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ASAIO Journal 2025 Pulmonary

Thrombocytopenia During Venovenous Extracorporeal Membrane Oxygenation in Adult Patients With Bacterial, Viral, and COVID-19 Pneumonia

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Contact of blood with artificial surfaces triggers platelet activation. The aim was to compare platelet kinetics after venovenous extracorporeal membrane oxygenation (V-V ECMO) start and after system exchange in different etiologies of acute lung failure. Platelet counts and coagulation parameters were analyzed from adult patients with long and exchange-free (≥8 days) ECMO runs (n = 330) caused by bacterial (n = 142), viral (n = 76), or coronavirus disease 2019 (COVID-19) (n = 112) pneumonia. A subpopulation requiring a system exchange and with long, exchange-free runs of the second oxygenator (≥7 days) (n = 110) was analyzed analogously. Patients with COVID-19 showed the highest platelet levels before ECMO implantation. Independent of the underlying disease and ECMO type, platelet counts decreased significantly within 24 hours and reached a steady state after 5 days. In the subpopulation, at the day of a system exchange, platelet counts were lower compared with ECMO start, but without differences between underlying diseases. Subsequently, platelets remained unchanged in the bacterial pneumonia group, but increased in the COVID-19 and viral pneumonia groups within 2–4 days, whereas D-dimers decreased and fibrinogen levels increased. Thus, overall platelet counts on V-V ECMO show disease-specific initial dynamics followed by an ongoing consumption by the ECMO device, which is not boosted by new artificial surfaces after a system exchange. *ASAIO Journal* 2025; XX:XX–XX

Key Words: ECMO, platelet, dysfunction, artificial surface, thrombocytopenia, coagulation disorder

Venovenous extracorporeal membrane oxygenation (V-V ECMO) is a rescue-supportive treatment in acute respiratory distress syndrome.[1] Despite improvements in ECMO technology, thrombosis and hemorrhage are common and severe complications.[2–4] Acquired platelet dysfunction[5,6] as well as thrombocytopenia may be responsible and adjusted with transfusion or risk factor modification.[7]

The development of moderate (platelet count <150/nL) and severe thrombocytopenia (platelet count <50/nL) on ECMO is seen with a prevalence of up to 24%[7–9] and 6.3–26.6%,[10–13] respectively. Possible causes for a decrease in platelet count are the patient's primary disease, toxic drug effects, type of anticoagulation, and foreign surfaces/shear forces of the ECMO system.[8,9]

The aim was to compare platelet kinetics after ECMO start and after system exchange in different etiologies of acute lung failure and different ECMO types to evaluate the impact of different diseases and different naive artificial surfaces/blood pumps at initiation and during ongoing ECMO therapy. To exclude any influencing factors (such as early death and early exchanges), only patients with long and exchange-free runs were included at both time points.

Materials and Methods

Study Design

This is a retrospective single-center analysis on prospectively collected data (Regensburg ECMO Registry, January 2010 to February 2022) from consecutive adult patients that required V-V ECMO (n = 520, Figure 1) because of bacterial, viral, and coronavirus disease 2019 (COVID-19) pneumonia at the university hospital of Regensburg, Germany. For etiologies

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Submitted for consideration June 2024; accepted for publication in revised from January 2025.

Disclosure: The authors have no conflicts of interest to report.

The authors are participants of the Priority Program (Toward an Implantable Lung) (SPP 2014) funded by the German Research Foundation (DFG), Project No. 447721607.

K.L. designed the concept, analyzed the data, and prepared the manuscript. A.P., L.K., M.G. contributed to the study design, interpretation of data, and critically revised the manuscript. K.-A.H. checked statistical statements and revised the manuscript. T.M. introduced clinical aspects and did critical revision of the manuscript. M.L. designed the concept, supervised the study, and critically revised the manuscript.

Respective data are included in the article or the Supplemental Digital Content, http://links.lww.com/ASAIO/B405, and further inquiries for this study can be directed to the corresponding author.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML and PDF versions of this article on the journal's Web site (www.asaiojournal.com).

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DOI: 10.1097/MAT.0000000000002383

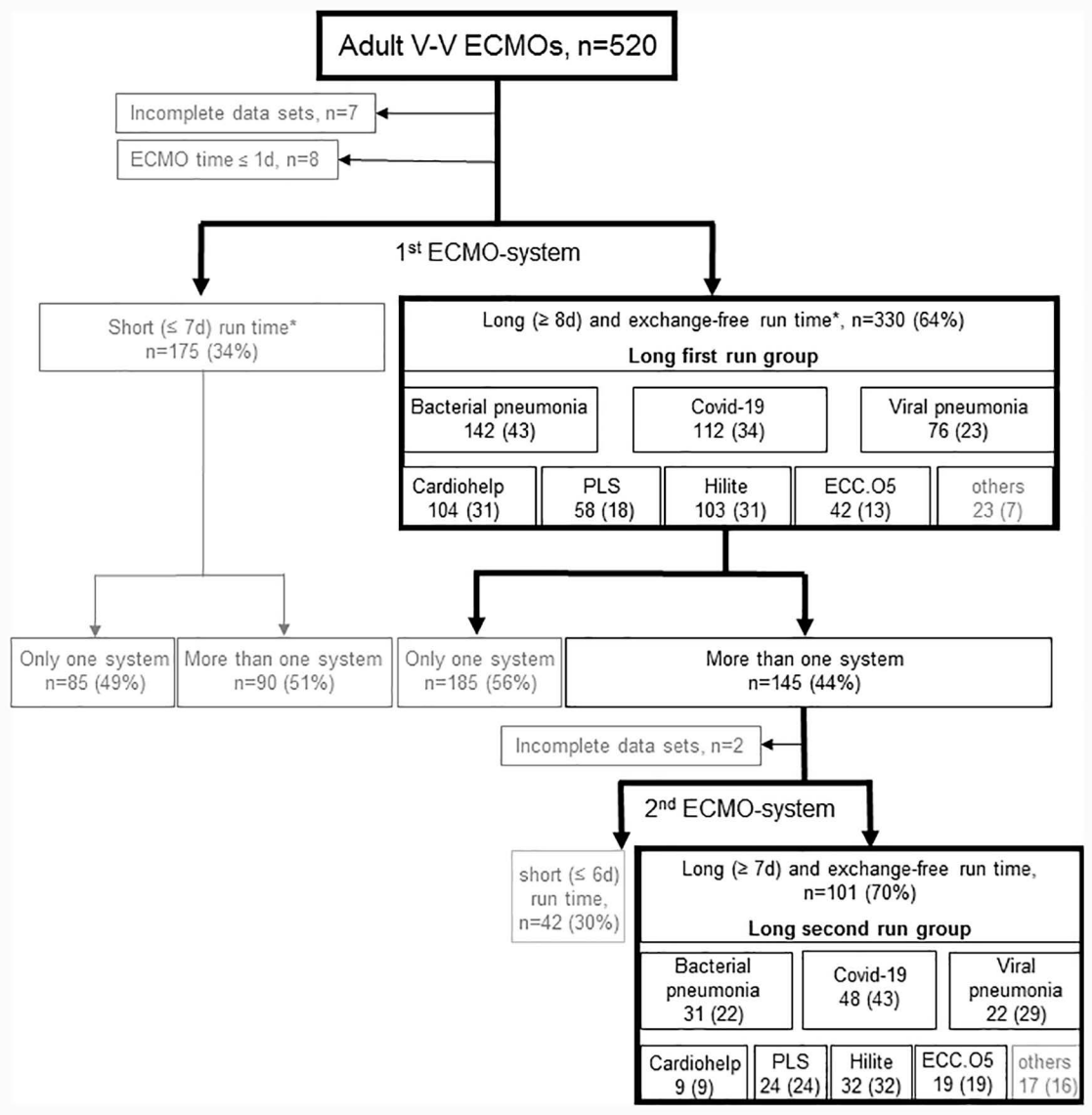

Figure 1. Flowchart of the study patients. Patients with incomplete datasets of platelet counts after ECMO start, ECMO time ≤1 day, and short run times of the first ECMO system (≤7 days) were excluded. The "long-first-run group" included patients with long (≥8 days) and exchange-free first runs. *Run times were defined as the time of the first system until the exchange or end of therapy. The long-first-run group was subdivided into patients with only one ECMO system (excluded) and with more than one system (n = 145). The "long-second-run group" included all patients that required a second ECMO system with long (≥7 days) and exchange-free runs (time from the day of exchange to the end of therapy or exchange of the second system). Both study groups regarded the underlying disease (bacterial, viral, and COVID-19 pneumonia) and different first ECMO systems (Cardiohelp; PLS; HiliteLT7000; ECC.O5 [see Table S1, Supplemental Digital Content, http://links.lww.com/ASAIO/B406]; other systems: iLA [Novalung, Heilbronn, Germany], Nautilus oxygenators [Medtronic, Minneapolis, MN], Paragon oxygenators [Chalice Medical, Nottinghamshire, UK], PALP [Maquet]). Data are shown as n (%). COVID-19, coronavirus disease 2019; iLA, interventional lung assist; PALP, pump-assisted lung protection; V-V ECMO, venovenous extracorporeal membrane oxygenation.

of the underlying pneumonias and treatment strategies, see Supplemental Digital Content, http://links.lww.com/ASAIO/B405.

At ECMO start, only patients with long (≥8 days) and exchange-free first ECMO runs (n = 330) were included (long-first-run group) to eliminate other influencing factors (early death and early exchange). Patients with incomplete data sets (n = 7), ECMO run times ≤1 day (n = 8), and ECMO runs ≤7 days (n = 175) were excluded.

A subpopulation of the long-first-run group, patients requiring a system exchange with a long and exchange-free second ECMO-system run (≥7 days, n = 101) (long-second-run group) was analyzed analogously.

Both study groups were subdivided according to underlying disease and ECMO systems used.

Extracorporeal Membrane Oxygenation Management

Extracorporeal membrane oxygenation management, indications, and limitations have been described previously.[9,14,15] Anticoagulation, renal replacement therapy (RRT), blood flow, and ventilator policies were described in detail in the

Supplemental Digital Content, http://links.lww.com/ASAIO/B405.

The ECMO systems included Cardiohelp HLS and PLS (Getinge/Maquet, Rastatt, Germany), DP3 system (Fresenius/Xenios, Heilbronn, Germany), Life-Box (SorinGroup/LivaNova, Milan, Italy), and others (Figure 1, see Table S1, Supplemental Digital Content, http://links.lww.com/ASAIO/B406). To show the effect of ECMO-system pressures, pump speed, and recirculation of our commonly used ECMO flows and cannula configuration on platelet counts, 90 patients with a Cardiohelp were analyzed accordingly (see Supplemental Digital Content, http://links.lww.com/ASAIO/B405).

Exchange Reasons

Reasons for a system exchange included acute clot formation (acute oxygenator or pump head thrombosis), elective reasons (technical-induced coagulation disorder; coagulation disorder/hypofibrinogenemia; worsened gas transfer), suspected infection and mechanical failure[16–22] (for details, see Supplemental Digital Content, http://links.lww.com/ASAIO/B405).

Data Collection and Statistical Analysis

Data were acquired from the Regensburg ECMO Registry. Data are median (IQR, interquartile range) or n (%). Laboratory parameters included daily measurements of the displayed parameters. Procalcitonin (PCT) and interleukins (IL-6, IL-8) were determined before, on day 1 and every 5 days after ECMO start. Thrombocytopenia was classified as severe (platelet counts ≤50/nl) and moderate (platelet counts 49–149/nl).

Patient data were pseudonymized. The study was approved by the ethics committee of the University of Regensburg (#20-2051-104). Statistical analysis was done using SigmaStat 3.5 (SYSTAT Software, San Jose, CA); for details on the used tests, see Supplemental Digital Content, http://links.lww.com/ASAIO/B405.

Results

Dynamics of Platelet Counts After Extracorporeal Membrane Oxygenation Initiation

To rule out selection bias, patients who required V-V ECMO were subdivided into a group with short (≤7 days) and a group with long (≥8 days) (exchange-free) first runs (Figure 1). Patient characteristics were comparable, except for a clinically irrelevant higher arterial pH (apH) and international normalized ratio (INR), a higher proportion of patients with COVID-19, significantly longer run times of the first ECMO system and total ECMO times for the long-first-run group (see Table S2, Supplemental Digital Content, http://links.lww.com/ASAIO/B407 and see Table S3, Supplemental Digital Content, http://links.lww.com/ASAIO/B408).

After ECMO start, platelet counts in both groups decreased significantly from disease-specific levels. Between short and long-first-run groups, platelet counts/dynamics were comparable and patients with COVID-19 presented significantly higher levels compared with the other disease groups (see Figures S1A and S2A, Supplemental Digital Content, http://links.lww.com/ASAIO/B405). Below, only data of the long-first-run group were analyzed.

Patient Characteristics and Extracorporeal Membrane Oxygenation Data of the Long-First-Run Group

Before ECMO start (Table 1), the COVID-19 group had a lower sequential organ failure assessment (SOFA) score ($p < 0.001$) and required less RRT ($p = 0.004$) compared with bacterial and viral pneumonia groups. There were no differences in age, body mass index, lung injury score, anticoagulation, and baseline ventilation data (except for $PaCO_2$, apH) of the disease groups. However, the viral pneumonia group included more females ($p = 0.013$). Patients with COVID-19 presented lower levels of C-reactive protein (CRP), IL-6, IL-8, and PCT. Lactate dehydrogenase (LDH) levels were significantly lower in the bacterial pneumonia group ($p < 0.001$). There were no clinically relevant differences in the initial coagulation status of the disease groups.

The initial platelet count was lowest in the viral pneumonia (164 [108–221]/nL) and highest in the COVID-19 (273 [207–384]/nL) and bacterial pneumonia (221 [142–312]/nL) groups ($p < 0.001$). The frequency of patients with severe thrombocytopenia in all disease groups was less than 5%. Moderate thrombocytopenia was seen in 8%, 25%, and 37% of patients with COVID-19, bacterial, and viral pneumonia, respectively ($p < 0.001$).

The high proportion of Cardiohelp systems (43%, $p < 0.001$) (Table 2) in the COVID-19 group is because of the higher interhospital transportation rate (67%, $p = 0.014$). Patients with COVID-19 were predominantly supported with single-lumen cannulas (98%, $p < 0.001$) and slightly bigger cannulas because of the desired blood flow (see Table S4, Supplemental Digital Content, http://links.lww.com/ASAIO/B409).

The amount of technical-induced complications (see Table S5, Supplemental Digital Content, http://links.lww.com/ASAIO/B410) that required a system exchange and the total amount of oxygenators per patient were similar between the disease groups (Table 2). Run times of >12 days of the first system were more often in the COVID-19 group (66%, $p < 0.001$) accompanied by significantly longer total ECMO times (24 [16–39] days) compared with the bacterial (14 [10–22] days) and viral pneumonia (15 [11–23] days) groups ($p < 0.001$). The run times of the second ECMO systems were also longer in the COVID-19 group compared with the bacterial pneumonia group ($p = 0.002$).

One-third of the patients (109/330) required RRT. On trend, more patients in the bacterial pneumonia group required RRT before and during ECMO support compared with viral pneumonia and COVID-19 groups (Table 2). Transfusion requirements, successful weaning, and in-hospital mortality were similar between disease groups. However, the two latter were numerically worse in patients with COVID-19.

Platelets, Coagulation, and Inflammation of the Long-First-Run Group

Within the first week of ECMO therapy, there was a varying decrease in platelets from disease-specific levels pre-ECMO to a common level of all patients irrespective of the underlying disease of around 150/nL platelets (Figure 2A). Although none of the patients with COVID-19 presented a severe thrombocytopenia within 5 days, the prevalence was significantly higher for bacterial (11%) and viral (8%) pneumonia

Table 1. Patient Characteristics Before Long and Exchange-Free First ECMO Runs Stratified by the Underlying Disease (Long-First-Run Group)

Parameter	Bacterial Pneumonia	COVID-19	Viral Pneumonia	*p* Value
N	142	112	76	
Female, n (%)	40 (28)	25 (22)	32 (42)	0.013*
Age (years)	56 (47–63)	55 (48–62)	53 (45–59)	0.132
BMI (kg/m^2)	27.8 (23.9–31.2)	29.0 (26.0–32.9)	28.0 (24.3–32.9)	0.091
SOFA score	12 (9–14)†	9 (9–12)	13 (10–15)‡	<0.001
LIS	3.3 (3.0–3.7)	3.3 (3.3–3.7)	3.3 (3.3–3.7)	0.234
RRT, n (%)	18 (13)	4 (4)	14 (18)	0.004*
Anticoagulation, H/A/E n (%)	118/23/1 (83/16/1)	87/21/4 (78/19/3)	64/11/1 (84/14/1)	0.432*
Minute ventilation (L/min)	11 (8–13)	10 (8–12)	11 (9–12)	0.945
PEEP (cm H_2O)	15 (11–16)	15 (13–16)	15 (14–17)	0.083
PIP (cm H_2O)	33 (30–36)	32 (30–35)	35 (30–37)	0.109
PaO_2/FiO_2 (mm Hg)	72 (59–88)	68 (57–84)	67 (57–84)	0.287
$PaCO_2$ (mm Hg)	71 (55–88)	62 (53–75)	61 (49–77)§	0.022
apH	7.23 (7.14–7.31)†	7.30 (7.22–7.36)	7.26 (7.18–7.34)	<0.001
CRP (mg/L)	166 (61–275)	133 (35–210)	184 (73–280)	0.046
IL-6 (pg/mL)	174 (49–2539)†	92 (58–445)	488 (102–1939)‡	0.001
IL-8 (pg/mL)	76 (33–189)†	55 (32–90)	134 (54–361)‡§	<0.001
PCT (µg/L)	2.8 (1.0–17.5)†	0.6 (0.3–1.2)	2.5 (0.9–10.3)‡	<0.001
LDH (U/L)	370 (275–561)†	443 (339–642)	563 (343–930)§	<0.001
INR	1.2 (1.0–1.3)†	1.1 (1.0–1.2)	1.0 (1.0–1.2)§	<0.001
aPTT (seconds)	40 (34–52)	37 (32–46)	39 (34–57)	0.070
ATIII (%)	70 (50–81)†	76 (66–87)	68 (55–85)‡	<0.001
D-dimers (mg/L)	5 (2–12)	4 (2–9)	5 (3–9)	0.540
Fibrinogen (mg/dL)	598 (462–755)	593 (463–693)	481 (399–619)‡§	<0.001
Platelets (/nL)	221 (142–312)†	273 (207–384)	164 (108–221)‡§	<0.001
Thrombocytopenia: pre, ≤50/51–149/≥150, n (%)	6/36/100 (5/25/70)	0/9/103 (0/8/92)	3/28/45 (4/37/59)	<0.001*
1 day, ≤50/51–149/≥150, n (%)	8/55/79 (5/39/56)	1/18/93 (1/16/83)	8/40/28 (10/53/37)	<0.001*
5 days, ≤50/51–149/≥150, n (%)	16/56/70 (11/39/49)	0/29/83 (0/26/74)	6/37/33 (8/49/43)	<0.001*

Data are median (interquartile range) and n (%). Thrombocytopenia was subdivided into severe (≤50/nL), moderate (51–149/nL), normal (≥150/nL). Statistic used χ^2 Test and one-way ANOVA (analysis of variance) with pairwise comparison .

*χ^2 Test.

†Bacterial pneumonia *vs.* COVID-19 ($p < 0.05$).

‡Viral pneumonia *vs.* COVID-19 ($p < 0.05$).

§Bacterial pneumonia *vs.* viral pneumonia ($p < 0.05$).

apH, arterial pH; aPTT, activated partial thromboplastin time; ATIII, antithrombin III; BMI, body mass index; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; H/A/E, heparin/argatroban/enoxaparin; IL-6, interleukin-6; IL-8, interleukin-8; INR, international normalized ratio; LDH, lactate dehydrogenase; LIS, Murray lung injury score; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2/FiO_2, ratio of partial pressure of arterial oxygen and fraction of inspired oxygen; PCT, procalcitonin; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; RRT, renal replacement therapy before ECMO; SOFA, sequential organ failure assessment.

(Table 1). Although all groups showed a significant platelet decline within 24 hours after ECMO start (bacterial, −18%; COVID-19, −10%; viral, −15%; $p = 0003$), in the viral pneumonia group there was no further decrease from day 1 to 8. The platelet decline was prolonged in the bacterial pneumonia and COVID-19 groups. From days 2 and 4, there were no significant changes in the bacterial pneumonia and COVID-19 groups, respectively. Moderate thrombocytopenia was seen in 39%, 53%, and 16% of the patients in the bacterial, viral pneumonia, and COVID-19 groups, respectively ($p < 0.001$).

Decreased platelet counts were accompanied by a significant increase of D-dimer levels within 4 days (all groups), a significant decrease of fibrinogen levels within 1 (bacterial pneumonia), 2 (COVID-19), and 3 days (viral pneumonia), and a significant increase of antithrombin III (ATIII) within 2 (bacterial pneumonia and COVID-19) and 3 days (viral pneumonia) after ECMO start (Figure 3A, B, and D). International normalized ratio remained unchanged (Figure 3C). Disease-dependent differences were only observed for fibrinogen (day 0–2), ATIII (day 0–4), and INR (day 0–3) (Figure 3A–D). Median free plasma hemoglobin levels were below a critical level of 100 mg/L in all disease groups (Figure 3E). All over the observation period, blood flow was highest in the COVID-19 group with a significant reduction within 4–8 days (Figure 3H).

Despite a higher proportion of females in the viral pneumonia group, platelet counts decreased significantly within 1 day on ECMO independent of body mass index (BMI) (Table 1) and sex in the different disease groups (see Figure S2, Supplemental Digital Content, http://links.lww.com/ASAIO/B405). Platelet kinetics after ECMO start were independent of the type of initial anticoagulation (see Figure S3, Supplemental Digital Content, http://links.lww.com/ASAIO/B405). No data are available on the fluid balance of the different groups. Therefore, we included hemoglobin and albumin data. Independent of the disease groups, hemoglobin levels decreased significantly within 1 day on ECMO and remained unchanged within the next 7 days. Albumin levels depended on the underlying disease but initial levels remained unchanged over time (see Figure S4, Supplemental Digital Content, http://links.lww.com/ASAIO/B405).

The dynamics of our blood flow policy and cannulation strategy on blood trauma, platelet counts, and recirculation were analyzed in 90 patients with a Cardiohelp system (see Figure S5, Supplemental Digital Content, http://links.lww.com/

Table 2. Data During and After ECMO Support of Long-First-Run Group Patients Stratified by the Underlying Disease

Parameter	Bacterial Pneumonia	COVID-19	Viral Pneumonia	*p* Value
N	142	112	76	
Oxygenators/patient [min–max]	1 (1–2) [1–7]	1.5 (1–2) [1–5]	1 (1–2) [1–12]	0.135
Blood pumps, n (%)				0.011*
Cardiohelp	36 (25)	48 (43)	21 (28)	
Rotaflow	31 (22)	24 (21)	21 (28)	
DP3	48 (34)	34 (30)	23 (30)	
Dideco	27 (19)	6 (5)	11 (14)	
First oxygenator model, n (%)				<0.001*
Cardiohelp	35 (25)	48 (43)	21 (28)	
PLS	30 (21)	9 (8)	19 (25)	
Hilite 7000LT	47 (33)	34 (30)	22 (29)	
ECC.O5	27 (19)	4 (3)	11 (14)	
Other	3 (2)	17 (15)	3 (4)	
Total ECMO time (days)	14 (10–22)#	24 (16–39)	15 (11–23)*	<0.001
Run time of first ECMO system†, range, n (%)				<0.001*
8–12 days	85 (60)	38 (34)	46 (61)	
>12 days	57 (40)	74 (66)	30 (39)	
Run time of first ECMO system† (days), n = 330	11 (9–15)‡	16 (11–24)	11 (10–15)§	<0.001
Patients with exchanges¶, n (%)	55 (39)	56 (50)	34 (45)	0.197*
Run time of second ECMO system‖ (days)	8 (5–12)‡	11 (7–19)	9 (5–14)	0.002
Patients with long second ECMO system#, n (%)	31 (22)	48 (43)	22 (29)	0.001*
Run time of long second ECMO system# (days), n = 101	10 (8–13)	12 (9–21)	11 (9–19)	0.170
Thrombocytopenia				
ex**, ≤50/51–149/≥150, n (%)	3/22/6 (10/71/19)	4/28/16 (8/58/33)	6/9/7 (27/41/32)	0.094
1 day ex**, ≤50/51–149/≥150, n (%)	4/21/6 (13/68/19)	2/29/17 (4/60/35)	6/9/7 (27/41/32)	0.038
5 days ex**, ≤50/51–149/≥150, n (%)	4/19/8 (13/61/26)	2/20/26 (4/42/54)	4/8/10 (18/36/45)	0.059
RBC per day	0.26 (0.08–0.50)	0.14 (0.06–0.33)	0.23 (0.00–0.44)	0.170
FFP per day	0.00 (0.00–0.03)	0.00 (0.00–0.12)	0.00 (0.00–0.00)	0.134
PC per day	0.00 (0.00–0.00)	0.00(0.00–0.00)	0.00 (0.00–0.00)	0.423
RRT, n (%)	56 (38)	21 (19)	32 (42)	<0.001*
Successful weaning, n (%)	109 (78)	74 (67)	58 (76)	0.195
In-hospital mortality, n (%)	44 (31)	46 (41)	23 (30)	0.245

Data are median (IQR) or n (%). Listed blood pumps and oxygenator models identified the ECMO systems that were implanted at ECMO start. Statistic used χ^2 Test and one-way ANOVA (analysis of variance) with pairwise comparison.

*χ^2 Test.

‡Bacterial pneumonia *vs.* COVID-19 ($p < 0.05$).

§Viral pneumonia *vs.* COVID-19 ($p < 0.05$). ‡ and § stand for the statistical comparison, while†, ‖, ¶, # defined time ranges or patient groups** stands for the definition of thrombocytopenie grouping.

†Run time of first ECMO-system included run time after ECMO start to end of therapy or to the first exchange.¶Patients with exchanges included all patients that required at least one ECMO-system exchange.

‖Run time of the second ECMO system included run times after first exchange to end of therapy or to second exchange.

#Patients with long runs of the second ECMO system included all patients with run times of the second ECMO system of ≥7 days (n = 101).

**Thrombocytopenia was subdivided into severe (≤50/nL), moderate (51–149/nL), normal (≥150/nL) after implantation of the second ECMO system.

COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; ex, exchanged; FFP, fresh frozen plasma (1 FFP contains 230 ml plasma); IQR, interquartile range; RBC, red blood cells; PC, platelet concentrate (1 PC contains 250 ml and 2–4 × 10^{11} platelets); RRT, renal replacement therapy.

ASAIO/B405). There was no evidence of a significant recirculation (central venous oxygen saturation, <75%; mean inlet partial pressure of carbon dioxide, 50 mm Hg) or blood trauma as the negative inlet pressures usually were more than −40 mm Hg and the return postoxygenator pressures were less than 120 mm Hg.

Effect of Extracorporeal Membrane Oxygenation Type on Platelet Dynamics of the Long-First-Run Group

Independent of the ECMO type, platelet count significantly decreased within 1 day after ECMO start ($p < 0.001$) but was not different between ECMO types (Figure 4C) and not associated with differences in pump speed (Figure 4A) or blood flow (Figure 4B).

Patient Characteristics and Exchange Reasons of the Long-Second-Run Group

The frequency of system exchanges was highest in the COVID-19 (48%) and lowest in the viral pneumonia group (22%) (see Table S5, Supplemental Digital Content, http://links.lww.com/ASAIO/B410). There was a higher proportion of acute oxygenator thrombosis in the bacterial pneumonia group (19%) compared with COVID-19 (4%) and viral pneumonia (9%). In the COVID-19 group coagulation disorder/hypofibrinogenemia dominated as exchange reason (44%) compared with bacterial (19%) and viral (14%) pneumonia. Acute events occurred most frequently in the bacterial pneumonia (42%) compared with the COVID-19 (21%) and viral (18%) pneumonia groups.

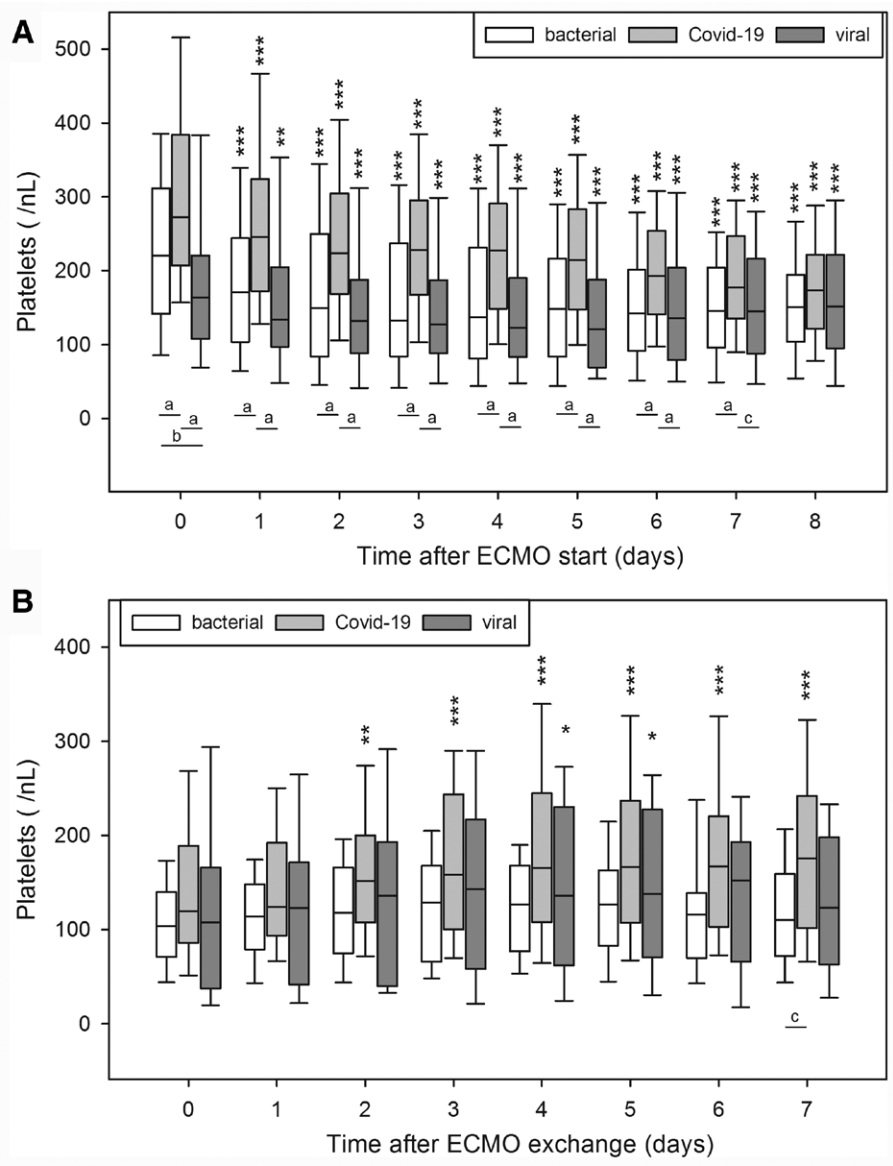

Figure 2. Dynamics of platelet counts of patients from the long-first-run group (**A**) and the long-second-run group (**B**) stratified by the underlying disease. **A**: Time line of platelet count within 8 days after ECMO start. The decline was significant for patients with bacterial (n = 142), viral (n = 76), and COVID-19 (n = 112) pneumonia (each, $p < 0.001$). Patients with COVID-19 presented the highest platelet counts until day 7 after ECMO start. **B**: Time line of platelet count within 7 days after ECMO exchange. Although platelet count remained unchanged in the bacterial pneumonia group (n = 31), platelet count increased significantly in the COVID-19 group (n = 48) (within 2 days, $p < 0.01$) and in the viral pneumonia group (n = 22) (within 4 days, $p < 0.05$). There were no differences in the platelet count comparing the disease groups. Boxes are median, IQRs, minimum and maximum values. Statistics: two-way ANOVA for time lines compared with data before ECMO or at the exchange day (day 0) (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$); one-way ANOVA for comparison at respective time points (a: $p < 0.001$; b: $p < 0.01$; c: $p < 0.05$). ANOVA, analysis of variance; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range.

Platelets, Coagulation, and Inflammation of the Long-Second-Run Group

The first system (n = 101) was exchanged after median run times of 10 (10–16) days (bacterial pneumonia), 15 (10–24) days (COVID-19), and 12 (9–20) days (viral pneumonia) ($p = 0.083$). In contrast to ECMO initiation, on the day of exchange and immediately thereafter, there was no difference in platelet counts between disease groups (bacterial, 104 [71–140]/nL; COVID-19, 120 [86–189]/nL; viral, 108 [38–166]/nL). Although platelet counts remained at the level of the exchange day in the bacterial pneumonia group, there was a significant increase in the COVID-19 ($p < 0.001$) and viral pneumonia groups ($p = 0.002$) within 2 and 4 days after system exchange, respectively (Figure 2B).

The frequency of severe thrombocytopenia on the day of exchange (11%) was comparable to day 5 after ECMO start (10%) in the bacterial pneumonia group, although severe thrombocytopenia increased in the COVID-19 (0–8%) and viral pneumonia (8–27%) groups. Within 5 days, the proportion of patients with normal platelet counts increased in all groups (Table 2).

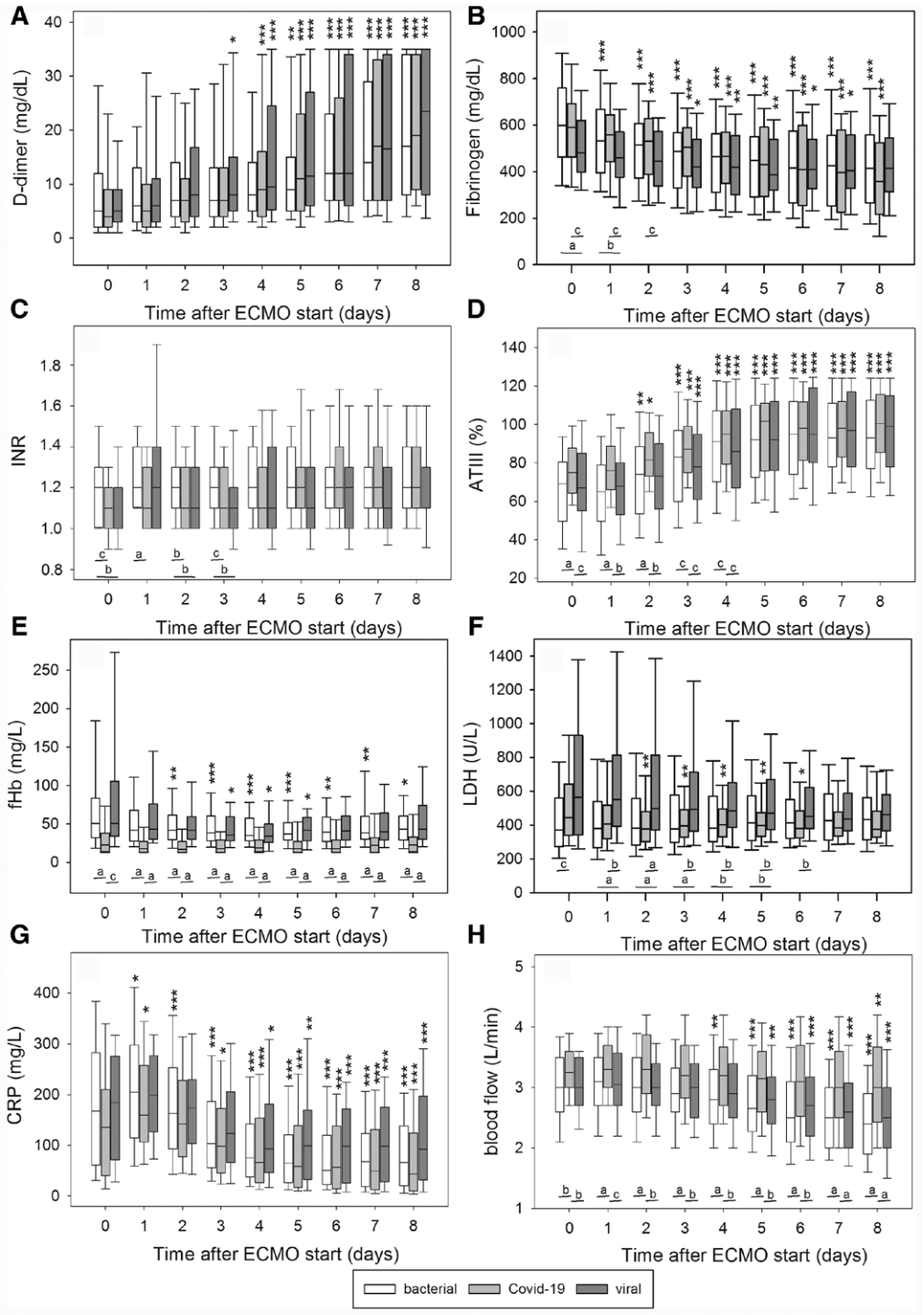

Figure 3. Dynamics of D-dimers (A), fibrinogen (B), INR (C), ATIII (D), fHb) (E), LDH) (F), CRP, (G) and blood flow (H) from the long-first-run group stratified by the underlying disease. Time line of respective parameters within 8 days after ECMO start of patients with bacterial, viral, and COVID-19 pneumonia. Increase of D-dimers was significant (each, $p < 0.001$). Decline of fibrinogen was significant for bacterial and COVID-19 (each, $p < 0.001$) and viral ($p = 0.002$) pneumonia. INR remained unchanged. Increase of ATIII was significant (each, $p < 0.001$). Decline of fHb was significant for bacterial and viral ($p < 0.001$, $p = 0.004$) but not for COVID-19 pneumonia. fHb from COVID-19 were significantly lower compared with bacterial and viral pneumonia. Decline of LDH was significant only for COVID-19 ($p < 0.001$). LDH from viral pneumonia was significantly higher compared with bacterial and COVID-19 pneumonia. Alterations in CRP were significant (each, $p < 0.001$). Independent of the underlying disease, blood flow was reduced within 4–5 days (each, $p < 0.001$). Patients with COVID-19 require significantly higher blood flow rates. Boxes are median, IQRs, minimum and maximum values. Statistics: two-way ANOVA for time lines compared with data before ECMO (day 0) (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$); one-way ANOVA for comparison at respective time points (a: $p < 0.001$; b: $p < 0.01$; c: $p < 0.05$). ANOVA, analysis of variance; ATIII, antithrombin III; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; fHb, free hemoglobin; INR, international normalized ratio; IQR, interquartile range; LDH, lactate dehydrogenase.

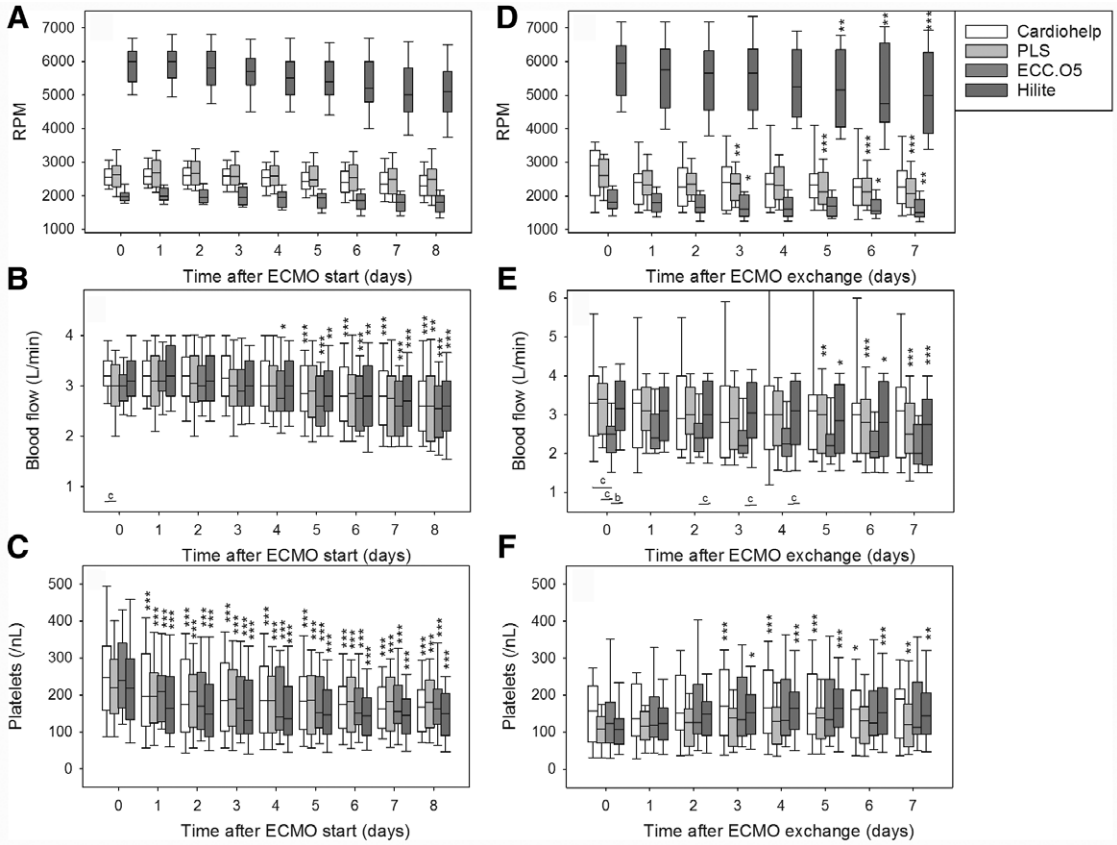

Figure 4. Dynamics of pump speed, blood flow, (B, E) and platelet count (C, F) of the long-first-run group (n = 330) (**A–C**) and of the long-second-run group (n = 101) (**D–F**) of different ECMO systems. (**A, D**) Pump speed (RPM) was highest for the DP3 of the Hilite system and lowest for the revolution of the ECC.O5 system. **A**: Pump speed remained unchanged until day 5 after ECMO start and decreased thereafter. **D**: Pump speed remained unchanged until day 3–6 after the ECMO exchange and decreased thereafter. **B**: Blood flow remained unchanged until 4–5 days after ECMO start (independent of ECMO type) and (**E**) until 5–7 days after ECMO exchange. **C**: The decline of platelet counts after ECMO start was independent of ECMO type. **F**: After the exchange, platelet count significantly increased for the Cardiohelp and Hilite systems ($p < 0.001$, $p < 0.05$) or remained unchanged (PLS and ECC.O5). There were no differences between ECMO systems at individual time points. Boxes are median, IQRs, minimum and maximum values. Statistics: two-way ANOVA for time lines compared with data before ECMO or at the exchange day (day 0) (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$); one-way ANOVA for comparison at respective time points (a: $p < 0.001$; b: $p < 0.01$; c: $p < 0.05$). ANOVA, analysis of variance; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; RPM, rounds per minute.

In all disease groups, D-dimer levels decreased significantly within 1 day after exchange (Figure 5A). Three days after exchange, D-dimers showed the lowest values in all groups. From day 3 to day 7 after exchange, in the COVID-19 and bacterial pneumonia groups D-dimers significantly increased again. Independent of the disease group, fibrinogen levels, INR, ATIII, and free hemoglobin remained unchanged (Figure 5B–G). Patients with COVID-19 had higher blood flow rates on the day of exchange (Figure 5H). Within the next 1 day, blood flow was significantly reduced in all disease groups because of respiratory improvement.

Effect of Extracorporeal Membrane Oxygenation Type on Platelet Counts of the Long-Second-Run Group

After a system exchange, platelet counts increased or remained unchanged for the next 7 days independent of the ECMO system (Figure 4F). Pump speed and blood flow of all systems remained unchanged until 3 to 5 days and decreased subsequently (Figure 4D and E).

Discussion

This study compares the response of the plasmatic and cellular coagulation system to naive artificial surfaces of different ECMO systems at start and during ongoing V-V ECMO therapy. It is shown for the first time that the initial exposure of blood to a new artificial surface of an ECMO system resulted in a significant drop of platelet counts starting from different disease-specific pre-ECMO levels to a lower disease-independent platelet level within 1 week. The resultant steady state might indicate a balance between the production and consumption of platelets. The renewed contact of these circulating platelets with a new second artificial surface after an ECMO-system exchange did not lead to a further drop in platelets but platelets rather remained at the existing steady-state level or even slightly increased. The initial response is driven by the foreign surface of the ECMO system as well as by the effect of the blood pump, but the response after a system exchange happened under similar blood flows and might therefore be caused by a changed platelet function during

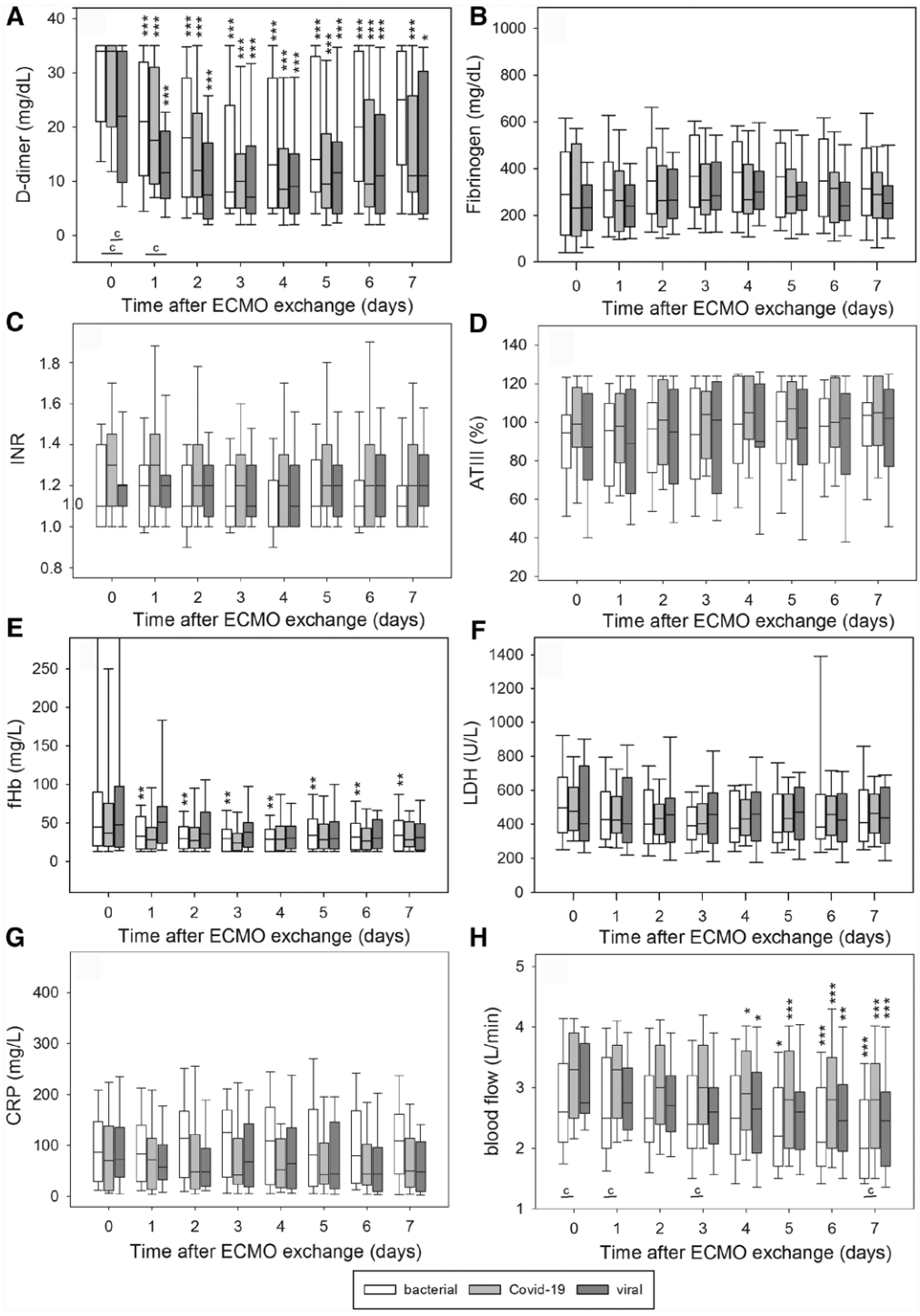

Figure 5. Dynamics of D-dimers (A), fibrinogen (B), INR (C), ATIII (D), fHb) (E), LDH) (F), CRP, (G) and blood flow (H) from the long-second-run group (n = 101) stratified by the underlying disease. The levels of D-dimers decreased significantly (each, $p < 0.001$) within 24 hours after the exchange, reached a minimum after 3–4 days, and tended to increase subsequently. At the day and one day after exchange, D-dimers from the viral group were significantly lower compared with the bacterial and COVID-19 groups (each, $p < 0.05$). The levels of fibrinogen, INR, and ATIII activity remained constant until 7 days after exchange. fHb decreased significantly only in the bacterial group ($p < 0.001$). LDH and CRP remained unchanged until day 7 without disease-specific differences. Blood flow was reduced within 4–5 days after exchange (each, $p < 0.001$). Patients with COVID-19 had significantly higher blood flow rates. Boxes are median, IQRs, minimum and maximum values. Statistics: two-way ANOVA for time lines compared with data at the exchange day (day 0) (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$); one-way ANOVA for comparison at respective time points (a: $p < 0.001$; b: $p < 0.01$; c: $p < 0.05$). ANOVA, analysis of variance; ATIII, antithrombin III; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; fHb, free hemoglobin; INR, international normalized ratio; IQR, interquartile range; LDH, lactate dehydrogenase.

ECMO. Furthermore, these findings were independent of the used ECMO system.

Previous ECMO studies did not distinguish between the etiologies of respiratory failure.[23] Appropriate subgroup analyses failed until the COVID-19 pandemic.[24,25] Other studies confirmed our data of lower SOFA scores, a lower proportion of females,[4,26] and higher initial levels of fibrinogen, ATIII, and platelet counts[27] in patients with COVID-19.

Contact of blood with artificial surfaces of the ECMO circuit and high shear stress on the blood from the pumps is common to all patients with ECMO. A consequence is the development of coagulation disorder, which necessitates a system exchange in 30–50% of ECMO runs.[17,18] Platelets are essential in this process.[8] Within 1 day on ECMO, 21% of the patients presented a thrombocytopenia and almost all patients developed a platelet dysfunction.[8]

At the ECMO start, we saw a clear influence of the underlying disease on plasmatic coagulation and platelet count. The patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) showed the least inflammatory response and the least limitations in coagulation and platelet count, whereas the other entities did not differ clinically relevant.

Within the first week of ECMO therapy, there was a varying decrease in platelets to a common level (150/nl) irrespective of the underlying disease. A drop with subsequent "steady state" concentration was also determined in a non-COVID-19 group but at a lower level (<150/nl).[7] The development of a severe thrombocytopenia in our patient groups depended on the primary disease. Although none of the patients with COVID-19 presented severe thrombocytopenia within 5 days, the prevalence was significantly higher for the other etiologies (bacterial pneumonia, 11% and viral pneumonia, 8%) and is in the same range as described in the literature (6.3–26.6%).[8]

The kinetics of platelet decline depended also on the primary disease. Although all groups showed a significant decrease within the first 24 hours after ECMO start, in the viral pneumonia group, there was no further decrease from day 1 to 8. However, the median value of this group was already around 170/nl before ECMO. The decline was prolonged in the bacterial pneumonia and COVID-19 groups. From day 4, there were no significant changes in the COVID-19 group, which is in line with the findings from Kalbhenn *et al.*[28] Kohs *et al.*[7] showed prolonged platelet kinetics of patients with non-COVID ECMO.

Furthermore, there was activation of coagulation with an increase of D-dimers, a decrease of fibrinogen, but an increase of ATIII. There were no differences in hemolysis or inflammatory parameters, as a possible further trigger of coagulation activation and the changes seen were independent of oxygenator and pump type. Similar activation of coagulation after ECMO implantation was also found in a randomized study with no differences in the ECMO systems used.[9] Only pumpless interventional lung assist (iLA) systems averted a platelet loss.[29] We concluded for the first phase of ECMO therapy with regard to platelets that, starting from a different level depending on the underlying disease, a new steady state with regard to thrombopoiesis and platelet consumption was reached during ongoing ECMO therapy. Therefore, this reaction is driven by the combined effect of the blood pump and the artificial surface of the ECMO circuit.

Other reasons for differences in platelet decline may be differences in cell mass according to body mass and sex. However, despite a higher proportion of females in the viral pneumonia group, the kinetics and absolute platelet counts were comparable. Differences in fluid balance could be another reason for a differing platelet decline. Respective data failed in our database. As the only surrogate markers, hemoglobin and albumin levels in the different disease groups over time suggest that there should be no clinically relevant difference in fluid balance. The anticoagulant had no effect on platelet counts and kinetics.

The connection to a new ECMO system—equivalent to a new virginal artificial surface—in the bloodstream during ongoing ECMO therapy showed a different response of the coagulation system. There were neither differences in inflammatory, coagulation, and hemolysis parameters nor blood flows comparing the disease groups and trajectories reflected successful treatment of the underlying disease. The steady-state level of the platelet count on day 8 after ECMO start maintained up to the day of exchange. However, the prevalence of moderate thrombocytopenia increased in all study groups but especially in the COVID-19 group (day 5 on ECMO, 26%; day of exchange, 67%). On the same blood flow, the introduction of a new artificial surface caused by the system exchange did not cause a further decrease in platelet counts which is in contrast to results of in vitro studies. Platelets remained unchanged (bacterial pneumonia) or even increased significantly (COVID-19 and viral pneumonia). Within 4 days after exchange, there was a moderate increase in platelets, a dramatic decrease in D-dimers and a slight increase in fibrinogen, reflecting the resolution of ECMO-associated coagulation disorder by ECMO-system exchange. Subsequently, coagulation activation started again: platelet and fibrinogen decreased, D-dimers increased. However, because of the heterogeneity of the data and the low sample size, differences were not statistically significant. The recovery of coagulation parameters after a system exchange was already described.[17,18] However, only a time period of 3 days was assessed with similar results, so that the delayed reactivation of the coagulation could not be shown. Kohs *et al.*[7] also described an increase in platelet count within 12–15 days after ECMO start but without any specification of system exchanges or transfusion events. In the present study, only total transfusion requirements were documented, no statement about the time dependency was possible.

The immediate drop of platelets after ECMO start was often associated with cytolysis, consumption,[30] or platelet dysfunction.[5,6] This included a decrease in the expression of platelet surface markers, the formation of platelet–leukocyte aggregates, and defects of granule secretion.[30–34] Unfortunately, no tests to differentiate between chemical and mechanical activation were performed. Therefore, especially in view of the heterogeneity of the oxygenators and pumps used and the use of RRT, no comment can be made on their contribution to platelet activation and thrombocytopenia. The changes in platelet phenotype and function are retained with therapy progress.[33] This might be responsible for unaltered platelet counts when these cells come in contact to a new oxygenator surface. The reduced platelet adhesion could result from a decrease in platelet fibrinogen receptor expression,[33] which mainly mediates platelet adhesion to surface-bound fibrinogen.[35,36] This would mean that fibrinogen would

again have to be adsorbed on the new surface.[37] However, fibrinogen levels remained unchanged, which could be explained by the large productive capacity of fibrinogen and the rather small amount of fibrinogen attached to the new surface. General consumption because of the improvement in coagulation disorder after system exchange, resolution of the underlying disease, and improvement in liver function caused by the resolution of multiorgan failure must also be considered.

The platelet lifespan in the bloodstream is only 7–10 days.[38] Another reason for the recovery of platelet counts after implantation of a new ECMO system might be the production of platelets from the bone marrow. If a system exchange contributes to a stimulation of the thrombopoiesis or if this is caused mainly by the amelioration of inflammation and its toxic effects on the bone marrow in the course of the underlying disease is not known. Determination of mean platelet volume would be a possibility to quantify the proportion of younger, larger platelets, possibly because of rapid production and release from the bone marrow. However, respective data were not included in our database.

This study has some limitations. It is a single-center retrospective analysis. Patient stratification resulted in small sample sizes. Patient selection could also explain differences as an oxygenator run time of at least 8 days was an important inclusion criterion. However, no clinically relevant differences were found when comparing patients with shorter run times.

In conclusion, platelet counts decreased from disease-specific different levels at ECMO start and declined to a lower disease-independent steady state after 8 days. A system exchange with new naive artificial surfaces did not cause a further decrease in platelet counts. Thus, overall platelet counts on ECMO depend on disease-specific effects especially initially and on an ongoing consumption by the ECMO, which is not aggravated by new artificial surfaces after a system exchange. The effect is independent of the used ECMO system.

Acknowledgments

The authors thank all members of the ECMOcenter for their active support.

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