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MAIN TEXT

Multi-organ dysfunction syndrome in patients undergoing extracorporeal life support

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Abstract

Background: Multiple organ failure is a common complication in patients undergoing ECLS significantly affecting patient outcomes. Gaining knowledge about the mechanisms of onset, clinical course, risk factors, and potential therapeutic targets is highly desirable.

Methods: Data of 354 patients undergoing ECLS with one-, two, three-, and four organ failures were retrospectively analyzed. Incidence of multiple organ dysfunction (MODS), its impact on survival, risk factors for its occurrence, and the impact of proinflammatory mediators on the occurrence of MODS in patients undergoing ECLS were investigated.

Results: The median follow-up was 66 (IQR 6; 820) days. 245 (69.2%) patients could be weaned from ECLS, 30-day survival and 1-year survival were 194 (54.1%) and 157 (44.4%), respectively. The duration of mechanical support was 4 (IQR 2; 7) days in the median. Increasing severity of MODS resulted in significant prolongation of mechanical circulatory support and worsening of the outcome. Liver dysfunction had the strongest impact on patient mortality (OR = 2.5) and survival time (19 vs 367 days). The serum concentration of analyzed interleukins rose significantly with each, additional organ affected by dysfunction ($p < 0.001$). All analyzed proinflammatory cytokines showed significant predictivity relative to the occurrence of MODS with interleukin 8 serum level prior to ECLS showing the strongest predictive potential for the occurrence of MODS (AUC 0.78).

Conclusion: MODS represents a frequent complication in patients undergoing ECLS with a significant impact on survival. Proinflammatory cytokines show prognostic capacity regarding the occurrence and severity of multi-organ dysfunction.

KEYWORDS

cardiac failure, extracorporeal life support, extracorporeal membrane oxygenation, interleukins, mortality, multi-organ failure, risk factors

1 | INTRODUCTION

Extracorporeal life support (ECLS) is a technology that offers short- and intermediate-term mechanical support for cardiac and pulmonary functions. Its application has become widespread with a rising number of ECLS-centers and expansion of support for patients with cardiac and respiratory failure. Mortality to hospital discharge for patients with cardiac failure varies around 50%.[1]

However, complications and mortality rates following ECLS therapy are still relevant and need further investigation.[2] Most frequent systemic complications and causes of death associated with ECLS are neurologic complications, bleeding, liver dysfunction, kidney failure, infections, sepsis, and multi-organ dysfunction and failure.[3,4]

Multi-organ dysfunction and failure can result from a wide spectrum of pathophysiological mechanisms believed to culminate in a common cascade of adverse events.[5] Together with endocrine, mitochondrial, and microcirculatory processes, a proinflammatory status plays an integral role in the development of the MODS on a cellular level.[6] Hence, MODS is believed to be caused by a devastating imbalance between systemic inflammatory response and its counter-regulation.

The prognostic value of cytokine levels in the context of MODS has already been analyzed in patients with polytrauma,[7] complex surgical interventions, sepsis, and adult respiratory distress syndrome (ARDS).[8] Likewise, numeral studies were initiated to understand inflammatory response following cardiopulmonary bypass during cardiac surgery[9] and in patients with long-term mechanical circulatory support devices (VADs).[10]

The prognostic effect of serum cytokine levels on the survival of patients undergoing ECLS therapy has also been established.[11–13] However, the pathophysiological mechanisms of cytokines and their impact on survival in this setting remain poorly understood.

The present study analyzes the incidence of MODS during ECLS, its impact on survival, risk factors for its occurrence as well as the influence of the proinflammatory interleukins 6, 8, 2, and tumor necrosis factor-α on the occurrence of MODS in the clinical course of patients undergoing extracorporeal life support.

2 | MATERIALS AND METHODS

2.1 | Study design and definition of organ failure

A retrospective, observational study was initiated to analyze clinical aspects of MODS during ECLS as well as the relationship between the serum cytokine levels and the occurrence of MODS. Patients were classified into four groups according to the number of failing organs. As all patients had undergone ECLS implantation in sense of veno-arterial extracorporeal membrane oxygenation (ECMO), all patients suffered at least cardiocirculatory failure.

The diagnosis of ARDS was based on the Murray Score, which includes chest x-ray score, hypoxemia score, positive end-expiratory pressure, and expiratory system compliance. A final score of more than 2.5 established the diagnosis of ARDS.[14]

Acute renal failure was defined by the parameters of the kidney disease improving global outcomes (KDIGO) clinical practice guidelines for AKI, namely Stage 3 of KDIGO criteria: serum creatinine increase >3 times baseline, serum creatinine increases to >4.0 mg/dl (353 μmoL/L), initiation of renal replacement therapy.[15]

The simultaneous occurrence of an increase of spontaneous INR of more than 1.5, a threefold increase in transaminases, and bilirubin of more than 2.5 mg/dl defined acute hepatic dysfunction.[16]

For the summary assessment of inotropic and vasopressor support, a vasoactive-inotropic score (VIS) was calculated according to the following method[17]: VIS = dopamine dose [$mg\,kg^{-1}\ min^{-1}$] + dobutamine [$mg\,kg^{-1}\ min^{-1}$] + 100 × epinephrine dose [$mg\,kg^{-1}\ min^{-1}$] + 50 × levosimendan dose [$mg\,kg^{-1}\ min^{-1}$] + 10 × milrinone dose [$mg\,kg^{-1}\ min^{-1}$] + 10 000 × vasopressin [$units\,kg^{-1}\ min^{-1}$] + 100 × norepinephrine dose [$mg\,kg^{-1}\ min^{-1}$].

2.2 | Indication and management of ECLS

Initiation of ECLS was carried out in patients undergoing cardio-pulmonary resuscitation (CPR) according to the guidelines of the European Council of Resuscitation, which was performed for at least 10 min without return of spontaneous circulation or sufficient heart rhythm. Also, patients with a systolic blood pressure of less than 90 mm Hg for more than 30 min, mean arterial blood pressure below 60 mm Hg, oliguria (less than 0.5 ml/kg/h), and a cardiac index of less than 2.2 $L/min/m^2$ during optimal inotropic support were deemed candidates for ECLS. Postcardiotomy low cardiac output syndrome in patients unable to be weaned from cardiopulmonary bypass (CBP) was also considered an indication of ECLS.

Arterial cannulation was performed with cannulas inserted into the ascending aorta, femoral, or subclavian artery. Venous return was accomplished by cannulas through the femoral vein or right atrium. 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 before entering the membrane oxygenator, and serum lactate levels.

2.3 | Analysis of cytokines

Blood samples were collected before and on day 1 after ECLS initiation. Samples were immediately transported to the laboratory. IL6 levels were analyzed using electrochemiluminescence (Cobas e411, Roche Diagnostics, Rotkreuz, Switzerland). IL8 and TNF-alpha levels were measured by chemiluminescence (Immulite 1000, Siemens Healthcare Diagnostics, Erlangen, Germany). sIL2R levels were analyzed by a two-site chemiluminescent immunometric assay (Immulite 1000, Siemens Healthcare Diagnostics, Erlangen, Germany).

2.4 | Statistical methods

The collected data were analyzed using IBM SPSS 25 (SPSS, Inc., Chicago, IL, USA) and SigmaPlot 12.5 (Systat Software Gmbh, Erkrath, Germany).

To analyze differences between groups of patients with a different number of organ failure/dysfunction Kruskal-Wallis one-way analysis of variance on ranks for skewed variables, with post hoc test between the groups as pairwise multiple comparison procedure (Dunn's Method), and a chi-square test for a categorical variable was performed.

Mann–Whitney *U* test was chosen to evaluate differences between two groups presenting nonparametric data.

To analyze the predictive potential of interleukins on occurring organ failure/dysfunction receiver-operating characteristic (ROC) analysis was carried out at time points corresponding to the number of organ failure/dysfunction.

To evaluate a prognostic impact on patient survival, survival analysis by log-rank was provided.

Odds ratios were calculated during the analysis of risk factors for MODS and their strength.

3 | RESULTS

The present study included 354 patients who underwent extracorporeal life support at a tertiary care center in the period from 2009 until 2020. The median follow-up was 66 (IQR 6; 820) days. The duration of mechanical support was 4 (IQR 2; 7) days in the median. 245 (69.2%) patients could be weaned from ECLS, 30-day survival and 1-year survival were 194 (54.1%) and 157 (44.4%), respectively, 144 (40.1%) patients survived to current follow up.

Coronary artery disease was the most frequent underlying diagnosis leading to ECLS (44% of cases). Apart from dilative cardiomyopathy, pulmonary embolism, rhythmic events, and sepsis, a variety of miscellaneous conditions complete the underlying diagnoses. A total of 243 (68%) patients underwent cardiopulmonary resuscitation prior to ECLS initiation (Table 1).

3.1 | Multi-organ dysfunction

With cardiocirculatory failure leading to ECLS therapy, all patients were defined to present with at least 1 failing organ system. In 85 (24%) patients no further organ dysfunction occurred. Multi-organ dysfunction syndrome affecting 2 organs was diagnosed in 130 (37%) patients, and 3 and 4 organs were affected in 95 (27%) and 44 (12%) patients, respectively. Regarding the distribution of affected organs, ARDS proved to occur most frequently (201 patients, 56.8%), followed by renal (164 patients, 46.3%), and liver (87 patients, 24.6%) dysfunction.

Increasing severity of MODS, as defined by an increasing number of affected

organs, resulted in significant prolongation of mechanical circulatory support (Table 1).

The occurrence of MODS significantly affected patients' long-term survival, with patients' prognoses worsening significantly with each additional organ affected by MODS (Figure 1).

Liver involvement had the greatest impact on patient mortality with an increase in mortality risk (odds ratio 2.5; 95% CI 1.45–4.27, $p < 0.05$) and a striking impact on median survival (19 vs 367 days, $p < 0.05$). While the occurrence of renal failure also led to a significant worsening of both mortality risk (odds ratio 2.1; 95% CI 1.37–3.29, $p < 0.05$) and median survival (25 vs 890 days, $p < 0.05$), the occurrence of ARDS alone did not significantly affect mortality (odds ratio 0.99, 95% CI 0.64–1.52, $p = 0.95$) or survival (64 vs 76 days, $p = 0.78$).

3.2 | Risk factors associated with MODS

Pre-existing sepsis at the time of ECLS onset was associated with an increased risk of 3 or 4 organs being affected by dysfunction (odds ratio 3.4, 95% CI 1.56–7.61, $p < 0.05$). However, if ECLS was preceded by cardiac surgery or

TABLE 1 Baseline characteristics and outcome data

Category	All patients	Number of affected organs				*p*-value
		1	2	3	4	
Number of patients	354	85	130	95	44	–
Age, years	57.924 ± 13.438	57.124 ± 15.025	58.158 ± 14.000	58.077 ± 12.200	58.452 ± 11.238	0.975
Women *n*, (%)	95 (26.8%)	19(22.4%)	34 (26.2%)	30 (31.6%)	12 (27.3%)	0.574
BMI, kg/cm^2	27.64 ± 6.3	26.27 ± 3.66	27.55 ± 5.88	27.68 ± 5.77	30.45 ± 10.56	0.073
CPR n, (%)	243 (68.6%)	65(76.5%)	97 (74.6%)	59 (62.1%)	22 (50%)	**0.004**
ECLS postsurgery *n*, (%)	77 (21.8%)	12 (14.1%)	38(29.2%)	21 (22.1%)	6 (13.6%)	**0.031**
Follow-up, days	66(6; 820)	286 (6; 975)	86 (4; 857)	41(6; 574)	20(6; 389)	0.2
Days of ECLS	4 (2; 7)	3 (2; 5)	4 (2; 6)	6(3; 10)	7(3; 10)	**<0.001**
30 days survival	192 (54.24%)	54 (63.53%)	70 (53.85%)	50 (52.63%)	18 (40.91%)	0.261
1st year survival	157 (44.35%)	50 (58.82%)	61 (46.92%)	34 (35.79%)	12 (27.27%)	0.07
Survival to last follow-up	144 (40.68%)	44 (51.76%)	57 (43.85%)	31 (32.63%)	12 (27.27%)	**0.043**
Cannulation						
Seldinger *n*, (%)	320 (90.4%)	79 (92.9%)	115 (88.5%)	84 (88.4%)	42 (95.5%)	0.404
Distal perfusion *n*, (%)	167 (47.2%)	40 (47.1%)	52 (40.0%)	51 (53.7%)	24 (54.5%)	0.154
Underlying disease						0.002[a]
CAD *n*, (%)	158 (44.6%)	41(48.2%)	65(50.0%)	39 (41.1%)	13 (29.5%)	0.089[a]
DCM *n*, (%)	14 (4.0%)	3 (3.5%)	6 (4.6%)	5 (5.3%)	0 (0.0%)	[a]
PE *n*, (%)	34 (9.6%)	9 (10.6%)	12 (9.2%)	10 (10.5%)	3 (6.8%)	[a]
Rhythmic event *n*, (%)	29 (8.2%)	14 (16.5%)	5 (3.8%)	8 (8.4%)	2 (4.5%)	[a]
Septic shock *n*, (%)	30 (8.5%)	4 (4.7%)	6 (4.6%)	11 (11.6%)	9 (20.5%)	[a]
Other *n*, (%)	88 (25.1%)	14 (16.5%)	36 (27.7%)	22 (23.2%)	17 (38.6%)	0.041[a]

Note: Data are expressed as the median and interquartile range (25th–75th) or number (percentage). Bold marked values are evaluated as significant.

Abbreviations: BMI, body-mass-index; CAD, coronary artery disease; CPR, cardiopulmonary resuscitation; DCM, dilatation cardiomyopathy; ECLS, extracorporeal life support; MAP, mean arterial pressure; MOF/D, multi-organ failure/dysfunction, PE, pulmonary embolism.

[a]Taking into account that in some groups the frequency of the value was less than 5, the test cannot be considered reliable.

CPR, the risk of suffering MODS with 3 or 4 organs affected was significantly reduced (Table 1).

Initiation of ECLS resulted in immediate stabilization, notable by a significant increase in MAP with simultaneous significant ($p < 0.001$) reduction of the vasoactive-inotropic score. MAP showed differences 24 h after the onset of ECLS with respect to the later severity of MODS; these differences proved to be small with respect to absolute values, but statistically significant. More marked differences were found in the vasoactive-inotropic score, both before ECLS and after 24 h of therapy (Table 2).

Pre-oxygenator mixed venous saturation did not differ significantly with respect to the severity of MODS during the clinical course until the full development of MODS. Also, no significant difference in central venous saturation among patients undergoing ECLS with and without sepsis (75.5% vs 73%, $p = 0.359$) was observed.

Although absolute values of lactate serum concentration prior to and 24 h after ECLS initiation differed significantly between patients with a different manifestation of MODS severity, only lactate serum concentration after 24 h showed moderate predictivity with respect to the development of 4 organ MODS (AUC 0.70, 95% CI 0.63–0.79, $p < 0.05$).

3.3 | Proinflammatory cytokines

The serum concentration of the proinflammatory cytokines IL 6, IL 8, TNF-alpha, and sIL2R differed significantly with respect to the number of organs affected by dysfunction during the subsequent clinical course. This holds true for measurements prior to ECLS initiation as well as after 24 h following the start of ECLS. Serum levels of these markers increased significantly with each additional organ affected by dysfunction (Table 3, Figure 2).

ROC analysis showed significant predictivity of all proinflammatory cytokines regarding the occurrence of MODS with 3 or 4 organs involved. The strongest predictive potential was shown by the serum level of IL 8 prior

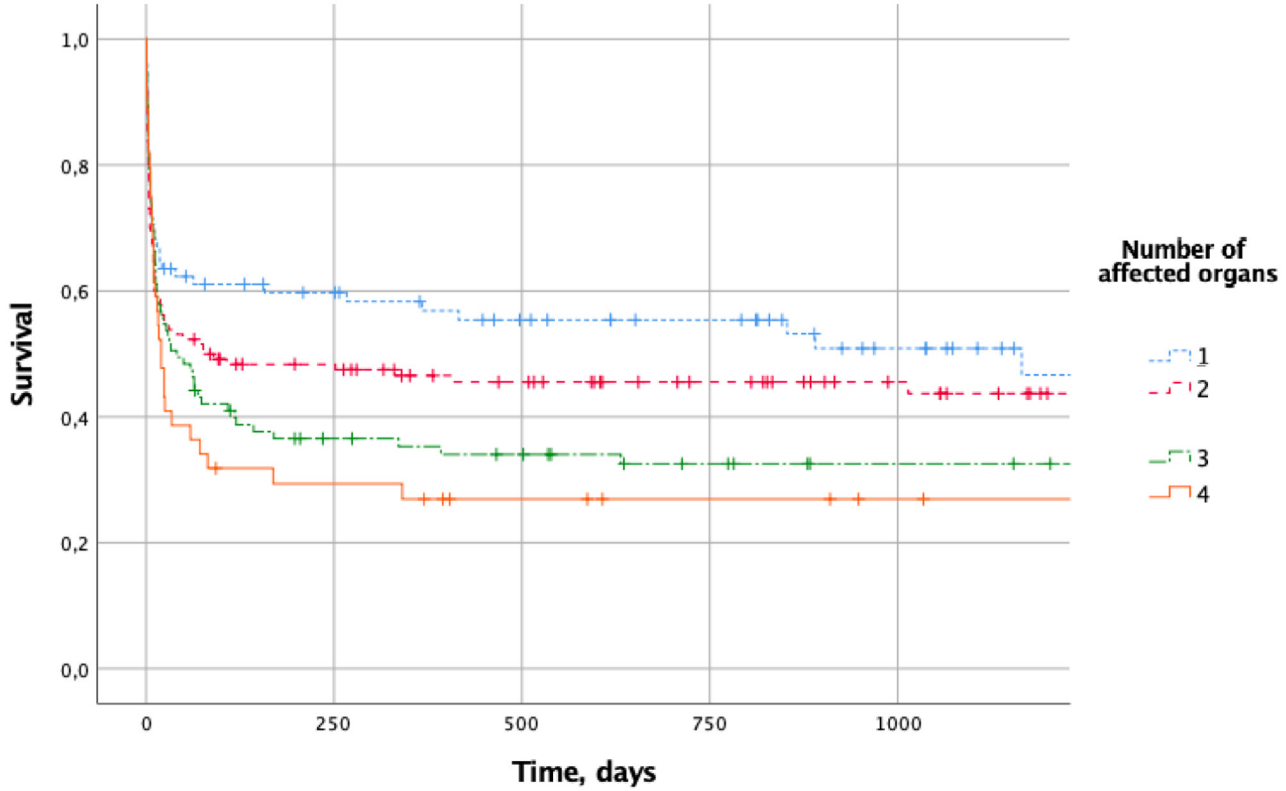


FIGURE 1 Kaplan–Meier survival curves between different groups of organ failure/dysfunction [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Hemodynamic parameters before and during ECLS

Category	All patients	Number of affected organs				*p*-value
		1	2	3	4	
Number of patients	354	85	130	95	44	
MAP before ECLS, mm Hg	54.5	50.0	55.0	55.0	56.5	0.365
MAP at 1st day after ECLS mm Hg	64.0	66.0	64.0	64.0	62.0	**0.016**
Lactate before ECLS, mg/dl	85.0	83.0	82.0	78.0	104.5	**0.049**
Lactate at 1st day after ECLS. mg/dl	36.0	26.0	30.0	41.0	72.5	**<0.001**
Vasoactive-inotropic score before ECLS	57	36	49	63	95.5	**<0.001**
Vasoactive-inotropic score after ECLS	9.5	5	8	12	19	**<0.001**
Lowest level of central venous saturation during ECLS, %	76.61	77.75	77.0	75.9	75.938	0.815

Note: Data are expressed as median or number. Bold marked values are evaluated as significant.

Abbreviations: ECLS, extracorporeal life support; MAP, mean arterial pressure.

to ECLS regarding the occurrence of a four organ MODS (AUC 0.78, 95% CI, 0.71–0.84, $p < 0.05$) (Figure 3).

Comparing cytokine profiles with respect to prognostically relevant underlying conditions, a significantly lower serum level of sIL2 was found in patients who underwent CPR at the time of ECLS implantation (Table 4). Furthermore, patients diagnosed with sepsis at the time of ECLS onset presented with significantly higher interleukin serum levels (Table 4).

Depending on the individual organs involved, there were no significant differences regarding the cytokines analyzed.

4 | DISCUSSION

The occurrence of MODS is a common complication with a strong impact on the outcome of patients treated with ECLS.

TABLE 3 Cytokine levels in relationship to MOF/D

	One MOF/D	Two MOF/D	Three MOF/D	Four MOF/D	*p*-value between groups	[a]$p < 0.05$ number between paired groups
Preimplantation TNF-alpha, pg/ml	11	15	17	19	$p < 0.001$	4
1st day TNF-alpha, pg/ml	13	17	21	21.5	$p < 0.001$	3
Preimplantation sIL-2R, U/ml	668	815.5	1136	2579	$p < 0.001$	4
1st day sIL-2R, U/ml	1021	1098.5	1706	3036	$p < 0.001$	4
Preimplantation IL6, pg/ml	218	347.5	740	1870.5	$p < 0.001$	5
1st day IL6, pg/ml	201	210.5	324	815	$p < 0.001$	2
Preimplantation IL8, pg/ml	63	83	172	442	$p < 0.001$	5
1st day IL8, pg/ml	57	73.5	125	375.5	$p < 0.001$	4

Note: Data are expressed as a median.

Abbreviations: IL6, interleukin-6; IL8, interleukin-8; MOF/D, multi-organ failure/dysfunction; sIL2R, soluble interleukin-2 receptor; TNF-alpha, tumor necrosis factor alpha.

[a]Number of statistically significant differences between compared groups as predictor of sensitivity of failure. Post hoc test between the groups as pairwise multiple comparison procedure (Dunn's Method).

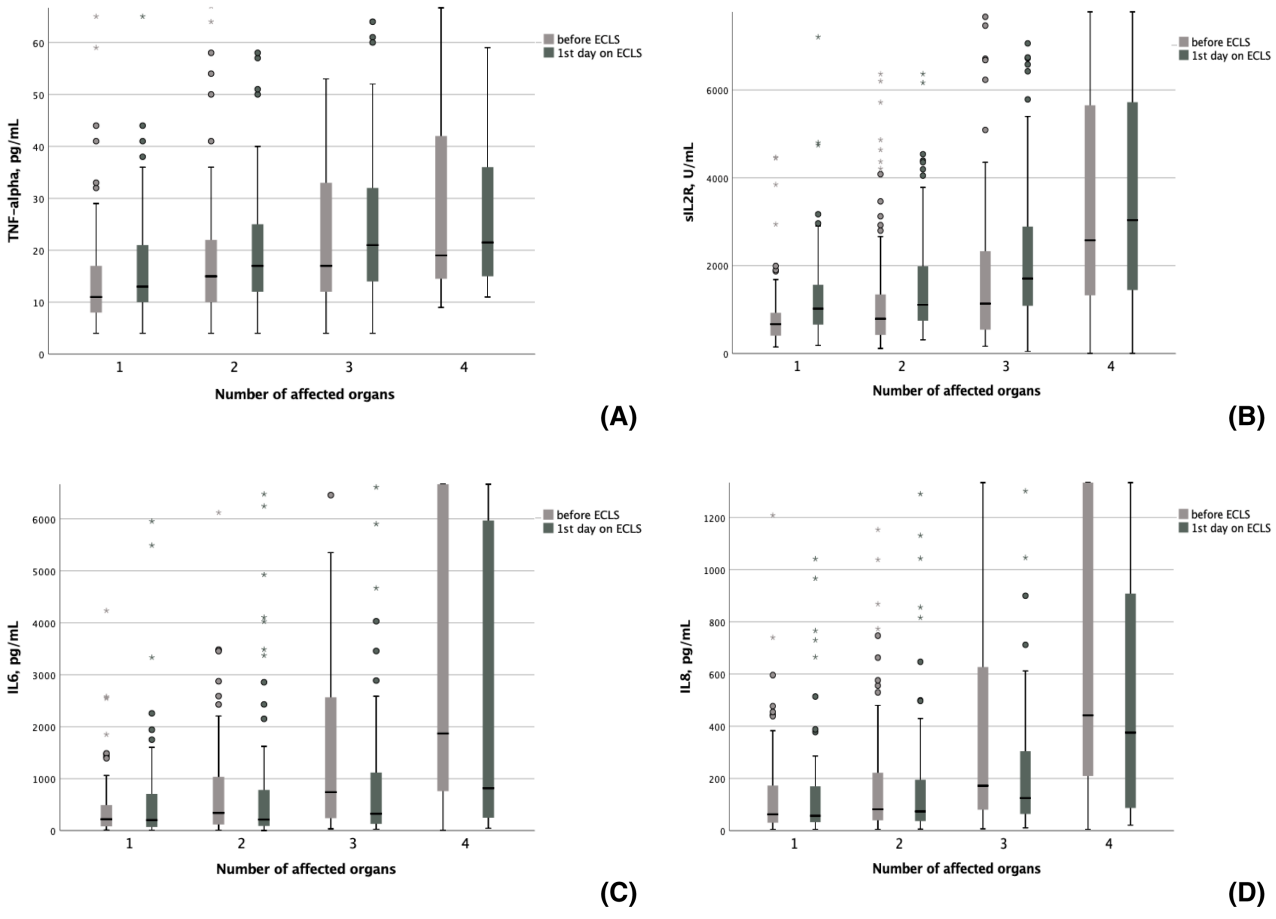
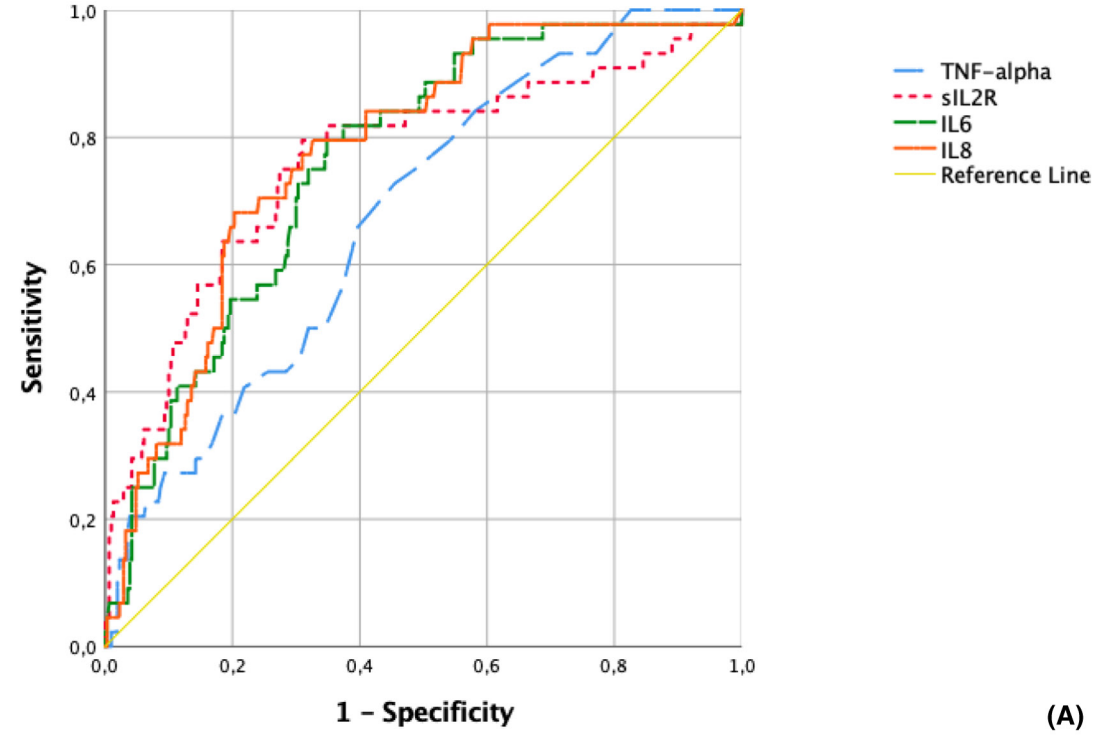


FIGURE 2 Comparison of TNF-alpha (A), sIL2R (B), interleukin 6 (C), and interleukin 8 (D) values before ECLS implantation and on 1st day of ECLS between groups with 1,2,3 and 4 organ failure

The distribution of organs affected, as well as the worsening of prognosis with each additional organ involved, is consistent with analyses of MODS in other intensive care entities.[8,10]

A vast number of studies were performed to assess the prognosis of patients who undergo ECLS, including studies analyzing the impact of certain laboratory



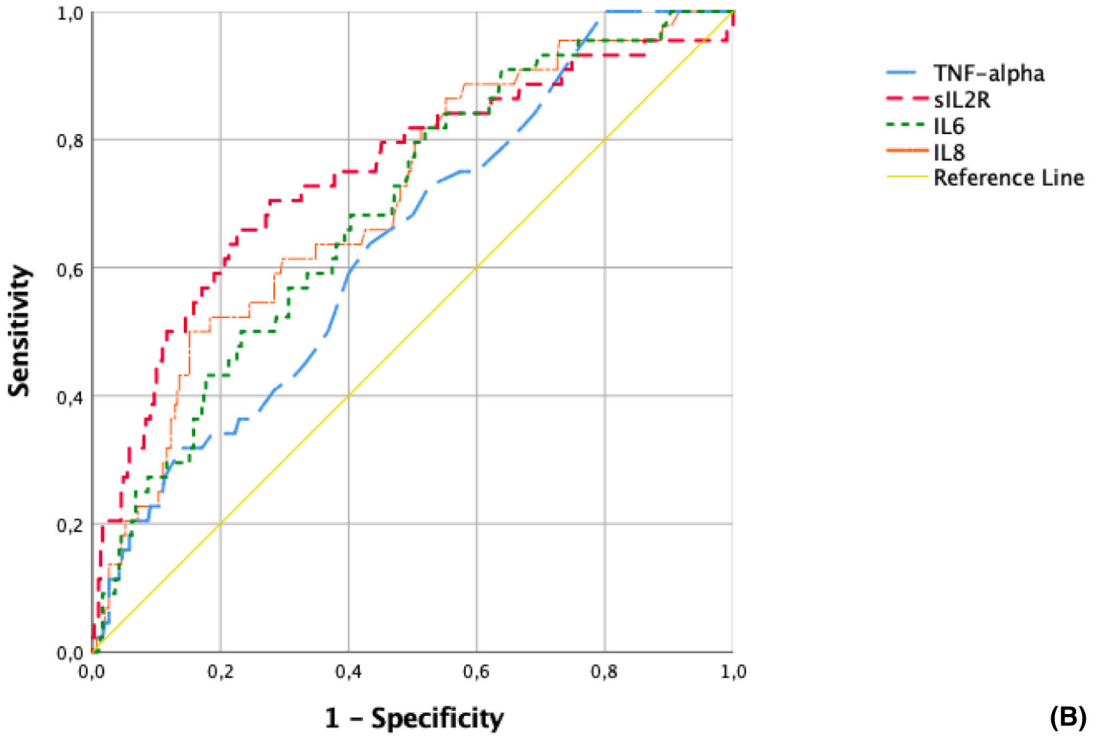


FIGURE 3 Receiver-operating characteristic curves analyzing the predictive value of IL6, IL8, TNF-alpha und sIL2R serum levels prior to (A) and on 1st day (B) of ECLS therapy for four organs failure/dysfunction [Color figure can be viewed at wileyonlinelibrary.com]

values.[18] Also, specific scores have been developed to evaluate the prognosis during the first hours of extracorporeal support.[19,20] Moreover, the analysis of several cytokines[11] showed predictive capacity with respect to the outcome of ECLS patients, even prior to the implantation itself. The resulting prognostic reliability proved

TABLE 4 Impact of sepsis, cardiotomy, and cardiopulmonary resuscitation on cytokines

	With sepsis	Without sepsis	*p*-value	Postcardiotomy	Without cadiotomy	*p*-value	With CPR	Without CPR	*p*-value
Preimplantation TNF-alpha, pg/ml	32.5 (16.75; 79.75)	14 (10; 22.75)	**<0.001**	15 (10.5; 23)	15 (10; 24)	0.912	15 (10; 23)	16 (12; 26)	0.107
At 1st TNF-alpha, pg/ml	33 (13.75; 61.75)	18 (11; 25)	**0.002**	16 (11; 22)	19 (12; 29)	0.052	18 (12; 27)	17 (12; 25)	0.758
Preimplantation sIL2R, U/ml	3353 (1672.75; 7088.25)	817.5 (425.25; 1481)	**<0.001**	1132 (484; 2247.5)	873 (458.5; 1620.5)	0.222	751 (422; 1341)	1411 (663; 3057)	**<0.001**
At 1st day sIL2R, U/ml	3516.5 (1681.25; 7271.25)	1262 (773.75; 2108)	**<0.001**	1515 (990.5; 2928.5)	1315 (762; 2174)	**0.040**	1205 (754; 1939)	1834 (1110; 3752)	**<0.001**
Preimplantation IL6, pg/ml	3549.5 (252.5; 32 643.25)	385.5 (127.75; 1362)	**<0.001**	488 (217.5; 1645.5)	386 (120; 1404.5)	0.187	409 (120; 1373)	388 (187; 2152)	0.320
At 1st day IL6, pg/ml	874.5 (161.75; 11 836.5)	257.5 (96.250; 822.75)	**0.013**	257 (132.5; 707.5)	263 (86.5; 1074)	0.787	266 (97; 1066)	250 (111; 722)	0.583
Preimplantation IL8, pg/ml	365 (88.5; 719.75)	110 (46; 354)	**<0.001**	106 (54; 299)	122 (45; 408.5)	0.847	111 (40; 377)	153 (56; 426)	0.113
At 1st day a IL8, pg/ml	161.5 (63.25; 5212.25)	91.5 (39.25; 240.75)	**0.025**	84 (44.5; 214)	98 (39; 301.5)	0.584	109 (46; 301)	82 (35; 219)	0.251

Note: Data are expressed as the median and interquartile range (25th; 75th). *p*-value according to Mann–Whitney *U* test. Bold marked values are evaluated as significant.

Abbreviations: CPR, cardiopulmonary resuscitation; IL6, interleukin-6; IL8, interleukin-8; IQR, interquartile range; TNF-alpha, tumor necrosis factor-alpha; sIL2R, soluble interleukin-2 receptor.

to be comparable to scores consisting of a variety of factors.[19,20]

Concerning pathophysiology most authors refer to the development of a systemic inflammatory response syndrome leading to multi-organ failure, taking into account the dynamics of cytokines, and selected laboratory values that could determine changes in certain organs or organ systems.[5,7,8,10] To our knowledge, a relationship between cytokine levels, clinical development of multiple organ failure, and its prognostic value in patients undergoing ECLS has not been previously realized. A reasonable cause may be the complexity in assessing and determining the dysfunction or failure of a specific organ or organ system. Thus, laboratory parameters may be caused by the occurrence of organ dysfunction as well as by ECLS therapy itself. As an example, bilirubin could characterize the liver function and may be caused by hemolysis in ECLS. Similarly, the diagnosis of ARDS is complicated by the presence of an oxygenator in the ECLS circuit.

The prognostic impact of proinflammatory cytokines irrespective of a pathophysiological content on the outcome of patients undergoing ECLS has already been analyzed.[11,12]

The present analysis shows a relationship between the level of cytokines and their prognostic ability through the prism of multiple organ failure. We found that pre-implantation levels of interleukin 6, interleukin 8, and the soluble interleukin 2 receptor were accurate predictors of multiple organ dysfunction increasing in line with a rising number of organ failures. Interleukin 8 and the soluble interleukin 2 receptor proved to be the most reliable cytokines as prognostic indicators of MODS during ECLS. At the same time, a significant difference in survival was found between groups of these patients, with survival rates decreasing with increasing severity of organ dysfunction and failure. This correlation offers an explanation for the prognostic effect of some interleukins on the survival of patients undergoing ECLS.

Interestingly, the strongest prognostic value is given by the level of cytokines prior to ECLS implantation, indicating that the inflammatory response is mainly caused by factors unrelated to the extracorporeal support.

Moreover, the analysis revealed that patients undergoing ECLS, who have not undergone pre-implantation CPR are more susceptible to develop severe MODS and thus an unfavorable outcome after ECLS implantation. Paralleling cytokine serum levels to this observation show the sIL2R serum levels, both before implantation and 24 h after implantation, were significantly lower in patients that underwent CPR. It may be assumed that the acute onset of disease in patients with CPR is a causal factor in the lower incidence of MOF in this group. This encourages further investigation of the possible causes of inflammatory triggers in ECLS-patients prior to its initiation.

Whereas a significantly higher incidence of MOF was noted for septic patients, central venous saturation did not differ significantly between septic and non-septic patients, such it may be assumed that general oxygen supply in patients undergoing ECLS is not responsible for the higher incidence of MOF in septic patients, whereas severe inflammation in septic shock may play a role.

Concerning demographic risk factors for the development of MOF no significant age differences concerning the number of affected organs could be detected, although the incidence of MOF in patients suffering shock without undergoing ECLS shows an age correlation.[21] This may be due to the lower age range as well as generally lower age of patients being deemed eligible for ECLS compared to the population of intensive care patients without ECLS.

A possible pathophysiological concept for the development of multi-organ failure in ECLS patients may be the onset of endothelial dysfunction due to hemodynamic disorders prior to ECLS implantation. Consequently, a whole cascade of systems is triggered, including cytokine-induced capillary leakage, activation of coagulation, and complement system cascades, which exacerbate a vicious circle of microcirculatory and cellular hypoxia on the already hypoxically challenged parenchyma caused by the underlying hemodynamic disorder.[22]

These inflammatory processes in the pathophysiology of MODS during and following ECLS could explain the occurrence of multi-organ failure during ECLS despite sufficient cardiac index, determined by ECLS flow, and despite sufficient general oxygen supply, determined by pre-oxygenator venous saturation.

Even though inflammation is not the sole trigger that leads to the development of multiple organ failure, the combination of initial hemodynamic compromise, intensive care therapy, and inflammation may culminate in a vicious circle resulting in the development of MODS.

The prognostic impact of interleukins on ensuing clinical course and patient outcome prompts the question of whether it is merely a diagnostic and prognostic feature, or whether serum interleukins represent a worthwhile therapeutic target.

Previous studies on the reduction of interleukin serum levels for therapeutic purposes have yielded controversial results.[23–26]

5 | LIMITATIONS

Possible limitations of this study are the period of 11 years during which data were collected, taking into account changing features of ECLS patient management and

technical tools over time. Furthermore, the underlying patient population presents rather heterogeneous. The retrospective nature of the analysis as well as reporting the experience of a single center may also be a restriction for definitive conclusions.

6 | CONCLUSION

The occurrence of multi-organ dysfunction and failure presents a frequent and prognostically relevant complication during the clinical course of patients undergoing ECLS therapy. Besides underlying conditions and hemodynamics, proinflammatory cytokines show prognostic capacity with respect to the occurrence and severity of multi-organ dysfunction and failure and such appear to be involved in the pathophysiological pathway of the development of multi-organ dysfunction and failure in ECLS patients.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

Kozakov participated in the design of the study, was the main coordinator of the study, performed the statistical analysis, and revised the manuscript. Philipp participated in the coordination of the study, collected data, and revised the manuscript. Provaznik participated in the design of the study and helped draft the manuscript. Lubnow, Lunz, Keyser, and Rupprecht collected data and helped draft the manuscript. Schmid participated in the design and coordination of the study and revised the manuscript. Schopka conceived of the study, participated in the design and coordination of the study, and helped draft the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL

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.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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