43, 40%). In contrast, Guo et al.[9] reported about thrombosis within oxygenators in 7 of 8 COVID-19 patients on ECLS (88%). The authors used different definitions for AOT. While in our study, AOT was an acute event that emerged after a median run time of 4 (2–13) days with an increase in dpMO, Guo et al.[9] identified oxygenator thrombosis after a median run time of 17 (14–20) days associated with hyperfibrinolytic processes. They classified these events with D-dimers >10 µg/ml, fibrinogen <150 mg/dl, and a sustained decrease in the platelet count that normalized temporarily after exchange. Moreover, in three of seven patients thrombi were again formed on the new oxygenator.[9] Both, AOT and hyperfibrinolysis were rarely seen/described in previous ECLS-supported patients.[29] The incidence of hyperfibrinolysis as a reason for a system exchange during V-V ECLS of non-COVID patients was 3%[18] compared to 19% (13/69) in the present study of COVID-19 patients. The main reason for this discrepancy may be the hypercoagulability and secondary hyperfibrinolysis after a COVID-19 infection ending in an increased risk of thrombosis.[9,18,30] The hypercoagulability observed in critically ill COVID-19 patients could arise from pulmonary vascular endothelial cell injuries, inflammatory processes, exocytosis of unusually large von Willebrand Factor multimers, and platelet activation.[30] Guo et al.[9] introduced only eight COVID-19 patients that all showed high levels of DD and FDP throughout, high levels of fibrinogen at the early

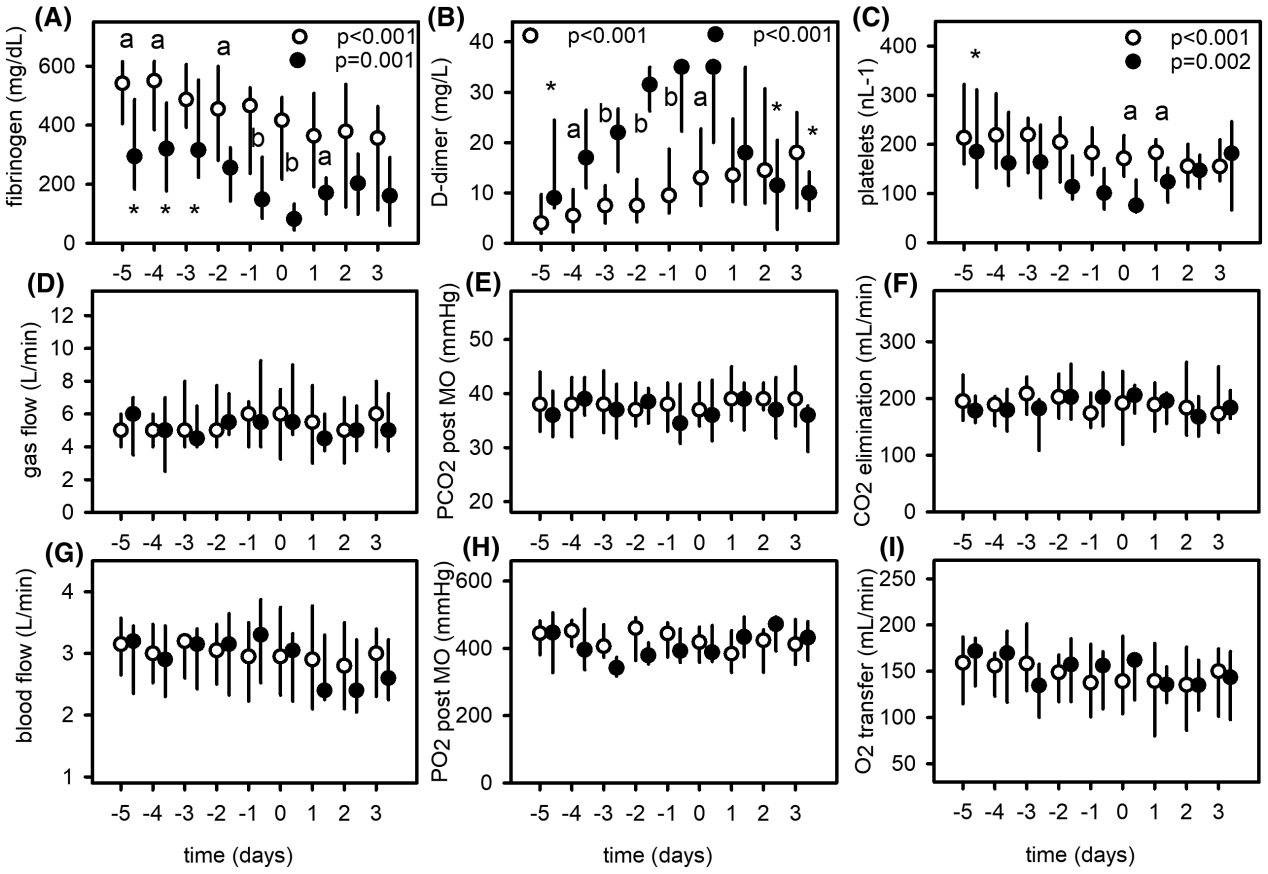

FIGURE 5 Device-induced hyperfibrinolysis without WGT as a reason for an elective system exchange. Time line of respective values (median, IQR) before and after system exchange; "day 0" = system exchange. Patients with system exchange (black dots, $n = 6$). (A) Fibrinogen concentrations decreased significantly below 200 mg/L and recovered after exchange. (B) D-dimer levels significantly increased before and decreased after exchange. (C) Platelet counts decreased before and recovered after exchange. System exchange had no effect on (D) gas flow rate, (E) partial pressure of CO_2 at the outlet of the MO, (F) CO_2 elimination, (G) blood flow, (H) partial pressure of O_2 at the outlet of the MO, and (I) O_2 transfer. White dots presented data from patients of the reference group ($n = 20$). Statistical differences in the time lines of patient groups are shown next to the dots within the graphics (two-way ANOVA on ranks). *$p < 0.05$ compared to day 0 (only black dots). a, $p < 0.05$; b, $p < 0.010$ compared to the reference group at specified times

stage, and consumption of fibrinogen and platelets at the later stage during ECLS support. The authors recommended changing the system in these cases. However, our data indicate that the use of ECLS during severe COVID-19 infection does not necessarily induce hyperfibrinolysis. A special feature of these patients is the significant decrease in platelet count without cessation of anticoagulation that is essential to prevent COVID-19-related thrombosis. Actually, in ECLS patients with initial thrombocytopenia there is a high risk of bleeding. Therefore, attempts are made to reduce or stop anticoagulation in these patients in order to prevent thrombosis.[31] However, none of our COVID-19 patients had thrombocytopenia prior to ECLS. This is based on the described disease-related hypercoagulability of COVID-19 patients.

Data on long-term survival of COVID-19 patients on ECLS are limited. Li Bassi et al.[32] provides COVID-19 patients' survival advantages with ECLS organ support. In-hospital mortality was 94% with conventional therapy compared to 59% with ECLS support. On the other side, ECLS patients with and without COVID-19 showed no difference in 30d mortality.[33,34] While both studies presented a 30d mortality for COVID-19 patients of 54% and 46%, respectively, the present study showed lower mortality (36%). Current studies in 2021 do specify technical complications with a frequency of 11% to 88%,[5,9–11,15,16,26–28] however, there was no correlation with 30d mortality (range, 17% to 73%). The present study clearly showed that the occurrence of technical complications was associated with prolonged length of stay at the ICU and ECLS support times but had no effect on the successful weaning events and 30d-mortality.

Our study has several limitations. This study included subgroups with a small number of patients. Larger cohorts

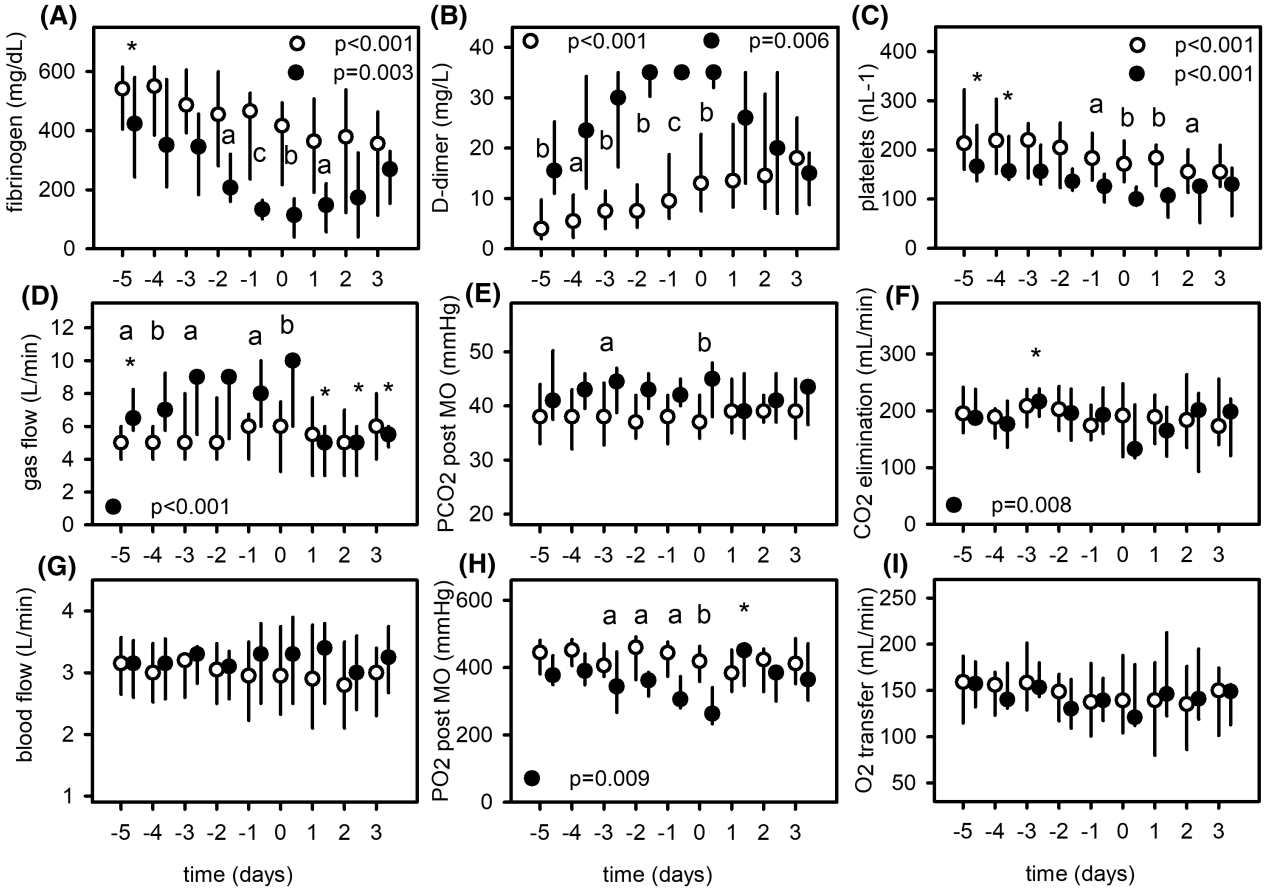

FIGURE 6 Device-induced hyperfibrinolysis with additional WGT as a reason for an elective system exchange. Time line of respective values (median, IQR) before and after system exchange; "day 0" = system exchange. Patients with system exchange (black dots, $n = 7$). (A) Fibrinogen concentrations decreased significantly below 200 mg/L and recovered after exchange. (B) D-dimer levels increased before and decreased after exchange. (C) Platelet counts decreased before and recovered after exchange. COD was accompanied by (D) a significant increase in gas flow rate before and decrease after exchange, (F) a decrease of CO_2 elimination before and improvement after exchange, (H) a decrease in the partial pressure of O_2 at the outlet of the MO before and increase after exchange. (E) partial pressure of CO_2 at the outlet of the MO, (G) blood flow, and (I) O_2 transfer remained unchanged. White dots in all graphs presented data from patients of the reference group ($n = 20$). Statistical differences in the time lines of patient groups are shown next to the dots (two-way ANOVA on ranks). *$p < 0.05$ compared to day 0 (only black dots). a, $p < 0.05$; *b*, p < 0.010; *c*, p < 0.001 compared to the reference group at specified times

are needed to confirm our findings. The data were derived from a single center and were collected retrospectively. Our study included patients from several waves of the COVID-19 pandemic. Changes in clinical practice over time may have influence the outcome of critically ill patients with COVID-19 on V-V ECLS.

5 | CONCLUSION

To conclude, we found a comparable survival rate in ECLS patients with COVID-19 independent of the requirement of technical-induced coagulation disorders with subsequent system exchanges. Close monitoring of circuit thrombosis even during COVID-19 illness is a prerequisite for successful organ support in difficult times.

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CONFLICT OF INTEREST

The authors have disclosed that they do not have any conflict of interest.

AUTHOR CONTRIBUTIONS

Karla Lehle carried out data analysis and interpretation, statistics, graphical presentation, and drafting of the article. Alois Philipp carried out the concept and design of the study, data collection and analysis, and critical revision of the article. Markus Ritzka and Maik Foltan were involved in data collection and critical revision of the article. Frank Schettler carried out data collection and analysis. Matthias

Lubnow carried out data interpretation and critical revision of the article. Thomas Müller carried out the concept and design of the study and supervised the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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