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Initial V-A ECMO Flow-Index and Its Association With Inflammation, Organ Failure, and Outcomes

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ABSTRACT

Background: Refractory cardiogenic shock remains associated with high mortality despite macrocirculatory stabilization with V-A ECMO. We investigated the association between initial ECMO flow-index, organ dysfunction, inflammatory activation, hemolysis, and clinical outcome.

Methods: In this retrospective single-center study, 553 patients receiving V-A ECMO between 2014 and 2024 were divided into low-flow ($< 1.63 \text{ L/min/m}^2$, $n = 269$) and high-flow ($\geq 1.63 \text{ L/min/m}^2$, $n = 284$) groups. Patients were additionally stratified according to eCPR status. Multivariable logistic regression was used to assess factors associated with multi-organ failure (MOF), and exploratory mediation analyses evaluated day-1 free hemoglobin and IL-6 as potential mediators.

Results: High-flow patients were more hemodynamically compromised, with higher lactate, vasoactive-inotropic support, inflammatory markers, and early hemolysis. After exclusion of cerebral death, MOF occurred more frequently in the high-flow group (32.7% vs. 23.0%, $p = 0.028$). Initial flow-index remained independently associated with MOF in the overall cohort (OR 1.102 per 0.1 L/min/m^2 , 95% CI 1.001–1.214, $p = 0.048$) and in the eCPR subgroup (OR 1.117, 95% CI 1.028–1.214, $p = 0.008$). Day-1 free hemoglobin was independently associated with MOF, and mediation analysis demonstrated a significant indirect effect through early hemolysis. No significant indirect effect through IL-6 was observed. Higher flow index was also associated with worse neurological outcome and reduced survival.

Conclusions: Higher initial V-A ECMO flow-index is associated with greater shock severity and multi-organ failure. Early hemolysis may partly contribute to this association, particularly in eCPR patients. These findings support individualized flow management with close monitoring of hemolysis and evolving organ dysfunction.

1 | Introduction

Refractory cardiogenic shock (rCS) remains a significant challenge, with in-hospital mortality rates ranging from 40% to 90%, depending on the etiology, clinical profile of the patient, and subsequent therapeutic interventions [1]. Despite considerable recent debate about the outcome of ECLS in patients with

rCS [2, 3], this method continues to be widely used in numerous centers [4]. It enables rapid stabilization of hemodynamics and, accordingly, ensures sufficient macrocirculation.

However, the management of patients on VA-ECMO is a complex and nuanced endeavor, given the risk of complications and the potential for adverse outcomes. The available evidence

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indicates that increased ECLS flow rate and concomitant improvements in macrocirculation can be ineffective in mitigating acute brain injury and, in fact, may be associated with its development [5].

Despite providing stable hemodynamics and seemingly adequate perfusion of organs, patients subsequently develop organ failure, which in some cases progresses to multiple organ failure [6]. This phenomenon highlights the need for a more holistic approach to VA-ECMO management, considering not just macrocirculation but also organ-specific effects. Therefore, we analyzed the effect of initial ECMO flow and its influence on the development of organ dysfunction, including multi-organ failure, and patient outcomes.

2 | Materials and Methods

2.1 | Study Design

A retrospective, observational study was initiated to analyze clinical aspects of initial ECLS flow and its influence on end-organs and outcomes. In particular, the stable flow generated during the first day after the ECLS initiation. To assess the flow rate in patients, we used the flow index, namely the VA-ECMO flow divided by the patient's body surface area (BSA). BSA was calculated according to the Mosteller formula.

Postcardiotomy patients and patients with sepsis, as well as patients who needed other temporary MCS (Impella, IABP) devices, were excluded from the study for a more precise assessment of all possible factors, including the cytokines and other inflammatory parameters caused by cardiogenic shock and its sequelae in ECLS patients.

The exploratory analysis was performed, and the normality of the distribution of ECMO flow was confirmed. We divided patients into two groups according to the mean flow-index value of 1.63 L/min/m².

The first group of patients (low flow) had an index of up to 1.629 L/min/m²; the second group of patients (high flow) had an index of 1.630 L/min/m² or more.

The diagnosis of ARDS was determined by the Murray score, which includes an assessment of chest X-ray, hypoxemia, positive end-expiratory pressure, and respiratory system compliance. A total score of more than 2.5 was used to establish the diagnosis of ARDS [7].

Acute renal failure was based on the parameters of the Kidney Disease Improving Global Outcomes (KDIGO) guidelines for AKI, namely Stage 3 of the KDIGO criteria: An increase in serum creatinine > 3 times the baseline, an increase in serum creatinine to > 4.0 mg/dL (353 μmol/L), or the initiation of renal replacement therapy [8].

A combination of a spontaneous increase in the INR above 1.5, a threefold increase in transaminases, and bilirubin exceeding 2.5 mg/dL was considered as acute liver dysfunction [9].

For the summary assessment of inotropic and vasopressor support, a vasoactive-inotropic score (VIS) was calculated according to the following method: $VIS = \text{dopamine dose [mg kg}^{-1} \text{ min}^{-1}] + \text{dobutamine [mg kg}^{-1} \text{ min}^{-1}] + 100 \times \text{epinephrine dose [mg kg}^{-1} \text{ min}^{-1}] + 50 \times \text{levosimendan dose [mg kg}^{-1} \text{ min}^{-1}] + 10 \times \text{milrinone dose [mg kg}^{-1} \text{ min}^{-1}] + 10000 \times \text{vasopressin [units kg}^{-1} \text{ min}^{-1}] + 100 \times \text{norepinephrine dose [mg kg}^{-1} \text{ min}^{-1}]$ [10].

2.2 | Indication and Management of ECLS

ECLS initiation was carried out in patients who underwent cardiopulmonary resuscitation (CPR) in accordance with the recommendations of the European Resuscitation Council, which was performed for at least 15 min without restoring spontaneous circulation or a sufficient heart rate. Also, patients with a systolic blood pressure below 90 mmHg for more than 30 min, a mean arterial pressure below 60 mmHg, oliguria (less than 0.5 mL/kg/h), and a cardiac index less than 2.2 L/min/m² under optimal inotropic support were accepted as candidates for ECLS.

Arterial cannulation was provided using cannulas inserted into the femoral artery. Venous return was carried out with cannulas through the femoral vein. Both cannulas were connected to various systems, including Cardiohelp, Rotaflow (Getinge, Rastatt, Germany), Deltastream (Xenos AG, Heilbronn, Germany), Sorin (Mirandola, Modena, Italy) pumps, as well as QUADROX Pls (Getinge, Rastatt, Germany) and HILITE (Xenos AG, Heilbronn, Germany) oxygenators.

Anticoagulation was performed with unfractionated heparin to achieve target values of aPTT (activated partial thromboplastin time) of 60 s in the absence of bleeding. Flow parameters, catecholamines, and fluids were set to maintain sufficient perfusion, verified by mean arterial pressure, partial arterial oxygen pressure in the right radial artery, venous blood oxygen saturation over 70% before entering the membrane oxygenator, and serum lactate levels, according to the ELSO Guidelines for Cardiopulmonary Extracorporeal Life Support [11].

2.3 | Statistical Methods

The collected data were analyzed using IBM SPSS 29 (SPSS Inc., Chicago, IL, USA), SigmaPlot 14.0 (Systat Software GmbH, Erkrath, Germany), and R version 4.5.0 (R Core Team, 2024).

Continuous variables were examined for normality using the Kolmogorov-Smirnov Test. Normally distributed variables were compared using the Student *t*-test, while non-normally distributed variables were compared using the Mann-Whitney U test as well as a chi-square test for categorical variable were performed. To evaluate a prognostic impact on patient outcome, survival analysis by Log-Rank was provided. Odds ratios were calculated to analyze risk factors and their strength.

Additional analyses were performed after stratification by eCPR status. Effect modification by eCPR status was assessed using flow group × eCPR interaction terms in logistic regression for binary outcomes and Cox regression for survival outcomes.

Patients with cerebral death were excluded from MOF analyses. Multivariable logistic regression assessed the association between initial V-A ECMO flow-index and MOF. Flow-index was analyzed continuously per 0.1 L/min/m²; age and CPR duration per 10 years and 10 min, respectively. Skewed biomarkers were log₂-transformed, so odds ratios reflect approximate doubling.

The overall model included age, sex, eCPR status, baseline lactate, VIS, IL-6, IL-8, and day-1 free hemoglobin. The eCPR model omitted eCPR status and included CPR duration. Model performance was summarized by χ^2 , Nagelkerke R², and classification accuracy.

Exploratory mediation analyses assessed day-1 free hemoglobin and IL-6 as potential mediators between flow-index and MOF, adjusting for their baseline values and relevant covariates. Indirect effects were estimated as $a \times b$ using 10000 bootstrap resamples. Confidence intervals excluding zero indicated statistical support. Given the retrospective design, findings were considered exploratory and not causal. Statistical significance was determined at the level of $p < 0.05$.

3 | Results

The present study included 553 patients who underwent extracorporeal life support at a tertiary care center in the period from 2014 to 2024. The duration of mechanical circulatory support was 4 days (IQR 2, 5; 7) days in median. 380 (68.72%) patients could be weaned from ECLS; overall survival was 36.5% (202 patients) with a median follow-up of 31 (IQR 5; 923) days and in-hospital mortality of 51.5% (285 patients). 76.1% (421 patients) were after eCPR, with a median CPR time of 40 min (Table 1).

Coronary artery disease was the most frequent underlying disease leading to ECLS (54.4% of cases). Besides dilated cardiomyopathy, pulmonary embolism, and rhythm disturbances, the list of underlying diagnoses included various other conditions. Patients were divided into two groups: The first group consisted of 269 patients, whose flow index was under 1,63 L/min/m² during the first day on ECLS. The second group consisted of 284 patients, whose flow index was under 1,63 L/min/m² during the first day on ECLS.

Resuscitated patients in the second group with a higher flow index also had significantly longer CPR time before ECLS initiation (35 vs. 44 min, $p = 0.003$).

Moreover, patients who received ECLS due to a rhythmic event had a significantly lower flow index (17.4% vs. 10.2%, $p = 0.013$, Table 1).

Overall survival was significantly better in the first group of patients (42% vs. 31.3%, $p < 0.001$) with lower in-hospital mortality (43.9% vs. 58.8%, $p = 0.001$, Figure 1).

3.1 | Neurological Outcomes

Neurological status was assessed in a subgroup of 407 patients, in which the clinical course allowed neurological assessment. In

the first group, there was a significantly better cerebral performance (CPC 1 and CPC 2 in 144 patients with lower flow (69.6%) vs. 110 patients with higher flow (55%), $p = 0.002$) and a lower cerebral death rate (OR 0.534; 95% CI 0.352–0.809, $p = 0.004$) compared to patients from the high flow group.

3.2 | Hemodynamics

Comparing the two groups of patients, an important point to note is that patients requiring a higher flow index were initially more hemodynamically compromised (MAP 50 mmHg vs. 45 mmHg, $p = 0.002$ in the first and second groups, respectively). The need for catecholamine support was initially significantly higher in the group of patients requiring more perfusion (31.25 vs. 48.95, $p = 0.002$). Despite the stabilization of hemodynamics and a decrease in catecholamine requirement on the 1st day of ECLS, a significant difference in MAP (65 mmHg vs. 64 mmHg, $p = 0.008$) and VIS (5.13 vs. 7.89, $p = 0.005$) still remained. This trend was also reflected in the metabolic profile of the patients, i.e., in the first group, lactate levels were significantly lower before ECLS initiation compared to the second group (69 mg/dL vs. 103 mg/dL, $p < 0.001$), and despite metabolic improvement on the first day, this trend persisted (24 mg/dL vs. 38 mg/dL, $p < 0.001$, Table 2).

3.3 | Cytokines, Blood Components and Parameters

The serum levels of IL6, IL8 and TNF-alpha prior to ECLS implantation were significantly higher in the group of patients requiring a higher level of mechanical perfusion. The same trend persisted for IL6 and IL8 on the first day afterwards. Whereas sIL2R increased during the first day, there was no significant difference between the two groups (Table 3).

There was no significant difference in the level of LDH and free hemoglobin before ECLS initiation, but on the first day of ECLS, the group with a higher flow index demonstrated significantly higher levels of both LDH and free hemoglobin, as well as the level of maximum free hemoglobin during the entire time on ECLS. The platelet counts before ECLS and on the first day of circulatory support did not differ between the groups, and there was no significant difference in the level of platelet transfusion between the groups, although their level decreased during the first day of ECLS ($p < 0.001$). Meanwhile, the transfusion of red blood cell concentrates was significantly greater in patients of the high-flow group (Table 4).

3.4 | Stratified Analysis According to eCPR Status

To address the heterogeneity of the study population, patients were additionally stratified according to eCPR status. Of 553 patients, 421 underwent eCPR (197 low flow and 224 high flow), whereas 132 patients presented with non-arrest cardiogenic shock (72 low flow and 60 high flow). Within the eCPR cohort, patients with a higher flow index had significantly longer CPR duration (35 vs. 44 min, $p = 0.003$), lower BMI, as well as higher lactate levels and vasoactive-inotropic support

TABLE 1 | Baseline characteristics and outcome data.

Category	All patients	Low flow	High flow	<i>p</i>
Number of Patients	553	269	284	
Age, years	59 [50,75; 66,4]	59,7 [52,3; 66,85]	57,95 [49,23; 66,08]	0.094
Women <i>n</i> (%)	137 (24,8%)	68 (25,28%)	69 (24,3%)	0.789
BMI kg/m ²	26,89 [24,22; 29,72]	27,78 [25,05; 32,87]	25,71 [24,01; 28,19]	< 0.001
CPR, patients	421 (76,1%)	197 (73,2%)	224 (78,9%)	0.12
CRP time, min ^a	40 [29; 62]	35 [25; 59]	44 [31; 65]	0.003
ECLS weaned	380 (68,72%)	199 (73,98%)	181 (63,73%)	0.009
Follow-up, days	31 [5; 923]	165 [7; 1152]	15 [3; 617,25]	< 0.001
Days of ECLS	4 [2,5; 7]	4 [2; 6,5]	4 [3; 7]	0.538
Distal perfusion <i>n</i> (%)	261 (47,2%)	95 (35,3%)	166 (58,5%)	< 0.001
In-hospital mortality, <i>n</i>	285 (51,5%)	118 (43,9%)	167 (58,8%)	0.001
1-year survival	233 (42,1%)	131 (48,7%)	102 (35,9%)	< 0.001
Overall survival	202 (36,5%)	113 (42,0%)	89 (31,3%)	< 0.001
Neurological outcome between 407 patients 207 patients with flow under 1,63 l/min/m ² and 200 patients with flow over 1,63 l/min/m ²				
CPC 1–2	254 (62,4%)	144 (69,6%)	110 (55%)	0.002
CPC 3–4	15 (3,69%)	7 (3,5%)	8 (4%)	0.741
CPC 5	138 (33,9%)	56 (27,0%)	82 (41%)	0.003
Multi-organ failure	144 (26,0%)	60 (22,3%)	84 (29,6%)	0.051
ALD	117 (21,2%)	54 (20,1%)	63 (22,2%)	0.544
AKF	139 (25,1%)	55 (20,5%)	84 (29,6%)	0.013
ARDS	342 (61,8%)	161 (59,9%)	181 (63,7%)	0.348
Underlying disease				
CAD	301 (54,4%)	138 (51,3%)	163 (57,4%)	0.15
DCM	34 (6,2%)	19 (7,1%)	15 (5,3%)	0.383
PE	73 (13,2%)	32 (11,9%)	41 (14,4%)	0.378
Rhythmic event	76 (13,7%)	47 (17,4%)	29 (10,2%)	0.013
Other	69 (12,5%)	33 (12,3%)	36 (12,7%)	0.885

Note: Data are expressed as median and interquartile range [25th–75th] or number (percentage). Significant rows ($p < 0.05$) are shown in bold.

Abbreviations: AKF, acute kidney failure; ALD, acute liver dysfunction; ARDS, acute respiratory distress syndrome; BMI, body mass index; CAD, coronary artery disease; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; DCM, dilated cardiomyopathy; ECLS, extracorporeal life support; PE, pulmonary embolism.

^aTaking into account that in some groups the frequency of the value was less than 5, the test cannot be considered reliable.

before ECLS initiation. A similar difference in initial shock severity was observed in the non-arrest cohort, with significantly lower MAP and higher lactate and VIS in high-flow patients (Table 5).

Differences in clinical outcome were predominantly observed in the eCPR cohort. High-flow eCPR patients had lower rates of ECLS weaning (73.1% vs. 61.2%, $p = 0.009$), higher in-hospital mortality (44.7% vs. 62.9%, $p < 0.001$), and lower 1-year (49.2% vs. 32.1%, $p < 0.001$) and overall survival (43.1% vs. 26.8%, $p < 0.001$). After exclusion of patients with cerebral death, multi-organ failure occurred more frequently in high-flow eCPR patients (20.5%

vs. 32.0%, $p = 0.026$). In contrast, no significant differences in mortality, survival, ECLS weaning, or multi-organ failure were observed between the flow groups in patients with non-arrest cardiogenic shock (Table 5).

The differences in inflammatory and hemolysis parameters were also mainly observed within the eCPR cohort. High-flow patients demonstrated higher LDH and free hemoglobin levels on the first day of ECLS, higher maximum free hemoglobin and NSE concentrations, as well as significantly higher IL-6 and IL-8 levels before and during the first day of ECLS. These differences were not observed in the non-arrest cohort. The complete

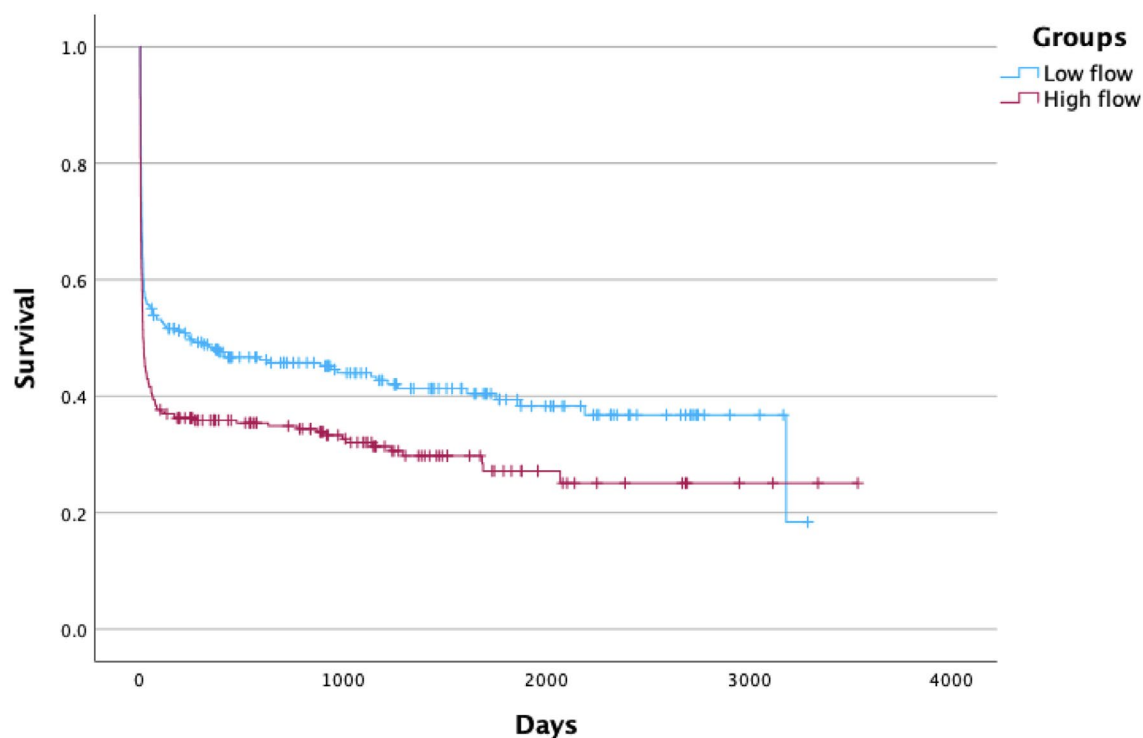


FIGURE 1 | Kaplan-Meier survival curves. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1111/aor.70257)]

TABLE 2 | Hemodynamic parameters before and during ECLS.

Category		Low flow	High flow	<i>p</i>
Number of Patients	553	269	284	
MAP before ECLS, mmHg	45 [35; 61]	50 [35; 62]	45 [30; 59]	0.002
MAP on the 1st day on ECLS mmHg	65 [60; 71]	65 [61; 72]	64 [58,25; 70]	0.008
Lactate before ECLS, mg/dl	85 [50; 126]	69 [39,25; 104,0]	103,0 [65,0; 139,0]	<0.001
Lactate on the 1st day on ECLS, mg/dl	30 [17; 62]	24 [14,5; 50,0]	38 [20,0; 73,0]	<0.001
Vasoactive-inotropic score before ECLS	39,22 [0,0; 93,93]	31,25 [0,0; 71,39]	48,95 [1,39; 110,23]	0.002
Vasoactive-inotropic score on the 1st day on ECLS	6,6 [1,42; 18,75]	5128 [0,0; 13,53]	7,89 [1927; 23,81]	0.005
Rotational speed index 2h on ECLS, RPM	1673,6 [1484,8; 1895,1]	1550,3 [1395,0; 1728,9]	1781,4 [1634,6; 1988,8]	<0.001
Rotational speed index 1d on ECLS, RPM	1606,12 [1396,1; 1842,5]	1510,2 [1334,0; 1699,9]	1724,0 [1542,4; 1935,5]	<0.001

Note: Data are expressed as median or number. There are no data on the amount of catecholamines in this group. Significant rows ($p < 0.05$) are shown in bold. Abbreviations: BMI, body mass index; ECLS, extracorporeal life support; MAP, mean arterial pressure.

stratified analysis of clinical, hemodynamic, laboratory, and inflammatory parameters is provided in Table S1.

Interaction analysis showed no significant interaction between flow group and eCPR status for multi-organ failure (p -interaction = 0.516), ECLS weaning (p -interaction = 0.400), in-hospital mortality (p -interaction = 0.096), acute kidney failure (p -interaction = 0.867), ARDS (p -interaction = 0.533), or 1-year survival (p -interaction = 0.111). However, a significant interaction was observed for overall survival (p -interaction = 0.026), indicating that the association between

higher initial flow and long-term mortality differed according to eCPR status.

3.5 | Organ Failure

With cardiocirculatory failure leading to ECLS therapy, all patients were defined as presenting with at least 1 failing organ system. In 135 (24,4%) patients, no further organ dysfunction occurred, including 72 (26,8%) patients with flow-index under 1,63 L/min/m² versus 63 (22,2%) patients with flow-index over

TABLE 3 | Analysis of interleukins between patients.

	Low flow	High flow	<i>p</i>
Preimplantation TNF-alpha, pg/ml	11 [8; 17]	13 [9; 18]	0.022
1st day TNF-alpha, pg/ml	15 [11; 23]	17 [11; 26]	0.072
Preimplantation sIL-2R, U/ml	638 [411; 1235]	619 [403; 1171]	0.649
1st day sIL-2R, U/ml	945 [640; 1603]	1046 [688; 1720]	0.295
Preimplantation IL6, pg/ml	159,0 [63,75; 484,0]	266,0 [102,0; 784,0]	<0.001
1st day IL6, pg/ml	138,0 [54,5; 380,0]	247,5 [99,25; 954,25]	<0.001
Preimplantation IL8, pg/ml	65,5 [32,75; 157,75]	103,0 [40,75; 273,5]	0.005
1st day IL8, pg/ml	69,0 [34,0; 130,0]	113,0 [49,0; 288,75]	<0.001

Note: Data are expressed as median or number. Significant rows ($p < 0.05$) are shown in bold.

Abbreviations: IL6, interleukin-6; IL8, interleukin-8; sIL2R, soluble interleukin-2 receptor; TNF-alpha, tumor necrosis factor alpha.

TABLE 4 | Blood components and parameters before and during ECLS.

Category	All patients	Low flow	High flow	<i>p</i>
Number of Patients	553	269	284	
ECs, units	2 [0; 6]	1 [0; 6]	3 [0; 6]	0.019
FFPs, units	0 [0; 3]	0 [0; 0]	0 [0; 4]	0.003
TCs, units	0 [0; 1]	0 [0; 1]	0 [0; 1]	0.811
LDH before ECLS, U/l	469 [300; 760,5]	444 [292; 718]	488 [312; 869]	0.176
LDH on the 1st day after ECLS, U/l	797 [439,5; 1557]	642 [400; 1191]	929 [509,5; 1854]	<0.001
Fibrinogen before ECLS, mg/dl	225 [144,75; 351]	236 [158,75; 344,5]	214 [137,5; 352,75]	0,188
Fibrinogen on the 1st day after ECLS, mg/dl	237 [177; 334,5]	248 [196; 348]	226 [172,25; 318,75]	0,019
Thrombocytes before ECLS, /nl	190 [139; 251]	190 [142; 238]	190 [136; 270]	0.65
Thrombocytes at 1st day after ECLS, /nl	131 [91;181,5]	133 [98,5; 187,5]	129,5 [84,25; 174,5]	0,183
Free hemoglobin before ECLS, mg/l	135 [48,5; 317,5]	116 [43,5; 287,5]	155 [56,25; 327,75]	0.057
Free hemoglobin 1st day after ECLS, mg/l	51 [30; 110,5]	41 [28; 74]	65 [34; 138]	<0.001
Maximum free hemoglobin during ECLS, mg/l	248 [113,5; 460]	221 [98,5; 406,5]	273 [127; 502,25]	0.021
Maximum of NSE, µg/l	58 [37,5; 122]	52 [35; 98,5]	68 [41,25; 158,25]	<0.001

Abbreviations: EC, erythrocyte concentrate; ECLS, extracorporeal life support; FFP, fresh frozen plasma; LDH, lactate dehydrogenase; NSE, neuron-specific enolase; TC, thrombocyte concentrates (platelet transfusions). Significant rows ($p < 0.05$) are shown in bold.

1,63 L/min/m². Two organ dysfunction was diagnosed in 274 (49,5%) patients, 137 (50,9%) patients with a lower index, and 137 (48,2%) patients with a higher index. Multi-organ dysfunction syndrome affecting 3 or more organs was diagnosed in 144 (26,0%) patients, 60 (22,3%) patients in the low-flow group vs. 84 (29,6%) in the second group ($p = 0.051$).

After excluding patients with cerebral death as a factor leading to early termination of ECLS, which made the manifestation of organ failure impossible, a total of 415 patients (213 in the first group and 202 in the second group) were analyzed; 115 (27.7%) of them developed failure of three or more organs. Interestingly, the incidence of organ failure was less pronounced in patients from the low-flow group: 49 (23%) vs. 66 (32.7%) patients, respectively ($p = 0.028$, Table 6).

3.5.1 | Multivariable Analysis of Multi-Organ Failure

After exclusion of patients with cerebral death, multivariable logistic regression analysis was performed to assess factors associated with the development of multi-organ failure. In the overall cohort, the regression model was statistically significant ($\chi^2(9) = 90.29$, $p < 0.001$), with a Nagelkerke R^2 of 0.334 and an overall classification accuracy of 80.7%. Initial flow index remained independently associated with multi-organ failure, with an increase of 0.1 L/min/m² being associated with higher odds of MOF (OR 1.102, 95% CI 1.001–1.214, $p = 0.048$). Age (OR 1.281 per 10 years, $p = 0.044$), VIS before ECLS (OR 1.113 per doubling, $p = 0.020$), IL-6 before ECLS (OR 1.245 per doubling, $p = 0.013$), and free hemoglobin on the first day of ECLS (OR 1.539 per doubling, $p < 0.001$) were also independently associated with the

TABLE 5 | Clinical characteristics and outcomes according to initial VA-ECMO flow-index, stratified by eCPR status.

Category	eCPR			Non-arrest cardiogenic shock		
	Low flow	High flow	<i>p</i>	Low flow	High flow	<i>p</i>
Age, years	59.8 [51.8; 67.7]	57.6 [49.27; 65.65]	0.049	59.25 [52.68; 64.22]	60.35 [49.65; 66.92]	0.869
Women, <i>n</i> (%)	55 (27.9%)	48 (21.4%)	0.122	13 (18.1%)	21 (35.0%)	0.027
BMI, kg/m ²	27.78 [25.26; 33.95]	25.95 [24.21; 28.34]	< 0.001	27.78 [24.49; 29.79]	25.25 [23.55; 27.68]	0.006
CPR duration, min	35 [25; 59]	44 [31; 65]	0.003	—	—	—
ECLS weaned, <i>n</i> (%)	144 (73.1%)	137 (61.2%)	0.009	55 (76.4%)	44 (73.3%)	0.686
Days of ECLS	3 [2; 5]	4 [2; 6]	0.063	6.5 [4; 9]	5 [3; 9]	0.203
In-hospital mortality, <i>n</i> (%)	88 (44.7%)	141 (62.9%)	< 0.001	30 (41.7%)	26 (43.3%)	0.847
1-year survival, <i>n</i> (%)	97 (49.2%)	72 (32.1%)	< 0.001	34 (47.2%)	30 (50.0%)	0.751
Overall survival, <i>n</i> (%)	85 (43.1%)	60 (26.8%)	< 0.001	28 (38.9%)	29 (48.3%)	0.275
Multi-organ failure, <i>n</i> (%)	30/146 (20.5%)	47/147 (32.0%)	0.026	19/67 (28.4%)	19/55 (34.5%)	0.463
AKF, <i>n</i> (%)	39 (19.8%)	64 (28.6%)	0.037	16 (22.2%)	20 (33.3%)	0.154
ARDS, <i>n</i> (%)	124 (62.9%)	151 (67.4%)	0.337	37 (51.4%)	30 (50.0%)	0.874
MAP before ECLS, mmHg	43 [33; 59]	40 [30; 55]	0.078	61 [55; 71.25]	55 [47.25; 64.25]	0.001
Lactate before ECLS, mg/dL	77 [54; 109]	110 [72.5; 138.5]	< 0.001	37 [22.5; 79.5]	75 [32.75; 131.75]	0.003
Lactate on the 1st day on ECLS, mg/dL	26 [16; 60]	44 [23; 76]	< 0.001	20.5 [13; 33]	21 [13.75; 49]	0.574
Vasoactive-inotropic score before ECLS	27.03 [0; 66.67]	41.16 [0; 104.17]	0.009	41.52 [17.72; 102.42]	85.53 [38.75; 134.72]	0.004
Vasoactive-inotropic score on the 1st day on ECLS	4.9 [0; 12.96]	9.39 [2.08; 24.91]	0.002	5.53 [0; 15.61]	5.85 [1.82; 18.82]	0.798
LDH on the 1st day after ECLS, U/L	616 [404; 1140]	970 [571; 1827.25]	< 0.001	857.5 [381.75; 1788.25]	795 [352.5; 2870]	0.537
Free hemoglobin day 1 after ECLS, mg/L	43 [28; 76]	68 [37; 141.25]	< 0.001	39 [29.75; 67.5]	45 [26.5; 122.75]	0.486
Maximum free hemoglobin during ECLS, mg/L	258 [118; 411]	294.5 [163.75; 531.75]	0.011	133 [76; 379]	149.5 [63.5; 321]	0.716
Maximum NSE, µg/L	59 [40; 118]	83.5 [50; 209.25]	< 0.001	35 [21.5; 53]	39 [24; 58.25]	0.551
Preimplantation IL-6, pg/mL	139.5 [62; 451.5]	274 [111.5; 853.25]	< 0.001	203 [72; 519.75]	201 [87; 626]	0.917
Day 1 IL-6, pg/mL	148 [67; 397]	331 [107; 1170]	< 0.001	108 [43.25; 352.25]	135 [66.5; 327.5]	0.335
Preimplantation IL-8, pg/mL	58 [31; 120.5]	88 [36; 275]	0.004	104 [45.5; 238]	134 [53; 235]	0.546
Day 1 IL-8, pg/mL	70.5 [38; 141]	124 [54.75; 354.75]	< 0.001	61 [24; 96]	72.5 [42.5; 132.75]	0.140

Note: Data are expressed as median and interquartile range [25th–75th] or number (percentage). CPR duration was analyzed only in the eCPR cohort. For MOF, patients with cerebral death were excluded, consistent with the primary MOF analysis. Significant rows ($p < 0.05$) are shown in bold. Abbreviations: AKF, acute kidney failure; ALD, acute liver dysfunction; ARDS, acute respiratory distress syndrome; BMI, body mass index; CPR, cardiopulmonary resuscitation; EC, erythrocyte concentrate; ECLS, extracorporeal life support; FFP, fresh frozen plasma; LDH, lactate dehydrogenase; MAP, mean arterial pressure; MOF, multi-organ failure; NSE, neuron-specific enolase; TC, thrombocyte concentrate; VIS, vasoactive-inotropic score.

development of MOF. Sex, eCPR, lactate before ECLS, and IL-8 showed no significant independent association (Table 7A).

Because the majority of patients underwent ECLS in the setting of eCPR, a separate multivariable analysis was also performed in this

subgroup. The model was statistically significant ($\chi^2(9)=49.77$, $p<0.001$), with a Nagelkerke R^2 of 0.326 and an overall classification accuracy of 79.4%. Initial flow index remained significantly associated with MOF also in the eCPR subgroup (OR 1.117 per increase of 0.1 L/min/m², 95% CI 1.028–1.214, $p=0.008$). Moreover, VIS before ECLS (OR 1.196 per doubling, $p=0.009$), IL-6 before ECLS (OR 1.494 per doubling, $p=0.012$), and free hemoglobin on the first day (OR 1.792 per doubling, $p<0.001$) were independently associated with MOF. CPR duration, age, sex, lactate before ECLS, and IL-8 were not significantly associated with MOF in this model (Table 7B).

TABLE 6 | Organ failure after exclusion of cerebral death.

Category	All patients	Low flow	High flow	<i>p</i>
Patients, <i>n</i>	415	213	202	
Multi-organ failure	115	49	66	0.028
ALD	99	47	52	0.38
AKF	112	43	69	0.001
ARDS	249	125	124	0.575

Note: Significant rows ($p<0.05$) are shown in bold.

3.5.2 | Exploratory Mediation Analysis

To further explore possible mechanisms underlying the association between initial flow index and multi-organ failure, exploratory mediation analyses were performed for early hemolysis and inflammatory activation. In the overall cohort, higher initial flow index tended to be associated with

TABLE 7A | Multivariable logistic regression model exploring factors associated with development of multi-organ failure in the overall cohort.

Category	B	S.E.	Wald	<i>p</i>	Odds ratio	95% CI for odds ratio	
						Lower bound	Upper bound
Initial flow-index, per +0.1 L/min/m ²	0.097	0.049	3.902	0.048	1.102	1.001	1.214
Age, per 10 years	0.248	0.123	4.062	0.044	1.281	1.007	1.630
Sex, female	−0.158	0.323	0.239	0.625	0.854	0.454	1.608
eCPR	−0.433	0.329	1.728	0.189	0.649	0.340	1.237
Lactate before ECLS, per doubling	0.215	0.152	2.010	0.156	1.240	0.921	1.670
VIS before ECLS, per doubling	0.107	0.046	5.447	0.020	1.113	1.017	1.217
IL-6 before ECLS, per doubling	0.219	0.088	6.198	0.013	1.245	1.048	1.480
IL-8 before ECLS, per doubling	0.025	0.107	0.054	0.816	1.025	0.832	1.263
Free Hb day 1, per doubling	0.431	0.106	16.589	<0.001	1.539	1.250	1.893

Note: Model $\chi^2(9)=90.29$, $p<0.001$; Nagelkerke $R^2=0.334$; classification accuracy = 80.7%. Patients with cerebral death were excluded. Significant rows ($p<0.05$) are shown in bold.

TABLE 7B | Multivariable logistic regression model exploring factors associated with development of multi-organ failure in the eCPR subgroup.

Category	B	S.E.	Wald	<i>p</i>	Odds ratio	95% CI for odds ratio	
						Lower bound	Upper bound
Initial flow-index, per +0.1 L/min/m ²	0.111	0.042	7.04	0.008	1.117	1.028	1.214
CPR duration, per 10 min	−0.050	0.097	0.271	0.603	0.951	0.787	1.149
Age, per 10 years	0.294	0.189	2.405	0.121	1.341	0.925	1.944
Sex, female	0.008	0.489	<0.001	0.987	1.008	0.386	2.628
Lactate before ECLS, per doubling	0.359	0.326	1.213	0.271	1.431	0.756	2.709
VIS before ECLS, per doubling	0.179	0.069	6.781	0.009	1.196	1.045	1.368
IL-6 before ECLS, per doubling	0.402	0.159	6.356	0.012	1.494	1.094	2.042
IL-8 before ECLS, per doubling	−0.233	0.194	1.445	0.229	0.792	0.541	1.159
Free Hb day 1, per doubling	0.583	0.175	11.127	<0.001	1.792	1.272	2.524

Note: Model $\chi^2(9)=49.77$, $p<0.001$; Nagelkerke $R^2=0.326$; classification accuracy = 79.4%. Patients with cerebral death were excluded. Significant rows ($p<0.05$) are shown in bold.

higher free hemoglobin on the first day of ECLS ($B=0.045$, $p=0.067$), while day-1 free hemoglobin was strongly associated with MOF (OR 1.55 per doubling, $p<0.001$). The direct effect of flow-index remained significant (OR 1.11, $p=0.049$). Bootstrap analysis demonstrated a significant indirect effect through day-1 free hemoglobin (indirect effect 0.0201, 95% CI 0.0004–0.0511).

This association was more pronounced in the eCPR subgroup. Initial flow-index was significantly associated with day-1 free hemoglobin ($B=0.085$, $p=0.019$), and free hemoglobin remained strongly associated with MOF (OR 1.79 per doubling, $p<0.001$). At the same time, the direct effect of flow-index remained significant (OR 1.11, $p=0.009$). The indirect effect through free hemoglobin was statistically supported by bootstrap analysis (0.0493, 95% CI 0.0049–0.1251), suggesting that early hemolysis may partially contribute to the association between higher initial flow-index and subsequent multi-organ failure.

A different pattern was observed for IL-6. Higher initial flow-index was associated with increased IL-6 levels on the first day both in the overall cohort ($B=0.0879$, $p=0.020$) and in the eCPR subgroup ($B=0.1132$, $p=0.035$). Day-1 IL-6 was also associated with MOF in both analyses. However, the bootstrap confidence intervals for the indirect effects included zero in the overall cohort (0.0139, 95% CI –0.0014–0.0391) as well as in the eCPR subgroup (0.0312, 95% CI –0.0025–0.0908). Therefore, no statistically supported indirect effect through IL-6 was demonstrated (Table S2).

4 | Discussion

ECLS ensures adequate macrocirculatory support for patients in refractory cardiogenic shock. However, despite sufficient perfusion of organs and systems, which is monitored by different parameters including MAP, the level of central venous oxygen saturation before the oxygenator and the level and dynamics of lactate in the blood serum, etc., it remains unclear whether patients tend to develop organ dysfunction. Demonstrating sufficient macrocirculatory support, possible microcirculatory changes observed in organs and systems during ECLS and evidence of their relationship to the level of ECLS flow are still controversial [12, 13]. Therefore, we analyzed factors associated with the initial flow-index and its possible relationship with subsequent organ failure and outcome. To our knowledge, this is one of the largest studies evaluating initial VA-ECMO flow in relation to organ dysfunction, inflammatory activation, hemolysis, and long-term outcome.

In our population, patients requiring a higher initial flow-index were more compromised in terms of hemodynamics, catecholaminergic support, and metabolic status before ECLS. This most likely reflects more severe cardiocirculatory failure and a greater need for mechanical support. The significantly higher rotational speed index in these patients additionally suggests that the higher flow was not related to vasoplegia alone but also to the need to compensate for markedly reduced native cardiac output. Thus, a high initial flow-index should primarily be interpreted as a marker of the severity and complexity of circulatory failure.

Nevertheless, the multivariable analysis showed that initial flow-index remained independently associated with the development of multi-organ failure after adjustment for clinical characteristics, markers of shock severity, inflammatory activation, and early hemolysis. This association was present in the overall cohort and remained significant in the eCPR subgroup. Therefore, although higher flow requirements clearly reflect more severe hemodynamic compromise, flow-index may also capture aspects of extracorporeal support intensity that are not fully represented by conventional markers of shock alone.

The findings in patients undergoing eCPR are particularly relevant. These patients are exposed to profound circulatory failure, ischemia-reperfusion injury, resuscitation-associated inflammation, and subsequent extracorporeal circulation. Interestingly, in our cohort, CPR duration itself was not independently associated with MOF in the multivariable model, whereas initial flow-index, VIS, pre-ECLS IL-6, and free hemoglobin on the first day remained significant. This suggests that the development of organ failure after eCPR cannot be explained by the duration of resuscitation or the preceding shock alone. Rather, several processes, including the severity of circulatory failure, inflammatory activation, and biological effects developing during extracorporeal support, may contribute simultaneously.

Of particular interest was the association between early hemolysis and multi-organ failure. Free hemoglobin on the first day of ECLS showed the strongest biomarker association with MOF in both multivariable models, with a more pronounced effect in the eCPR subgroup. Importantly, free hemoglobin levels before ECLS did not differ significantly between the low- and high-flow groups, whereas significantly higher levels were observed in patients with higher flow on the first day of support. The same pattern was observed for LDH. This temporal relationship suggests that hemolysis developed or increased during extracorporeal circulation. Higher indexed flow may be accompanied by greater mechanical stress within the pump, cannulas, oxygenator, and extracorporeal circuit. Free hemoglobin itself may further aggravate endothelial dysfunction, nitric oxide depletion, oxidative stress, and microcirculatory impairment, thereby contributing to secondary organ failure [14–17].

The exploratory mediation analysis supports a possible role of early hemolysis in this association. In both the overall cohort and the eCPR subgroup, bootstrap analysis showed an indirect effect of initial flow-index on MOF through day-1 free hemoglobin. At the same time, the direct association between flow-index and MOF remained significant. Thus, early hemolysis may explain part, but not all, of the relationship between higher initial flow-index and subsequent organ failure. The indirect effect was particularly evident in the eCPR subgroup, which may indicate that these critically compromised patients are especially susceptible to additional blood trauma during extracorporeal support. However, the mediation analysis remains exploratory, and due to the retrospective observational design, a causal relationship between higher flow, hemolysis, and MOF cannot be established.

Inflammatory activation showed a somewhat different pattern. Patients in the high-flow group already had higher levels

of IL-6, IL-8, and TNF-alpha before ECLS implantation, indicating a greater inflammatory burden at the time of support initiation, most likely related to prolonged shock, ischemia-reperfusion injury, and resuscitation-associated systemic activation. Differences in IL-6 and IL-8 remained present during the first day of ECLS. Moreover, pre-ECLS IL-6 was independently associated with MOF in both the overall cohort and the eCPR subgroup. Although a higher initial flow index was also associated with day-1 IL-6 and day-1 IL-6 was associated with MOF, the mediation analysis did not demonstrate a significant indirect effect through IL-6. Thus, inflammatory activation appears to be an important component of the high-risk clinical phenotype, consistent with previous studies [18]. However, our findings do not support IL-6 as a distinct mediator specifically linking the initial flow index to MOF.

In addition, patients in the high-flow group required more red blood cell transfusions. This may be related to hemolysis, bleeding, anticoagulation, hemodilution, or simply greater overall disease severity. Therefore, the increased transfusion requirement should not be interpreted as a direct consequence of higher flow alone, but it further reflects the more complex clinical course of these patients.

Neurological outcome was also less favorable in patients with higher initial flow index. Among patients in whom neurological assessment was possible, favorable cerebral performance was significantly more frequent in the low-flow group, and cerebral death occurred less often. This association is likely multifactorial. Longer CPR duration and higher lactate levels in the high-flow group suggest more prolonged cerebral and systemic hypoperfusion before ECLS initiation. Altered pulsatility, disturbed cerebral autoregulation, reperfusion injury, and microcirculatory dysfunction may additionally contribute to neurological injury during the early phase of VA-ECMO [17]. Previous studies have also shown an association between higher 24-h ECLS pump flow and acute brain injury [5]. In our cohort, this was accompanied by significantly higher maximum NSE levels in the high-flow group, a marker previously associated with neuronal injury and central nervous system dysfunction [19]. Since neurological assessment was possible only in a subgroup of patients, these findings should be interpreted cautiously. Nevertheless, they further underline the clinical relevance of initial flow-index as part of a broader risk profile.

The stratified analysis further demonstrated the importance of the underlying clinical indication. Patients undergoing eCPR represented the majority of the cohort and showed more pronounced differences between low- and high-flow groups regarding shock severity, inflammatory activation, hemolysis, organ dysfunction, and survival. However, the interaction between flow group and eCPR status was not significant for MOF, ECLS weaning, in-hospital mortality, acute kidney failure, ARDS, or 1-year survival. Therefore, although several adverse outcomes reached statistical significance mainly within the eCPR subgroup, there was no clear evidence that the association between initial flow and these outcomes differed substantially between eCPR and non-arrest cardiogenic shock. The smaller number of patients in the non-arrest cohort may additionally have limited the statistical power to detect such

differences. In contrast, a significant interaction was observed for overall survival, suggesting that the association between higher initial flow and long-term mortality was mainly present in patients undergoing eCPR. These results emphasize that flow-index should always be interpreted within the underlying clinical context.

Absolute ECMO flow is usually adjusted according to arterial pressure, oxygenation, venous saturation, lactate clearance, and clinical signs of organ perfusion. However, absolute flow does not account for differences in patient size. Flow-index may therefore provide a more individualized estimate of the intensity of circulatory support relative to body surface area and metabolic demand. A high early flow-index, particularly when accompanied by elevated lactate, high VIS, inflammatory activation, or early hemolysis, may identify patients who require closer surveillance.

Importantly, our results should not be interpreted as evidence that higher ECMO flow is generally harmful or should be avoided. In patients with profound shock, higher flow is often necessary to restore adequate systemic perfusion. At the same time, restoration of macrohemodynamics does not necessarily ensure organ protection. Higher extracorporeal flow may increase systemic pressure and oxygen delivery, but may also increase ventricular afterload, reduce pulsatility, promote blood trauma, and aggravate inflammatory activation [20, 21] while higher support intensity has also been associated with increased mortality [22].

Individualized VA-ECMO management should therefore combine macrocirculatory parameters with biological and organ-specific markers. Lactate kinetics, VIS, arterial pressure, venous oxygen saturation, pulsatility, hemolysis parameters, inflammatory markers, echocardiographic findings, and signs of end-organ recovery should be considered together rather than relying on flow alone. In particular, early monitoring for hemolysis may be important in patients requiring higher indexed flow and especially in those undergoing eCPR.

Finally, initial flow-index is unlikely to be a single trigger of organ failure. The extent to which the preceding "shock-hit" and initial hemodynamic instability contribute to subsequent MOF, compared with the effects of extracorporeal support itself, cannot be fully separated in the present study. Patients with the most profound hemodynamic compromise and the greatest inflammatory activation also required the highest initial flow rates. Therefore, initial flow-index should be regarded primarily as an integrated marker of circulatory severity and support intensity, while the observed association with early hemolysis suggests one possible biological pathway contributing to subsequent organ dysfunction.

4.1 | Ethics Statement

The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the University Medical Center of Regensburg (Reference No. 24-3948-104; 12. November 2024).

4.2 | Limitations

Potential limitations of this study are the 10-year period over which data were collected, acknowledging the changing characteristics of ECLS patient management and technical tools over time. Although regression analysis was used to adjust for relevant variables, residual confounding cannot be excluded. Moreover, the underlying patient population represents a rather heterogeneous group. The retrospective nature of the study performed at a single center may also limit the ability to provide definitive conclusions. Patient groups were divided based on the mean level of initial ECLS flow-index within our patient population. Additionally, only the impact of initial ECLS flow during the first day was analyzed.

5 | Conclusion

Higher initial VA-ECMO flow-index was associated with greater shock severity and remained independently associated with multi-organ failure. Early hemolysis may partly contribute to this association, particularly in patients undergoing eCPR, whereas no significant indirect effect through IL-6 was demonstrated. These findings support an individualized approach to VA-ECMO flow management with close monitoring of hemolysis and evolving organ dysfunction, while recognizing that higher flow primarily reflects the severity and complexity of circulatory failure.

Author Contributions

Kostiantyn Kozakov: conceptualization, methodology, formal analysis, data curation, project administration, writing – original draft. **Alois Philipp:** investigation, data curation, project administration, writing – review and editing. **Maik Foltan, Christian Schach, Sergey Vasin, Andreas Keyser, and Leopold Rupprecht:** investigation, data curation, writing – review and editing. **Zdenek Provaznik and Christof Schmid:** conceptualization, methodology, project administration, writing – review and editing. **Simon Schopka:** conceptualization, methodology, supervision, project administration, writing – review and editing. All authors read and approved the final manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Complete stratified analysis according to initial VA-ECMO flow-index and eCPR status. **Table S2:** Exploratory mediation analyses of early hemolysis and inflammatory activation in the association between initial V-A ECMO flow-index and multi-organ failure.