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Influence of immunosuppression in patients with severe acute respiratory distress syndrome on veno-venous extracorporeal membrane oxygenation therapy

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Abstract

Prognosis of patients suffering from acute respiratory distress syndrome (ARDS) is poor. This is especially true for immunosuppressed patients. It is controverisal whether these patients should receive veno-venous extracorporeal membrane oxygenation (VV ECMO) while evidence on this topic is sparse. We report retrospective data of a single-center registry of patients with severe ARDS requiring ECMO support between October 2010 and June 2019. Patients were analyzed by their status of immunosuppression. ECMO weaning success and hospital survival were analyzed before and after propensity score matching (PSM). Moreover, ventilator free days (VFD) were compared. A total of 288 patients were analyzed (age 55 years, 67% male), 88 (31%) presented with immunosuppression. Survival rates were lower in immunosuppressed patients (27% vs. 53%, $P < .001$ and 27% vs. 48% after PSM, $P = .006$). VFD (60 days) were lower for patients with immunosuppression (11.9 vs. 22.4, $P < .001$), and immunosuppression was an independent predictor for mortality in multivariate analysis. Hospital survival was 20%, 14%, 35%, and 46% for patients with oncological malignancies, solid organ transplantation, autoimmune diseases, and HIV, respectively. In this analysis immunosuppression was an independent predictor for mortality. However, there were major differences in the weaning and survival rates between the etiologies of immunosuppression which should be considered in decision making.

KEYWORDS

acute respiratory distress syndrome, extracorporeal membrane oxygenation, immunosuppression, outcome

1 | BACKGROUND

Veno-venous extracorporeal membrane oxygenation (VV ECMO) may improve survival in patients with severe acute respiratory distress syndrome (ARDS).[1-3] Thus, there was a substantial increase in the use of ECMO therapy over the recent years.[4] However, the outcome is strongly dependent on the underlying etiology of ARDS and the concomitant diseases and conditions, especially the presence of immunosuppression.[5-9]

Immunosuppressed patients with respiratory failure are at high risk which is reflected by high mortality rates. Hospital mortality in case of respiratory failure ranges from 17% to 72%.[10-15] The high mortality contributes to the underlying disease itself as well as to a more severe course of ARDS when immunosuppression is present.[16]

Previous trials showed an association of immunosuppression and increased mortality in patients with ARDS treated with ECMO.[5,6,17] Therefore, the use of ECMO in patients with immunosuppression is deemed critical, and the ELSO guidelines consider major pharmacologic immunosuppression as a relative contraindication for the use of ECMO support.[18]

However, the number of patients with immunosuppression is increasing steadily,[19] as the spectrum of immunosuppressive therapies as well as the volume of solid organ transplantations are increasing over the last years.[20,21] Thus, more patients with immunosuppression are admitted to the ICU because of respiratory failure[22] and a large number is treated with ECMO in case of ARDS despite underlying immunosuppression. In recently published trials, 20%-30% of ECMO patients showed some kind of immunosuppression.[2,5] Moreover, hospital survival of immunosuppressed non-ECMO patients with ARDS has improved over the years. However, mortality still remains high in case of severe ARDS (69%).[23] Additionally, there is a large spectrum of immunosuppressive conditions with very different survival rates as shown in various non-ECMO ARDS trials.[16]

Even if some studies, especially the IDEA study,[7] examined the use of VV ECMO in immunosuppressed patients, evidence on outcome still is limited. In addition to the opportunity to add data of a large ECMO center treating immunosuppressed patients, this study also includes a control group of patients with VV ECMO support without immunosuppression. We therefore performed a retrospective analysis to investigate the influence of immunosuppression and its etiologies on hospital survival, ECMO weaning success as well as ventilator free days at 30 and 60 days in patients with severe ARDS requiring VV ECMO support at our center.

2 | PATIENTS AND METHODS

We report retrospective data of a single-center registry of patients with severe ARDS treated with VV ECMO. All patients treated at the Interdisciplinary Medical Intensive Care Unit at the Medical Center, University of Freiburg, Germany, between October 2010 and June 2019 were registered. Patient identity data derived from the registry were blinded, and the study plan was approved by the local ethics committee (EK-Freiburg 151/14). The need for informed consent of the subjects was waived by the local ethics committee.

2.1 | Study population

Our center treats a large number of hematooncological patients and patients with autoimmune diseases. This leads to a high amount of patients with immunosuppression on our intensive care units (ICU), many of them requiring treatment for respiratory failure.

In this study, the status of immunosuppression was investigated and patients were divided into an "immunosuppression" and "no immunosuppression" group. The term immunosuppressed describes a reduced ability to fight infections and other diseases, which can be caused by underlying diseases and conditions as well as by drug therapy or treatment. Four subgroups of immunosuppression were defined: immunosuppression in cause of oncological malignancies (including hematologic malignancies and active solid tumors), caused by the disease itself or a related therapy (chemotherapy or hematopoetic stem cell transplantation (HSCT) within the last year) (oncological); immunosuppression in patients after solid organ transplantation (solid organ Tx); patients with autoimmune diseases and immunosuppressive therapies (cut off for steroids: ≥10 mg/day prednisolone equivalent) (autoimmune disease); and patients with immunosuppression caused by HIV (HIV).

In this study all patients suffered from severe ARDS. VV ECMO support was initiated in cases of severe hypoxic respiratory failure or CO_2-retention despite mechanical ventilation (MV) as suggested by the ELSO guidelines.

Primary endpoints were successful ECMO weaning and hospital survival. In addition to the hospital survival rate, cumulative incidences of 60-day mortality were calculated using competing risk regression. Free from ECMO support and alive for at least 48 hours after decannulation was defined as successful ECMO weaning. Unsuccessful weaning was defined as the inability to explant the ECMO device because of persistent respiratory failure or death during ECMO support and the need for recannulation within 48 hours. Moreover, ventilator free days (VFDs, absence of invasive MV) were analyzed for the first 30 and 60 days, respectively. VFD's were set to zero if the patient died within the first 30 or 60 days after ECMO implantation.

Furthermore, pulmonary pathogen spectrum ascertained by broncho alveolar lavage (BAL) and tracheal secretions (TS) was investigated.

To compare the patients' disease severity, the RESP,[6] SOFA,[24] and APACHE-II[25] scores as well as the Horowitz index (PaO_2/FiO_2) were analyzed at the time of ECMO initiation.

2.2 | ECMO center and ECMO management

Our institution features a 24/7 ECMO-center localized within a tertiary hospital with a 30-bed medical ICU.

Cannulations in our ECMO center are performed by two experienced intensivists and a perfusionist using Seldinger's technique without primary surgical cut down. All members of the ECMO team can be gathered within 30 minutes. Typical numbers for veno-arterial and veno-venous cannulation are 65 and 45 per year, respectively. There is a 24/7 outreach team. For this research, only in-house cases were considered. As ECMO systems, either SCPC (Sorin Centrifugal Pump Console, LivaNova, London, UK) or Cardiohelp (Maquet Getinge Group, Rastatt, Germany) was used.

Cannulation was performed predominately via the jugular vein using a dual-lumen cannula (Avalon, Maquet, Rastatt, Germany). For patients without life threatening bleeding, anticoagulation was provided by intravenous unfractionated heparin aiming at a partial thromboplastin time 1.5 times upper normal limit. The management of vasopressors and fluid therapy was driven by clinical judgment of the ECMO experienced intensivist in charge and has been reported earlier.[26]

Treatment algorithms and standard operating procedures were subject to optimizations during the observational period, reflecting current state of the art recommendations and scientific knowledge.

Immunosuppression represents no absolute contraindication at our center. This is especially true for patients with respiratory failure in the context of active HIV or autoimmune diseases. Patients after solid organ transplantation are critically evaluated. Patients with an underlying oncological disease with a prognosis of >6 months are also evaluated for ECMO support in case of severe ARDS, depending on their clinical condition and comorbidities.

Whenever possible, spontaneous breathing modes like continuous positive pressure ventilation with pressure support were applied. Biphasic positive airway pressure (BIPAP) was the controlled MV mode that was used mostly at our institution. In very few patients, airway pressure release ventilation (APRV) was used, when considered beneficial. VV ECMO support was implemented in case of severe but potentially reversible respiratory failure, when lung-protective MV resulted in hypoxemia or hypercapnia. Lung-protective MV was defined as positive end expiratory pressure (PEEP) ≤ 15 cmH$_2$O, plateau pressure ≤ 30 cmH$_2$O, driving pressure ≤ 15 cmH$_2$O, and FiO$_2 \leq 50\%$.

After initiation of the VV ECMO support, invasivity of MV was reduced and ECMO flow was adjusted aiming for a peripheral oxygen saturation of 85%-90% and partial pressure arterial oxygen of approximately 50 mm Hg, respectively. Typical ventilator settings were as follows: PEEP 15 mm Hg, plateau pressure 25 cmH$_2$O, FiO$_2$ 50%, and respiratory rate 10/minute. Details on ventilator management and prone positioning procedures have been described earlier.[27]

2.3 | Statistical analysis

Continuous variables are presented as median and interquartile range (IQR), whereas IQR is displayed as Q1-Q3. Categorical variables are presented as numbers and percentages. Results of VFD are presented as mean $\pm$ SD.[28] Mann–Whitney U test was used for analysis of continuous variables, Pearson's Chi-squared test, or Fisher's exact test for categorical variables to investigate group differences depending on the status of immunosuppression. In addition, weaning success and survival of each subtype of immunosuppression was compared with the nonimmunosuppressed patients. Multivariate regression analysis was performed for univariate (dependent) predictors of hospital survival. Results are given as odds ratio ([OR], 95% confidence interval [CI]); a P value of $\leq .05$ was considered statistically significant. Propensity score matching was performed to adjust for disease severity and risk of death in the immunosuppression and nonimmunosuppression group using SPSS with a nearest neighbor matching algorithm using a caliper of 0.01. Matching was performed for variables with independent association to improved or reduced hospital survival in multivariate analysis (lung fibrosis, liver cirrhosis, and proof of pulmonary fungal infection) in all patients. In addition to the analysis of in-hospital mortality as a dichotomous endpoint, cumulative incidences of 60-day mortality were calculated using competing risk regression (Fine and Gray method) with discharge alive considered a competing event for the illustration of the time course of mortality for the patients in the two groups.[29] Statistical calculations were performed using IBM SPSS statistics 25.0 (Armonk, NY: IBM Corp, 2017) and Stata Version 15.1 (Stata Corp, College Station, TX, USA).

3 | RESULTS

3.1 | Patients

A total of 288 patients with complete medical data could be analyzed (age 55 [42.5-64] years, 67% male). A total of 88 (30.6%) patients presented with immunosuppression (Figure 1). Pre-existing pulmonary disease was present in 30.2% of the patients (9% lung fibrosis, 4.9% long-term oxygen therapy [LTOT], Table 1).

Both groups showed a similar profile of age and sex. BMI was lower in patients with immunosuppression. There was no difference in terms of underlying pulmonary disease, except for a higher rate of lung fibrosis in the immunosuppression group (15.9% vs. 6%, $P = .007$). Patients with immunosuppression showed a significant lower rate of comorbidities like nicotine abuse, coronary artery disease, and a trend for less hypertension. Though, more patients with immunosuppression required chronic hemodialysis.

FIGURE 1 Flow chart of the study. *Matching was performed for variables with independent association to improved or reduced hospital survival in multivariate analysis (lung fibrosis, liver cirrhosis, and proof of pulmonary fungal infection). VV ECMO, veno-venous extracorporeal membrane oxygenation
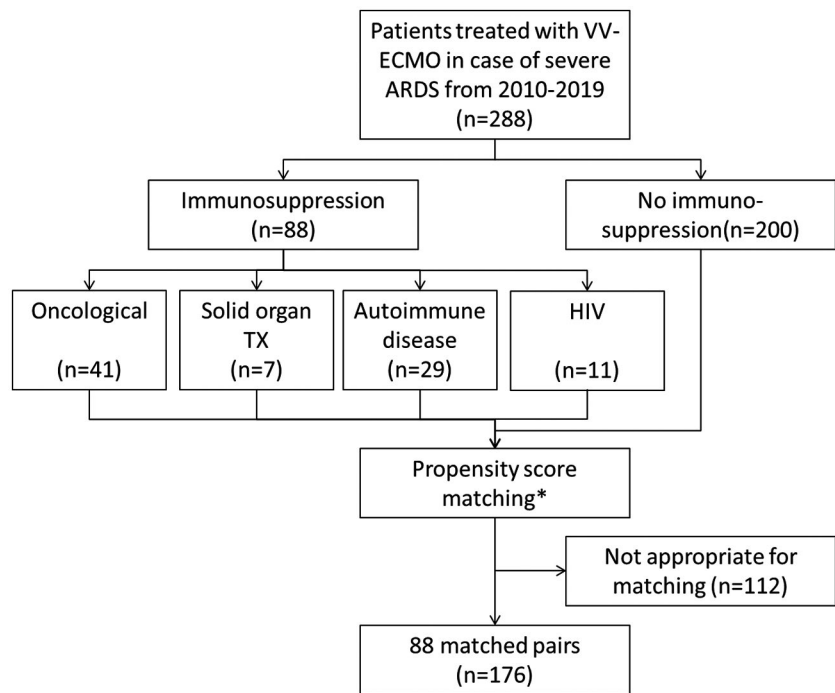
Horowitz index was higher in patients with immunosuppression. There was no difference in terms of duration of MV before ECMO implantation; average for both groups was 1 day. Patients without immunosuppression showed a higher rate of acute renal failure before ECMO.

APACHE II-score was higher in patients without immunosuppression (27 [22-32] vs. 24 [16-29], $P = .002$). Moreover, the RESP score was lower in patients with immunosuppression (0 [−2 to 2] vs. 2 [0-4], $P < .001$). A calculation of the RESP score without inclusion of immunosuppression showed identical results for both groups (2 [0-4], $P = .852$).

Patients with immunosuppression showed lower values of leukocytes, platelets, hemoglobin, hematocrit, and creatinine. ARDS was more often related to pneumonia and less often to aspiration in patients with immunosuppression.

Pulmonary pathogen spectrum revealed a high amount of viral and fungal infections in all patients (31.6% and 19.1%, respectively); 85% of pulmonary microbiological proofs were obtained by BAL. Patients with immunosuppression showed a different pulmonary pathogen spectrum, with more fungal (29.5% vs. 14.5%, $P = .003$) and less bacterial (22.7% vs. 50%, $P < .001$) infections.

3.2 | Procedural characteristics and outcome

ICU length of stay and ECMO duration were comparable between both groups, but the duration of MV was longer in the nonimmunosuppression group. ECMO implantation without previous intubation and invasive MV was used more often in patients with immunosuppression (15.9% vs. 4%, $P < .001$).

Patients with immunosuppression showed a lower weaning rate (37.5% vs. 60%, $P < .001$) and hospital survival (27.3% vs. 52.5%, $P < .001$) rate compared to patients without immunosuppression (Table 2). Moreover, VFD in the first 30 as well as 60 days after ECMO implantation were lower for patients with immunosuppression (4.0 ± 8.2 vs. 7.8 ± 9.9, $P = .001$ and 11.9 ± 20.4 vs. 22.4 ± 23.6, $P < .001$, respectively).

Cumulative incidence of 30 and 60 days in hospital death of patients with versus without immunosuppression was 69% versus 44% and 72% versus 46%, respectively ($P < .001$, Figure 2A).

3.3 | Analysis of immunosuppression as an independent predictor for mortality

A univariate analysis of all patients showed an association between increased mortality and age, lung fibrosis, liver cirrhosis, immunosuppression, proof of pulmonary fungal infection, and absence of a pulmonary microbiological proof. Furthermore, proof of pulmonary bacterial infection was associated with decreased mortality (Additional file 1, Table E1).

A multivariate analysis of these factors revealed immunosuppression as an independent predictor for mortality (Odds ratio 0.42 [0.23-0.76], $P = .005$, Additional file 1, Figure E1). Moreover, lung fibrosis, liver cirrhosis and proof of pulmonary fungal infection were independent predictor for mortality.

TABLE 1 Baseline characteristics

Demographics	All (n = 288)	Immunosuppression (n = 88)	No immunosuppression (n = 200)	P value
Age (years)	55 (42.5-64)	54.5 (39.3-65)	55 (45-63)	.756
Sex (male)	193 (67%)	56 (63.6%)	137 (68.5%)	.419
BMI (kg/m^2)	24.4 (23.4-29.2)	24 (21.8-27.5)	24.7 (23.5-30.1)	.004
Underlying pulmonary disease	87 (30.2%)	26 (29.5%)	61 (30.5%)	.871
COPD	25 (8.7%)	7 (8%)	18 (9%)	.772
Asthma	16 (5.6%)	2 (2.3%)	14 (7%)	.107
Lung fibrosis	26 (9%)	14 (15.9%)	12 (6%)	.007
Cystic fibrosis	7 (2.4%)	1 (1.1%)	6 (3%)	.344
LTOT	14 (4.9%)	5 (5.7%)	9 (4.5%)	.667
Pulmonary hypertension	8 (2.8%)	3 (3.4%)	5 (2.5%)	.665
Comorbidities				
Nicotine abuse	98 (34%)	20 (22.7%)	78 (39%)	.007
Hypertension	98 (34%)	23 (26.1%)	75 (37.5%)	.061
Diabetes mellitus	39 (13.5%)	8 (9.1%)	31 (15.5%)	.143
CAD	36 (12.5%)	4 (4.5%)	32 (16%)	.007
Chronic renal failure	21 (7.3%)	9 (10.2%)	12 (6%)	.204
Chronic hemodialysis	2 (0.7%)	2 (2.3%)	0 (0%)	.032
Liver cirrhosis	22 (7.6%)	6 (6.8%)	16 (8%)	.728
Procedural characteristics				
Oxygenation pre ECMO				
FiO$_2$ (%)	1 (0.8-1)	1 (0.7-1)	1 (0.8-1)	.207
Horowitz index (mm Hg)	70.9 (57.9-98.8)	77.3 (60.1-123.6)	67.3 (55.5-90)	.002
D(A-a)O$_2$ (mm Hg)	554 (418.5-598)	538 (381-592.5)	557.5 (428-601)	.139
Duration of MV before ECMO (days)	1 (0.2-3.3)	0.8 (0.1-4.7)	1.1 (0.2-2.9)	.716
<2 days	178 (61.8%)	51 (58%)	127 (63.5%)	.659
2-7 days	70 (24.3%)	24 (27.3%)	46 (23%)	
>7 days	40 (13.9%)	13 (14.8%)	27 (13.5%)	
Acute renal failure	96 (33.3%)	20 (22.7%)	76 (38%)	.011
Scores				
SOFA score	13 (11-15)	12.5 (10-15)	13 (11-15)	.489
APACHE-II score	26 (20-32)	24 (16-29)	27 (22-32)	.002
RESP score	1 (−1 to 3)	0 (−2 to 2)	2 (0-4)	<.001
RESP score (without immunosuppression)	2 (0-4)	2 (0-4)	2 (0-4)	.852
Laboratory pre ECMO				
Leukocytes (10^3/μL)	12.3 (6.7-19.2)	8.9 (3.4-14.1)	14.2 (7.3-21.6)	<.001
Platelets (10^3/μL)	157 (83-242)	112.5 (48-231.5)	175 (100-253)	<.001
Hb (g/dL)	9.9 (8.3-12.1)	9.3 (8-10.7)	10.3 (8.4-12.8)	<.001
Hematocrit (%)	30.3 (26.1-36.4)	28.5 (24.9-32.9)	32.2 (26.8-38.4)	.001
Creatinine (mg/mL)	1.3 (0.8-2.2)	1 (0.7-1.7)	1.4 (0.9-2.6)	.001
Urea (mg/dL)	65 (39-110)	63 (36.5-108.5)	65 (39-111)	.664
Bilirubin (mg/dL)	0.8 (0.4-1.7)	0.7 (0.4-1.4)	0.8 (0.4-1.8)	.434

(Continues)

TABLE 1 (Continued)

Demographics	All (n = 288)	Immunosuppression (n = 88)	No immunosuppression (n = 200)	P value
pH	7.2 (7.2-7.3)	7.2 (7.1-7.3)	7.2 (7.2-7.3)	.550
pO_2 (mm Hg)	66.3 (57.9-77.3)	71.1 (58.8-80.8)	64.5 (57.5-75.5)	.026
pCO_2 (mm Hg)	56 (46-72.5)	53.3 (44.3-73.3)	56.5 (46.8-71.7)	.414
Lactate (mmol/L)	1.9 (1.1-4.1)	1.7 (1.1-3.2)	2.1 (1.2-4.7)	.166
Causes of ARDS				.019
Pneumonia	205 (71.2%)	72 (81.8%)	133 (66.5%)	
Aspiration	25 (8.7%)	3 (3.4%)	22 (11.1%)	
Other injuries	58 (21.1%)	13 (14.8%)	45 (22.4%)	
Pulmonary pathogen spectrum				
Bacterial	120 (41.7%)	20 (22.7%)	100 (50%)	<.001
Viral	91 (31.6%)	33 (37.5%)	58 (29%)	.153
Fungal	55 (19.1%)	26 (29.5%)	29 (14.5%)	.003
Pneumocystis jirovecii	19 (6.6%)	19 (21.6%)	0 (0%)	<.001
None detected	95 (33%)	32 (36.4%)	63 (31.5%)	.419

Abbreviations: APACHE II score, acute physiology and chronic health evaluation; ARDS, acute respiratory distress syndrome; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; D(A-a)O_2, alveolar-arterial gradient of oxygen concentration; ECMO, extracorporeal membrane oxygenation; FiO$_2$, fraction of inspired oxygen; LTOT, long-term oxygen therapy; MV, mechanical ventilation; RESP score, respiratory extracorporeal membrane oxygenation survival prediction; SOFA score, sequential organ failure assessment.

TABLE 2 Outcome and procedural characteristics

	All (n = 288)	Immunosuppression (n = 88)	No immunosuppression (n = 200)	P value
Weaning successful	153 (53.1%)	33 (37.5%)	120 (60%)	<.001
Hospital survival	129 (44.8%)	24 (27.3%)	105 (52.5%)	<.001
VFD (30 days)	6.6 ± 9.6	4.0 ± 8.2	7.8 ± 9.9	.001
VFD (60 days)	19.2 ± 23.1	11.9 ± 20.4	22.4 ± 23.6	<.001
ICU length of stay (days)	13.4 (9-23.6)	11.9 (7-20.3)	14.1 (9.1-24.1)	.140
ECMO duration (days)	6.7 (3.9-12.3)	6.2 (4-11.3)	7.1 (3.9-12.8)	.346
MV duration (days)	12.4 (7.5-22.5)	11.1 (5.2-19.9)	13.9 (8.5-24.3)	.032
Dual-lumen cannula	244 (84.7%)	71 (80.7%)	173 (86.5%)	.206
Primary non IMV ECMO	22 (7.6%)	14 (15.9%)	8 (4%)	<.001
Tracheostomy	111 (38.5%)	31 (35.2%)	80 (40%)	.443
Hemodialysis	108 (37.5%)	25 (28.4%)	83 (41.5%)	.035

Note: Results of VFD are presented as mean ± SD.

Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IMV, invasive mechanical ventilation; MV, mechanical ventilation; VFD, ventilator free days.

3.4 | Propensity score matching analysis

Eighty-eight propensity score matched pairs (176 patients, Figure 1; Additional file 1, Table E2) could be analyzed. Successful ECMO weaning rate was 37.5% versus 56% (*P* = .015) with and without immunosuppression, respectively. Moreover, survival rate was lower in patients with immunosuppression (27.3% vs. 47.6%, *P* = .006).

Cumulative incidence of 30 and 60 days in-hospital death of patients with versus without immunosuppression was 70% versus 48% and 73% versus 51%, respectively (*P* = .002, Figure 2B).

3.5 | Etiologies of immunosuppression

Forty-one patients (46.5%, Figure 1) showed underlying oncological malignancies. Most patients were treated for hematooncological disease (61% leukemia, 29.2% lymphoma, and 9.8% with solid cancer). Twelve (29.2%)
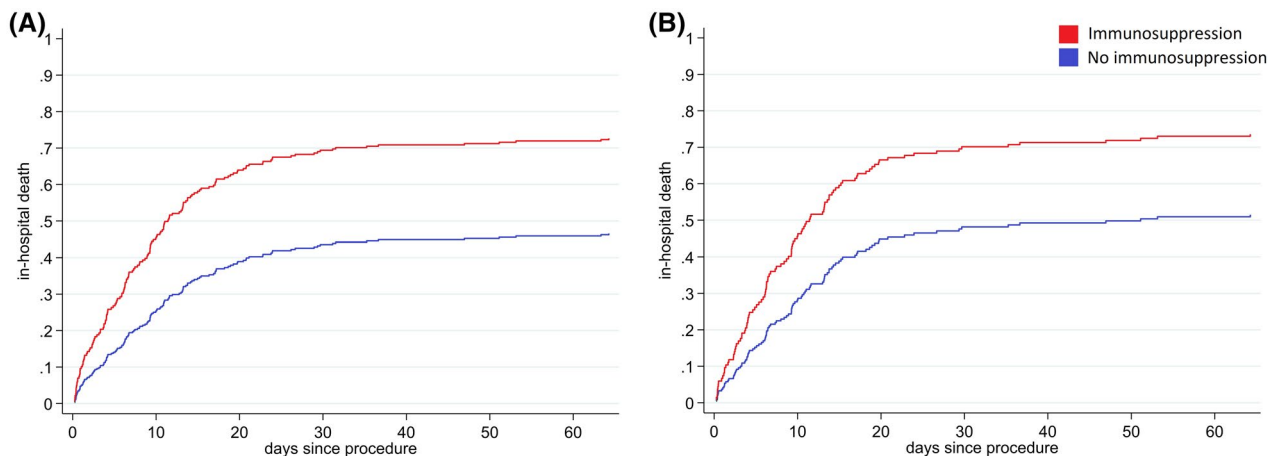
FIGURE 2 In-hospital deaths of patients with versus without immunosuppression. Fine-Gray model for in-hospital deaths, (A) whole cohort (n = 288): SHR 2.07 95%CI 1.50-2.85 *P* < .001, cumulative incidence of 30- and 60-day deaths of patients with versus without immunosuppression was 69% versus 44% and 72% versus 46%; (B) propensity score matched cohort (n = 176): SHR 1.84 95%CI 1.25-2.71 *P* = .002, cumulative incidence of 30- and 60-day deaths of patients with versus without immunosuppression was 70% versus 48% and 73% versus 51%. ECMO, extracorporeal membrane oxygenation [Color figure can be viewed at wileyonlinelibrary.com]

patients had received HSCT within the last year before index hospitalization.

Seven patients (8%) received immunosuppressive therapy after solid organ Tx (lung [3x], kidney [3x], liver [1x]). Twenty-nine patients (33%) had immunosuppression due to an autoimmune disease. Eleven patients (12.5%) presented with immunosuppression caused by HIV infection. HIV was diagnosed during index hospitalization. Therefore, all HIV patients were without previous antiretroviral treatment.

Subgroups of immunosuppression differed in baseline characteristics like age and sex (Additional file 1, Table E3). Rate of underlying pulmonary disease ranged from zero (HIV) to 48.3% (autoimmune disease).

There was no difference in the duration of MV before ECMO initiation between the oncological, solid organ Tx, and autoimmune disease group (0.1-1 day) except in the HIV group (5.3 days). Moreover, there were differences in pulmonary pathogen spectrum with a very high rate of *Pneumocystis jirovecii* infections (PJP) in HIV patients (72.7%), for instance.

The subgroups of immunosuppression showed distinct differences in the survival rates. Hospital survival for patients of the oncological and solid organ Tx group were significantly lower compared to patients without immunosuppression (19.5% and 14.3% vs. 52.5%, *P* < .001 and *P* = .047, respectively, Figure 3). Survival in patients with hematooncological and solid malignancies was similar (18.9% vs. 25%, *P* = 1.0).

There was a trend for a lower survival rate in patients of the autoimmune disease group (34.5%, *P* = .070). Patients of the HIV group showed a comparable survival to the patients without immunosuppression (45.5%, *P* = .761).

For patients of the oncological, autoimmune disease, and HIV group ECMO weaning rates were slightly higher than the survival rates (Figure 3). Patients of the solid organ Tx group showed a high weaning rate of 57.1% compared to low survival rate of 14.3%.

4 | DISCUSSION

In this trial, immunosuppression in patients with ARDS and ECMO support was strongly associated with decreased survival. Multivariate analysis confirmed immunosuppression as an independent risk factor for reduced survival. Furthermore, immunosuppression was associated with a markedly reduced rate of VFDs after 30 and 60 days.

However, subgroup analysis revealed large differences in weaning and survival rates for the underlying etiologies of immunosuppression.

When comparing patients with and without immunosuppression, it is particularly important to consider further comorbidities as well as initial disease severity. Interestingly, clinical characteristics of patients with immunosuppression did not differ from the other patients in terms of age, sex, and underlying pulmonary disease, except of a higher rate of lung fibrosis in the immunosuppression group. In contrast to that, immunosuppressed patients showed fewer other comorbidities. Moreover, immunosuppressed and nonimmunosuppressed patients differed significantly in blood count and in pulmonary pathogen spectrum. Leukocytes, platelets, hemoglobin, and hematocrit were lower in the immunosuppression group, setting these patients to a higher risk of death, as each of these parameters by itself is associated

FIGURE 3 Extracorporeal membrane oxygenation weaning and hospital survival rate of subgroups of immunosuppression. A, Patients with oncological malignancies showed the lowest extracorporeal membrane oxygenation (ECMO) weaning rate, followed by patients with autoimmune disease. The weaning rate of patients with solid organ Tx and HIV was comparable to immunocompetent patients. B, Patients with immunosuppression in case of oncological disease or after solid organ transplantation showed significantly reduced survival compared to patients without immunosuppression. Patients with autoimmune disease or HIV showed numerically but not significantly reduced survival rates [Color figure can be viewed at wileyonlinelibrary.com]
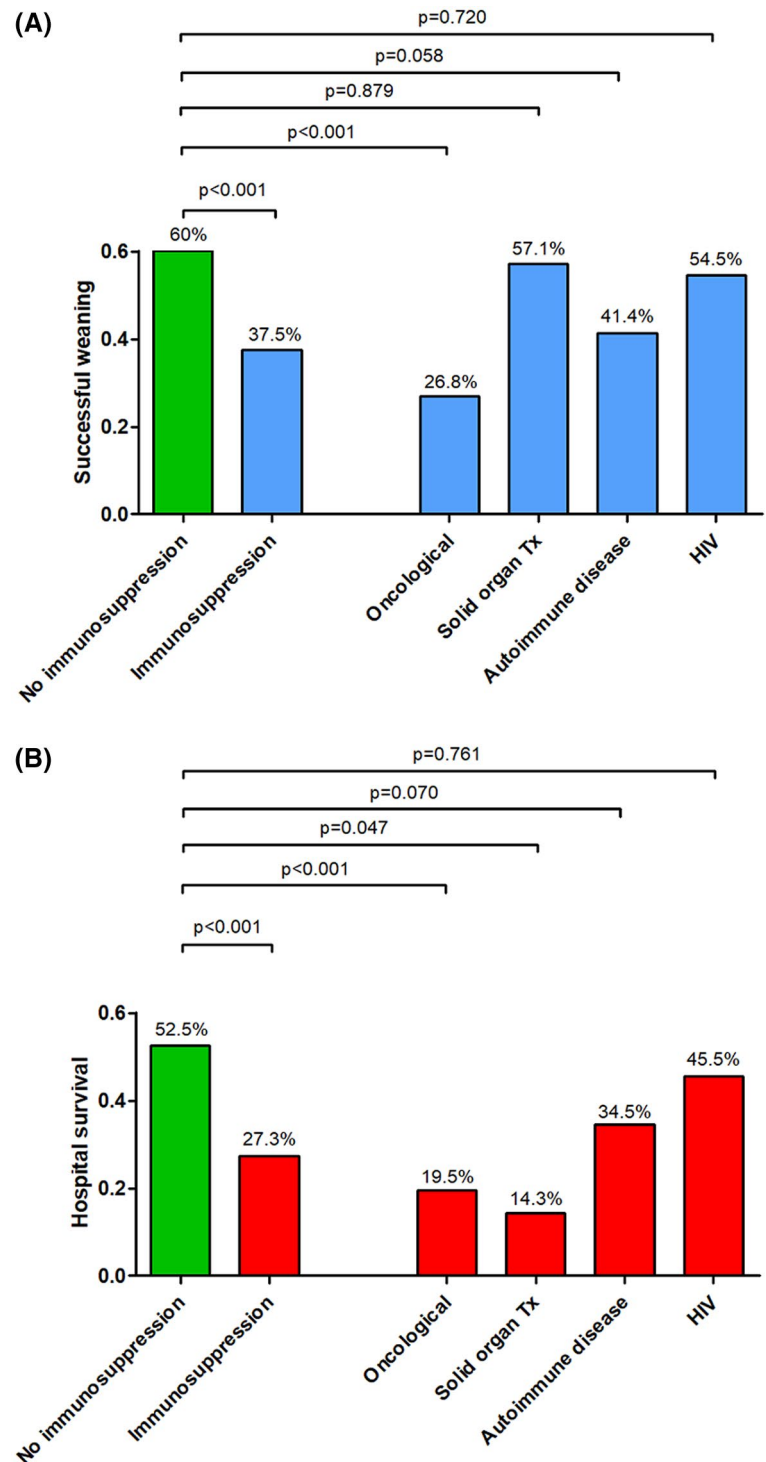
with increased mortality in ICU[24,25] and ECMO patients.[7] Especially, low platelet counts are associated with an increased risk for hemorrhage.[30]

In ARDS patients the pulmonary pathogen spectrum is of great interest, with fungal infections increasing mortality.[23] In this study, the rate of fungal infections was higher in the immunosuppressed group and fungal infections appeared as an independent predictor for survival.

An overall survival rate of only one out of four in immunosuppressed patients seems to be extremely low. On the other hand, survival of patients with severe ARDS and immunosuppression is significantly limited even when ECMO support is not required, as shown by a post hoc analysis of the LUNG SAFE study. Mortality rates in immunosuppressed versus immunocompetent patients were 46% and 31%, respectively.[22] Azoulay et al reported a

survival rate of 44% in a mixed ARDS cohort suffering from malignancies, solid organ transplants, or drug-related immunosuppression.[15]

However, immunosuppressed patients who survived their acute lung failure have a positive midterm prognosis. Schmidt et al showed that the 6-month survival rate of immunosuppressed ECMO patients was nearly the same compared to ICU survival (30% vs. 34%).[7]

Therefore, a detailed analysis of the underlying etiologies of immunosuppression appears to be of particular importance in order to identify the patients who will benefit most from this invasive and resource intense therapy.

Importantly, patients with HIV showed a markedly superior outcome in terms of ECMO weaning and survival compared to the other etiologies of immunosuppression. These patients were younger and had no underlying pulmonary diseases. Nevertheless, they showed average results in the SOFA, APACHE-II, and RESP score and the longest duration of MV to ECMO implantation. In addition, there was a very high rate of PJP infections, which are typically associated with a very high mortality, except in HIV ECMO patients.[31]

A large study investigating HIV patients (n = 2584) receiving MV due to respiratory failure showed a hospital survival rate of 55%.[32] The survival rate of HIV patients requiring ECMO therapy in our cohort was 46%, which is quite encouraging considering that ECMO support was necessary. In summary, these patients showed a favorable outcome and ECMO support definitely should not be withheld in cases of severe ARDS.

Patients of the autoimmune disease group presented with the second highest survival rate of the immunosuppressed subgroups. This is surprising because these patients showed a high rate of underlying pulmonary diseases (especially lung fibrosis) and the lowest RESP score. Therefore, our results are in contrast to the study of Na et al, showing a considerably lower survival rate in 24 ECMO patients receiving steroids or immunosuppressant's (nononcological and not for solid organ transplantation) of only 21%.[33]

There was a noticeable difference between the ECMO weaning and the survival rate of patients in the solid organ Tx group. The weaning rate was comparable to patients without immunosuppression, but almost every patient died in the further course of the hospital stay, indicating that survival in these patients maybe is more related to the underlying disease than to the ARDS itself. Therefore, indication for ECMO support in these patients should be taken with care. However, it has to be considered that three of the seven solid organ Tx patients had received lung transplantation.

Patients with underlying oncological disease were the largest subgroup in this analysis (90% of them with hematooncological malignancies). These patients showed the highest SOFA and APACHE-II score, reflecting severe organ failure. Hospital survival rates were noticeably low and even below the reported rates of Azoulay et al in non-ECMO ARDS patients with malignancies (31%).[23] Astonishingly, Na et al even reported 100% mortality in 18 ECMO ARDS patients with hematooncological malignancies.[33]

Hence, patients with oncological underlying disease are a very special cohort within the group of immunosuppressed patients showing a particularly poor prognosis. However, even if the prognosis of these seriously ill patients is limited due to their underlying disease and the severe respiratory failure, 20% survived their hospital stay. Moreover, Azoulay et al reported that 80% of ICU survivors with hematologic malignancies had no health-related quality of life alterations (physical and mental health similar to that of the overall cancer population) after discharge.[34]

4.1 | Limitations

This is a retrospective observational study and therefore contains the risk of selection and reporting bias. Therefore, despite using propensity score matching for outcome analysis, there still might be remaining confounders. Moreover, this is a single-center report and specific processes may influence the presented results. Together, due to these limitations, our findings should be considered as hypothesis-generating and should not prompt clinical decision-making. Moreover, ECMO-related complications were not assessed in this study, so influence of platelet levels on bleeding events could not be determined.

5 | CONCLUSION

In this analysis immunosuppression was strongly associated with increased hospital mortality. However, there were major differences in the weaning and survival rates between the etiologies of immunosuppression. The exclusion of an immunosuppressed patient from ECMO support should therefore be critically evaluated especially in regards to the underlying diseases.

CONFLICT OF INTEREST
The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS
All authors approved the final version of the manuscript.
Study design: Rilinger, Wengenmayer
Data collection: Rilinger, Wengenmayer

Data analysis and interpretation: Rilinger, Zotzmann, Bemtgen, Rieg, Biever, Duerschmied, Pottgiesser, Kaier, Bode, Staudacher, Wengenmayer

Drafted the manuscript: Rilinger, Wengenmayer

Revised the manuscript for important intellectual content: Zotzmann, Bemtgen, Rieg, Biever, Duerschmied, Pottgiesser, Kaier, Bode, Staudacher

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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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.