MAIN TEXT ARTICLE

Outcome of acute respiratory distress syndrome requiring extracorporeal membrane oxygenation in Covid-19 or influenza: A single-center registry study

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Abstract

Veno-venous extracorporeal membrane oxygenation (V-V ECMO) is used to sustain blood oxygenation and decarboxylation in severe acute respiratory distress syndrome (ARDS). It is under debate if V-V ECMO is as appropriate for coronavirus disease 2019 (Covid-19) ARDS as it is for influenza. In this retrospective study, we analyzed all patients with confirmed SARS-CoV-2 or influenza A/B infection, ARDS and V-V ECMO, treated at our medical intensive care unit (ICU) between October 2010 and June 2020. Baseline and procedural characteristics as well as survival 30 days after ECMO cannulation were analyzed. A total of 62 V-V ECMO patients were included (15 with Covid-19 and 47 with influenza). Both groups had similar baseline characteristics at cannulation. Thirty days after ECMO cannulation, 13.3% of all patients with Covid-19 were discharged alive from our ICU compared to 44.7% with influenza ($P = .03$). Patients with Covid-19 had fewer ECMO-free days (0 (0-9.7) days vs. 13.2 (0-22.1) days; $P = .05$). Cumulative incidences of 30-day-survival showed no significant differences (48.6% in Covid-19 patients, 63.7% in influenza patients; $P = .23$). ICU treatment duration was significantly longer in ARDS patients with V-V ECMO for Covid-19 compared to influenza. Thirty-day mortality was higher in Covid-19, but not significant.

KEYWORDS

acute respiratory distress syndrome, coronavirus disease 2019, extracorporeal membrane oxygenation, influenza, severe acute respiratory syndrome coronavirus 2

1 | INTRODUCTION

Most patients infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) show only mild symptoms, but some develop serious coronavirus disease 2019 (Covid-19) requiring hospital admission and intensive care treatment.[1-3] Among hospitalized Covid-19 patients, up to 20% will require mechanical ventilation and 2%-4% will

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receive veno-venous extracorporeal membrane oxygenation (V-V ECMO) support.[1-3] Clinical characteristics of Covid-19 are well described,[1,4,5] but understanding of pathophysiology, complications, cofactors, and specific treatment is incomplete.[6-8] The clinical presentation and pathophysiology of acute respiratory distress syndrome (ARDS) associated with Covid-19 differ from ARDS from other causes.[9] In fact, the definition of ARDS, an onset within 1 week of a clinical insult, does not apply for Covid-19[10]; acute respiratory failure in Covid-19 patients starts within a median of 12 days after illness onset.[5]

Considering limited specific therapeutic options existing for Covid-19 so far, V-V ECMO can be required for temporary organ support, if lung-protective mechanical ventilation is not sufficient to prevent hypoxia or severe hypercapnia.[11] Evidence for the use and outcome of V-V ECMO in Covid-19 is still limited,[11-14] although first results from larger cohorts and regstries have been published recently.[15,16] A retrospective cohort study of the Paris-Sorbonne University Hospital Network revealed a 31% probability of mortality 60 days after initiation of ECMO in Covid-19 patients; these results are similar to mortality rates observed in severe ARDS caused by other diseases and supported with V-V ECMO.[16,17]

Considering the different pathophysiological and clinical presentation, differences in the clinical course and outcomes of patients with ARDS due to Covid-19 or influenza A/B on V-V ECMO were suspected. It is under debate if V-V ECMO is as appropriate for Covid-19 ARDS as it is for influenza.

2 | PATIENTS AND METHODS

We conducted an investigator-initiated single-center retrospective registry study analyzing patients from the V-V ECMO Freiburg registry treated between October 2010 and June 2020. All patients treated at the Interdisciplinary Medical Intensive Care Unit at the Medical Center, University of Freiburg, Germany with reverse transcriptase polymerase chain reaction (rtPCR)-confirmed SARS-CoV-2 or influenza A/B infection and V-V ECMO were included in the analysis.

The study conforms to the 1975 Helsinki Declaration and was approved by the ethics committee of the Albert-Ludwigs University of Freiburg (151/14).

2.1 | Study population

All patients had ARDS and positive test results for SARS-CoV-2 or influenza A/B. We prespecified to compare all influenza patients to all Covid-19 patients in our registry. One of the main confounders hampering comparability between the two groups was the pandemic occurrence of Covid-19, which could not be attenuated by matching. V-V ECMO support was initiated in cases of severe hypoxic respiratory failure or CO_2 retention in spite of mechanical ventilation as suggested by the Extracorporeal Life Support Organization (ELSO) guidelines.[18] Mortality, intensive care unit (ICU) discharge, ECMO-free days (EFD, absence of ECMO support), and mechanical ventilator-free days (VFD, absence of invasive mechanical ventilation) within 30 days after initiation of ECMO were analyzed. VFD and EFD were counted as zero if the patient died within the first 30 days after ECMO cannulation or if the patient was transferred to another institution with invasive mechanical ventilation (MV) or ECMO. Successful V-V ECMO weaning was defined as being free from ECMO and alive for at least 48 hours after decannulation. Unsuccessful weaning was defined as the inability to explant the ECMO device because of persistent respiratory failure, death during ECMO support, or the need for recannulation within 48 hours.

To compare the patients' disease severity, RESP,[19] SOFA,[20] and APACHE II scores[21] were analyzed.

2.2 | ECMO center and ECMO management

The University of Freiburg Medical Center is a tertiary care hospital and a major referral center for the treatment of severe respiratory failure. All patients were treated on our 30-bed medical intensive care unit which has a 24/7 ECMO service. On average, 30-40 patients per year receive V-V ECMO support at our center. Cannulations were performed by two experienced intensivists and a perfusionist in Seldinger's technique without primary surgical cut down. Cannulation was mostly performed using a dual-lumen cannula (Avalon, Maquet, Rastatt, Germany) inserted in the right jugular vein; alternatively a bi-femoral approach was applied. SCPC (Sorin Centrifugal Pump Console, LivaNova, London, UK) or Cardiohelp (Maquet Getinge Group, Rastatt, Germany) ECMO systems were used. For anticoagulation, intravenous unfractionated heparin was administered aiming at a partial thromboplastin time 1.5 times above the normal limit; if heparin-induced thrombocytopenia was diagnosed, Argatroban was used. The management of vasopressors and fluid therapy was driven by clinical judgment of the ECMO experienced intensivist in charge and has been reported previously.[22]

Treatment algorithms and standard operating procedures were subject to revisions during the study period, reflecting current state-of-the-art recommendations and scientific knowledge.[18,23]

In all patients the mode of controlled MV was biphasic positive airway pressure (BIPAP). In some patients, airway

pressure release ventilation (APRV) was used, when considered beneficial. ECMO support was implemented in case of severe but potentially reversible respiratory failure, when lung-protective MV could not prevent 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 V-V ECMO support, invasiveness 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 55-60 mm Hg, respectively. Typical ventilator settings were as follows: PEEP 15 cmH$_2$O, plateau pressure 25 cmH$_2$O, FiO$_2$ 50%, and respiratory rate 10/min. Details on ventilator management and prone positioning procedures have been described previously.[24]

All ECMO circuits were checked at least once a day by a perfusionist and three times a day by the nurses and physicians on duty for visible thrombus formations. Indications for exchange of the whole ECMO system, except for the cannulas, were thrombus formation within the ECMO system posing a risk of thromboembolic events in the patient or ECMO system failure. In case of visible thrombus formation within the pump head only or running noise, potentially suggesting thrombus formation, an isolated change of the pump head was performed as long as gas exchange was sufficient and no further thrombus formation in the ECMO circuit was visible. All exchanges were carried out jointly by a registered nurse, a perfusionist and an ECMO specialist.

2.3 | Statistical analysis

All data were derived directly from our electronic patient files and entered into an electronic chart (Microsoft Excel 2010, Microsoft Corp., Redmond, WA, USA). For data analysis, SPSS 26 (IBM Statistics, Armonk, NY, USA), GraphPad Prism 5 (GraphPad Software, San Diego, CA, USA), and Stata 15.1 (Stata Corp, College Station, TX, USA) were used. Depending on the type of data, Student's t test, Unequal Variance t test, Mann-Whitney U test, Fisher's exact test, or Chi-square test were used. For VFD and EFD, Student's t test or Unequal Variance t test were used depending on variance homogeneity.[25] For all other continuous variables Mann-Whitney U test was used. For nominal variables, Fisher's exact test was used when number of expected values was smaller than five, otherwise the chi-square test was performed. A P value of $<.05$ was considered statistically significant. Cumulative incidences of mortality were calculated using competing risk regression (Fine and Gray method) with discharge alive as a competing event. Data are given as absolute numbers n (%), median and interquartile range (25th-75th) for all other continuous variables, if not stated otherwise.

3 | RESULTS

3.1 | Patient sample and baseline characteristics

Within the observation period, 305 patients were supported with V-V ECMO at the study center. Of these, 62 patients met the inclusion criteria. In 47 patients, influenza A/B was detected, 15 patients had Covid-19. Median age was 55.4 (45.2-62.5) years, six patients were older than 70 years and 23 (37.1%) were female.

Patients with Covid-19 were older than influenza patients (60.8 (54.1-67.0) and 52.7 (41.9-60.7) years, respectively; $P = .016$) and fewer were smokers (20% vs. 48.9%, $P = .048$). No significant differences were found for other baseline characteristics, such as body mass index (BMI), sex, and comorbidities (Table 1).

3.2 | Procedural characteristics

For patients with Covid-19, time on mechanical ventilation before V-V ECMO cannulation was longer (4.6 (3.0 −7.6) vs. 1.0 (0.1-2.6) days, $P < .001$). There were no significant differences between SOFA, RESP, and APACHE II scores at the time of ECMO cannulation (Figure 1A). Leukocytes and platelet count were higher in Covid-19 patients. All other laboratory findings were similar. Before initiation of ECMO, Covid-19 patients were treated with prone positioning more often (80.0% vs. 38.3%, $P = .005$) (Table 2).

3.3 | Outcome

Thirty days after connection to ECMO 44.7% of the influenza patients were discharged alive from our ICU compared to 13.3% of the Covid-19 patients ($P = .029$). Moreover, patients with influenza had more ECMO-free days than patients with Covid-19 (13.2 (0-22.1) days vs. 0 (0-9.7) days; $P = .050$) (Figure 1B). Cumulative incidence of mortality showed a probability of ICU death at 30 days of 36.3% in influenza patients compared to 51.4% in Covid-19 patients, but this difference was not statistically significant (Subdistribution Hazard Ratio (SHR) for Covid-19:1.60; 95%CI: 0.74-3.45; $P = .234$, Figure 2). ECMO duration, duration of mechanical ventilation, and ICU stay after ECMO cannulation were not different for the two groups.

Prone positioning after ECMO cannulation was performed more often in patients with Covid-19 (86.7% vs. 38.3%, $P = .001$). Hemodialysis was applied in 46.8% of the patients with influenza compared to 33.3% of the patients with Covid-19 ($P = .359$). The rate of ECMO pump head or system exchange due to thrombus formation was 33.3%

TABLE 1 Baseline characteristics of all patients

	Covid-19 (N = 15)	Influenza (N = 47)	P
Age (years)	60.8 (54.1-67.0)	52.7 (41.9-60.7)	**.016**
Body mass index (kg/m^2)	27.8 (24.7-31.0)	27.5 (23.9-34.9)	.799
Female	4 (27.7%)	19 (40.4%)	.337
Pulmonary disease	2 (13.3%)	12 (25.5%)	.484
Chronic kidney failure	0 (0%)	2 (4.3%)	1.000
Malignancy	1 (6.7%)	10 (21.3%)	.268
Liver cirrhosis	0 (0%)	2 (4.3%)	1.000
Immunosuppression	0 (0%)	8 (17%)	.181
Obesity	5 (33.3%)	18 (38.3%)	.729
Smoking	3 (20.0%)	23 (48.9%)	**.048**
Hypertension	5 (33.3%)	20 (42.8%)	.526
Diabetes mellitus	2 (13.3%)	8 (17.0%)	1.000
Coronary artery disease	0 (0%)	2 (4.3%)	1.000

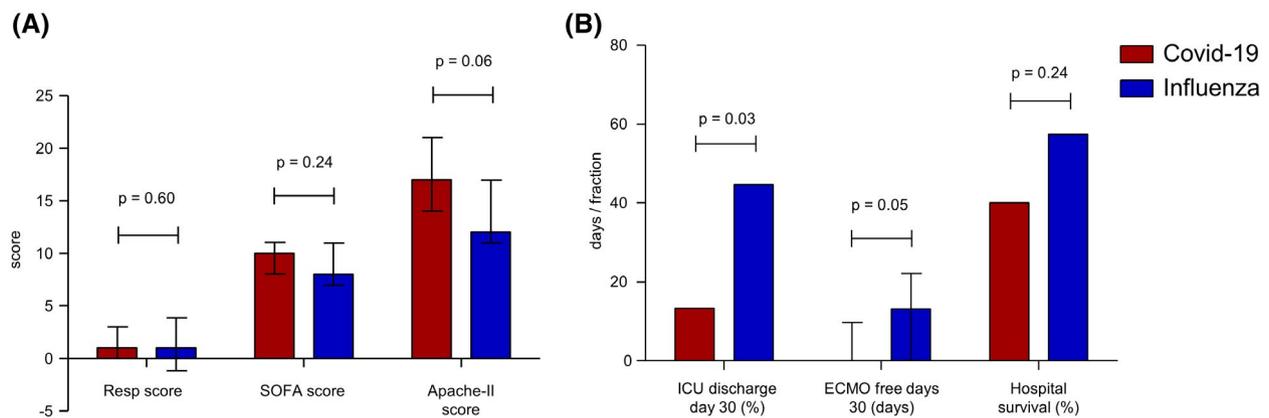*Note: P value reported in bold if difference is significant (P < .05).*

FIGURE 1 Baseline and procedural characteristics at V-V ECMO cannulation and outcome in Covid-19 and influenza patients with acute respiratory failure. (A) Shows baseline and procedural characteristics (median + IQR), (B) outcome data (median + IQR or fraction of patients) [Color figure can be viewed at wileyonlinelibrary.com]

in Covid-19 patients and 14.9% in patients with influenza (P = .142; Table 3).

4 | DISCUSSION

We here report a comparison of a single-center sample of patients with acute respiratory failure in Covid-19 or influenza (both confirmed by rtPCR), supported with V-V ECMO. Within the observation period of 30 days after V-V ECMO cannulation, 45% of the influenza patients were discharged alive from ICU compared to only 13% of the Covid-19 patients. Consistent with these findings, influenza patients had more ECMO-free days during the first 30 days after ECMO cannulation.

So far, no study has been published directly comparing patients with Covid-19 or influenza on V-V ECMO. In

one previous retrospective analysis comparing hospitalized ARDS patients (without V-V ECMO) caused by SARS-CoV-2 and H1N1 only 19.2% of the Covid-19 patients received invasive mechanical ventilation, as opposed to 85.5% of the influenza patients. In this study, hospital stay did not differ significantly between the groups (13 days and 16 days, respectively).[26]

Data on the duration of V-V ECMO in Covid-19 patients hardly exists. A recent registry study described a cohort of 32 patients with Covid-19 and V-V ECMO; 24 days after V-V ECMO cannulation 77.3% of the surviving patients still were on V-V ECMO.[13]

In another case series of 17 Covid-19 patients on ECMO, hospital stay in all surviving patients was longer than 30 days and in 81.8% the hospital stay was even longer than 50 days; only 18.2% of the surviving patients had a duration of mechanical ventilation of less than 20 days.[11] Another

TABLE 2 Procedural characteristics

	Covid-19 (N = 15)	Influenza (N = 47)	P
Duration of MV before ECMO (d)	4.6 (3.0-7.6)	1.1 (0.1-2.6)	**<.001**
pO$_2$ [mm Hg]	63.7 (51.9-78.9)	60.0 (56.0-71.6)	.844
pCO$_2$ [mm Hg]	63.8 (54.2-67.1)	60.8 (55.1-72.6)	.875
Horowitz index (mm Hg)	63.7 (51.9-94.5)	77.4 (59.5-150.0)	.095
PEEP (mm Hg)	15.0 (15.0-18.0)	15.0 (15.0-16.0)	.477
pH	7.30 (7.23-7.40)	7.28 (7.20-7.36)	.344
Prone positioning before ECMO	12 (80.0%)	18 (38.3%)	**.005**
Noradrenalin µg/kg/min	0.22 (0.04-0.35)	0.10 (0.00-0.40)	.123
SOFA score	10 (8-11)	8 (7-11)	.244
RESP score	1 (0-3)	1 (−1-4)	.601
APACHE-II score	17 (14-21)	12 (11-17)	.060
Leukocytes [10^3/µL]	10.0 (7.9-17.7)	7.5 (4.4-14.0)	**.049**
Platelets [10^3/µL]	286 (263-385)	158 (89-230)	**<.001**
Hematocrit [%]	32.8 (27.2-34.6)	35.0 (29.9-35.0)	.177
Creatinine [mg/dL]	1.2 (0.9-2.5)	1.1 (0.9-2.5)	.451
Urea [mg/dL]	65 (38-125)	54 (32-87)	.224
Bilirubin [mg/dL]	1.0 (0.3-2.1)	1.0 (0.7-1.0)	.893

Note: P value reported in bold if difference is significant (*P* < .05).

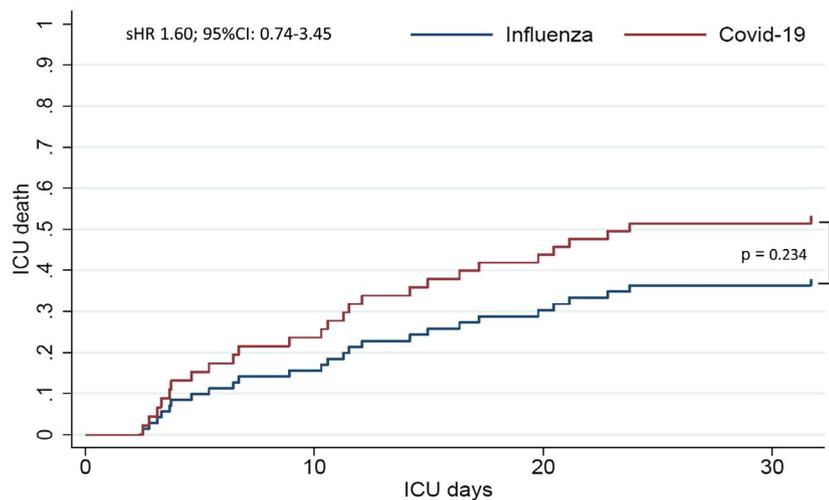Abbreviations: MV, invasive mechanical ventilation; PEEP, positive end expiratory pressure.

FIGURE 2 Cumulative incidence of mortality at 30 days in Covid-19 and influenza patients with V-V ECMO. Influenza: 36.34%; Covid-19:51.38%; *P* = .234 [Color figure can be viewed at wileyonlinelibrary.com]

retrospective registry study including 83 patients with Covid-19 and V-V ECMO showed a median duration of ECMO support of 20 days and ICU stay of 36 days, while the estimated probability of being alive and discharged from ICU was 17% after 28 days.[16] For influenza, a meta-analysis including 492 patients supported with V-V ECMO showed a median ECMO duration of 10 days, the median duration of mechanical ventilation was 19 days and ICU length of stay was 33 days.[27]

These very limited data from previous studies summarized above suggest that severe Covid-19 patients may require ECMO support, mechanical ventilation, and ICU treatment longer than patients with severe influenza virus infection, consistent with the findings of our study.

Cumulative incidence of 30-day mortality in Covid-19 compared to influenza was not statistically significantly different, though mortality was numerically higher in this studies' Covid-19 cohort. This may be due to the small number of cases. So far, there is only limited data on the outcome of Covid-19 patients with V-V ECMO and these results come primarily from small single-center observations. In these

TABLE 3 Treatment and outcome parameters

	Covid-19 (N = 15)	Influenza (N = 47)	P
ICU discharge day 30	2 (13.3%)	21 (44.7%)	**.029**
EFD 30	0 (0-9.7)	13.2 (0-22.1)	**.050**
EFD 30 of surviving patients (N = 6/27)	10.9 (4.7-23.7)	20.3 (16.7-23.8)	.132
VFD 30	0 (0-0)	0 (0-0)	.627
VFD 30 of surviving patients (N = 6/27)	0 (0-19.9)	0 (0-19.5)	.972
Survived day 30	8 (53.3%)	29 (61.7%)	.565
ECMO duration (d)	11.3 (7.8-23.8)	8.9 (4.8-15.1)	.247
Successful ECMO weaning	7 (46.7%)	29 (61.7%)	.304
MV duration after ECMO (d)	13.0 (10.0-36.3)	16.3 (8.2-24.6)	.639
Hospital Survival	6 (40.0%)	27 (57.4%)	.238
ICU stay after ECMO cannulation (d)	15.0 (10.6-42.3)	15.9 (8.9-24.6)	.353
Prone positioning after ECMO cannulation	13 (86.7%)	18 (38.3%)	**<.001**
Tracheostomy	6 (40.0%)	23 (48.9%)	.546
Hemodialysis	5 (33.3%)	22 (46.8%)	.359
APRV	32 (68.1%)	2 (13.3%)	**<.001**
Argatroban	5 (33.3%)	4 (8.5%)	**.031**
ECMO pump head or system exchange due to thrombus formation	5 (33.3%)	7 (14.9%)	.142

Note: P value reported in bold if difference is significant (P < .05). Results of VFD are presented as mean ± SD.

Abbreviations: APRV, airway pressure release ventilation; ECMO, extracorporeal membrane oxygenation; EFD 30, ECMO free days within 30 days after initiation of ECMO; ICU, intensive care unit; MV, invasive mechanical ventilation; VFD 30, ventilator free days within 30 days after initiation of ECMO.

reports, survival rates range from 0% to 100%.[1,4,5,28,29] A recent meta-analysis, summarizing data from 331 Covid-19 patients with V-V ECMO, described a mortality of 46%, consistent with the findings of this study.[30] Others described mortality rates of 36%-37% after 90 days.[15,16] Mortality in patients with influenza in this study's registry (42.6%) is similar to previous reported influenza cohorts with V-V ECMO support (37%).[27]

In our study cohort, prone positioning was used significantly more often for Covid-19 than for influenza. In our center, prone positioning has been part of ARDS treatment for several years.[24] Due to the lack of any specific therapy recommendations for Covid-19, following preliminary guidelines, we particularly concentrated on this treatment option.[31]

Additionally, Covid-19 patients received mechanical ventilation longer before initiation of ECMO. This observation may be explained by the fact that during a short period in April and May 2020, we treated a large number of Covid-19 patients and expected a further increase. In this situation, we feared to run out of ECMO consumables and machines, and therefore, used them sparingly. Furthermore, patients were transferred to us from other clinics at later stages of ARDS than before the Covid-19 pandemic for initiation of ECMO.

SARS-CoV-2 directly infects human kidney tubules to induce acute tubular damage.[32,33] Consequently, a higher rate of acute kidney injury in Covid-19 patients is discussed. In our patient cohort, we did not see any significant differences between the two groups in the rate of renal replacement therapy. However, renal replacement therapy showed a trend toward being more often used in patients with influenza (46.8% vs. 33.0%). We therefore hypothesize that most severe acute kidney injury requiring renal replacement therapy could be caused by the systemic injury in critical illness rather than being specific to SARS-CoV-2 or influenza.

We can only speculate on pathophysiological explanations for the clinical differences we observed, especially for the necessity for prolonged intensive care treatment of Covid-19. Examinations of the lung tissues from Covid-19 patients showed bilateral diffuse alveolar damage with cellular fibromyxoid exudates, while necrotizing bronchiolitis and extensive hemorrhage were shown in influenza patients.[34,35]

A highly activated coagulation cascade leading to micro- and macro-pulmonary embolisms, resulting in a pronounced ventilation-perfusion deficiency has also been discussed to increase acute respiratory failure in Covid-19.[36,37] Likewise, according to a recent analysis, patients with Covid-19 develop thrombus formation in the ECMO system more often when compared to other causes of ARDS.[38] We could not show a statistically significant higher rate of necessary ECMO pump head or system exchanges due to thrombus formation in our cohort, although the rate was numerically higher in Covid-19 patients. Whether this difference will be significant when considering higher case numbers or levels out has to be clarified in larger studies. Computed tomographies of the chest showed that ground-glass opacity was more common in patients with Covid-19 than in patients with influenza, whereas consolidations were more frequent in influenza patients.[9,26,39]

At this stage, we can only hypothesize whether these observations can explain the clinical differences observed in our patient sample, in particular the longer course of treatment for Covid-19. In addition to a better understanding of the pathophysiology of the SARS-CoV-2-induced lung failure, the results of ongoing studies examining specific treatment approaches in Covid-19 will contribute to a better understanding of the disease and differences of ARDS associated with other viral pathogens.[40-42]

4.1 | Limitations

Some limitations of this study have to be mentioned. We present single-center retrospective data, therefore, our results should be considered hypotheses-generating only and have to be confirmed in larger trials. Another limitation is the small sample size of only 15 patients with Covid-19 and 47 patients with influenza. Furthermore, influenza patients were included over a longer period of time since 2010, while the first Covid-19 patient was included in March 2020. Following scientific progress and revisions of clinical guidelines, treatment algorithms have changed over time, this may explain differences in treatments over time. ECMO-related complications were not assessed in this study. Clinical data were based on medical reports. Since we did not use structured clinical interviews, some variables are likely to be underreported.

5 | CONCLUSION

Patients with severe Covid-19, supported with V-V ECMO are less likely to be discharged from ICU within 30 days after initiation of ECMO than patients with influenza virus infection and V-V ECMO. Thirty-day mortality was higher in Covid-19, but not significant. Larger studies are needed in order to clarify if Covid-19 ARDS requiring V-V ECMO has worse long-term outcome compared to influenza or if survival levels out.

CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS
MJ, JR, DS, and AS carried out the data collection, design, and planning of this study. MJ, DS, and AS performed the statistical analysis. MJ and AS drafted the manuscript. All authors participated in the critical discussion of the study and interpretation of data. All authors read and approved the final manuscript.

CONSENT FOR PUBLICATION
Not applicable.

DATA AVAILABILITY STATEMENT
The data sets used and analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE
This retrospective study was approved by the ethics committee of the Albert Ludwigs University of Freiburg, file number 151/14.

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