A Mortality Prediction Score for Patients With Veno-Venous Extracorporeal Membrane Oxygenation (VV-ECMO): The PREDICT VV-ECMO Score

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Mortality prediction for patients with the severe acute respiratory distress syndrome (ARDS) supported with veno-venous extracorporeal membrane oxygenation (VV-ECMO) is challenging. Clinical variables at baseline and on day 3 after initiation of ECMO support of all patients treated from October 2010 through April 2020 were analyzed. Multivariate logistic regression analysis was used to identify score variables. Internal and external (Monza, Italy) validation was used to evaluate the predictive value of the model. Overall, 272 patients could be included for data analysis and creation of the PREDICT VV-ECMO score. The score comprises five parameters (age, lung fibrosis, immunosuppression, cumulative fluid balance, and ECMO sweep gas flow on day 3). Higher score values are associated with a higher probability of hospital death. The score showed favorable results in derivation and external validation cohorts (area under the receiver operating curve, AUC derivation cohort 0.76 [95% confidence interval, CI, 0.71–0.82] and AUC validation cohort 0.74 [95% CI, 0.67–0.82]). Four risk classes were defined: I ≤ 30, II 31–60, III 61–90, and IV ≥ 91 with a predicted mortality of 28.2%, 56.2%, 84.8%, and 96.1%, respectively. The PREDICT VV-ECMO score suggests favorable performance in predicting hospital mortality under ongoing ECMO support providing a sound basis for further evaluation in larger cohorts. *ASAIO Journal* 2024; 70:293–299

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The datasets used or analyzed during this study are available from the corresponding author on reasonable request, after deidentification, to achieve aims in the approved proposal. Proposals should be directed to jonathan.rilinger@universitaetsherzzentrum.de.

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Background

Selected patients with the severe acute respiratory distress syndrome (ARDS) may benefit from veno-venous extracorporeal membrane oxygenation (VV-ECMO).[1–6] Over the past years, ECMO is increasingly being used for the treatment of respiratory failure and ARDS.[7,8] During the coronavirus disease-2019 (COVID-19) pandemic, VV-ECMO played an important role in the treatment of patients with severe hypoxemic respiratory failure.[9,10] However, even though experience in the treatment of patients with VV-ECMO increased, mortality is high[8] and important questions remain with respect to indication and the selection of patients that benefit most from this invasive support option. Several scores for survival prediction have been developed to assist clinicians in deciding whether a patient should receive VV-ECMO support. However, these scores focus on the patient's clinical condition and disease severity before initiation of ECMO.[11–15] Difficulties remain with prognostication during ongoing ECMO support. ECMO is a highly resource-intensive support option that should be restricted to those that most likely benefit from it. Consequently, it would be helpful not only to determine prognosis before initiation of ECMO but also after ECMO has been started.

From a clinical perspective, an evaluation after the initial stabilization phase of the first two days and after reaching a steady state in therapy seems appropriate. Therefore, the aim

of this study was to develop a model for the prediction of the probability of mortality for ARDS patients on day 3 after initiation of VV-ECMO, once initial stabilization of the patients and a certain equilibrium have been achieved.

Methods

This study followed the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) reporting guidelines.[16]

Study Population

This study is based on data from a retrospective single-center registry of adult patients with severe ARDS supported with VV-ECMO. Diagnosis of severe ARDS in this study is following the Berlin definition.[17] VV-ECMO was initiated in patients with severe hypoxemic respiratory failure or hypercapnia despite invasive mechanical ventilation (MV), as suggested by Extracorporeal Life Support Organization (ELSO) guidelines.[18] For all patients, except for two individuals with severe pulmonary fibrosis, the primary therapeutic objective was lung function recovery."

All patients with severe ARDS supported with VV-ECMO in the Interdisciplinary Medical Intensive Care Unit at the Medical Centre, University of Freiburg, Germany from October 2010 through April 2020 were included. The study was approved by the University of Freiburg Ethics Committee (EK-Freiburg 553/19).

Extracorporeal Membrane Oxygenation Center and Extracorporeal Membrane Oxygenation Management

Our center provides a 24 × 7 ECMO service for in-hospital and out-of-center cannulation of ECMO. Treatment for ARDS and specifically respiratory support including MV in our institution is following current guidelines.[19] VV-ECMO support was implemented in case of severe but potentially reversible respiratory failure, when lung-protective MV did not prevent hypoxemia or hypercapnia following established criteria.[18,20] Lung-protective MV was defined as positive end-expiratory pressure (PEEP) ≤15 cmH_2O, plateau pressure ≤30 cm H_2O, driving pressure ≤15 cmH_2O, and FiO_2 ≤50%. The management of vasopressors and fluid therapy with the aim to minimize the application of fluid support as far as possible was driven by the clinical judgment of the ECMO-experienced intensivist in charge and has been reported earlier.[21] Treatment algorithms and standard operating procedures were subject to revisions during the observational period, reflecting current state-of-the-art recommendations and scientific knowledge. In particular, patient selection was adjusted with regard to comorbidities, so that patients with immunosuppression (detailed definition in the online data supplement, http://links.lww.com/ASAIO/B142) are only treated with ECMO after very careful evaluation and patients with lung fibrosis (with a few exceptions) are no longer supported with ECMO.[22]

After initiation of VV-ECMO, invasiveness of MV was reduced and ECMO settings were adjusted aiming at a peripheral oxygen saturation of 85%–90% and partial pressure arterial oxygen of approximately 60 mm Hg.[23] Details about ventilator management and prone positioning procedures have been described earlier.[24] To ensure optimal ECMO functionality, high gas flow recruitment maneuvers were performed at least once every eight hours. Additional information about ECMO management is available in the online data supplement (http://links.lww.com/ASAIO/B142).

We used for external validation a retrospective cohort of ECMO patients from Azienda Socio Sanitaria Territoriale (ASST) Monza (Monza, Italy), a large referral hospital for respiratory failure where a VV-ECMO program has been running since 1989. The case-volume of this center is 60–80 ECMO run per year (25–35 VV-ECMO).

Parameter Selection and Statistical Analysis

A team of experienced intensivists defined primary relevant factors known or suspected to be associated with patient mortality after review of the literature.[9,11,12,14,22,25–29] Both clinical relevance and practicability of collecting these parameters in clinical routine were considered. Therefore, the primary parameter selection was driven clinically, no data-driven variable selection was conducted. The focus of this analysis was on the parameters describing the patients' condition and level of support on day 3 to provide a prognostic assessment during ongoing ECMO support. However, to avoid ignoring established baseline predictors for survival/mortality in VV-ECMO, three of these parameters (age,[11,12] lung fibrosis[22,30,31] and immunosuppression[25,32] were also considered for score generation. In-hospital mortality was chosen as the endpoint or dependent variable, respectively.

The nonlinear relationship between continuous candidate variables and mortality was analyzed using logistic regression and restricted cubic splines. Continuous candidate variables were then converted into categorical variables, using thresholds for achieving the highest possible discrimination, to account for the nonlinearity in the relationship between certain continuous variables and the outcome. Thereafter, the candidate variables for score development were included in a multivariable logistic regression analysis with in-hospital mortality as the dependent variable using backward selection (threshold $p < 0.05$). Variables with a significant association were weighted using the beta coefficient to display the effect size of the variables on the endpoint hospital mortality. The score starts with a value of zero at the lowest probability of death, which increases with higher score levels. To increase the practicability of the score, a categorization into four risk classes was performed.

After score generation, the area under the receiver operating curve (AUC) of the observed mortality was calculated.[33] Additional internal validation was conducted using ten-fold internal cross-validation with the cvauroc command (Stata). Furthermore, external validation was performed at the ASST Monza University Hospital (Monza, Italy), whereby patients from the period of August 2009 to May 2021 were included. Moreover, the generated score was compared with the Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) and Sequential Organ Failure Assessment (SOFA) score pre-ECMO cannulation.

Continuous variables are presented as median (25th–75th percentile), categorical variables as numbers and percentages. Results of multivariate logistic regression analysis are given as odds ratio (OR) and 95% confidence interval (CI); a value

of $p \leq 0.05$ was considered statistically significant. Statistical calculations were performed using IBM SPSS statistics 25.0 (Armonk, NY: IBM Corp, 2017) and Stata 17.0 (StataCorp. 2021, Stata Statistical Software: Release 17, College Station, TX: StataCorp LLC). Figures were produced using Stata 17.0 (StataCorp. 2021, Stata Statistical Software: Release 17, College Station, TX: StataCorp LLC) and GraphPad Prism (V9, GraphPad Software, San Diego, CA).

Results

At our center, 295 patients were supported with VV-ECMO between October 2010 and April 2020. Out of these, on day 3 272 patients were still on ECMO (median age 56 [44–64] years, 66.9% male, Table 1). These patients showed a moderate level of underlying pulmonary disease. Twenty-six (9.6%) patients had underlying lung fibrosis. Almost one-third (29.8%) of the patients were immunosuppressed before ECMO cannulation. Prone positioning before ECMO support was performed in 69 patients (25.4%). Duration of MV before ECMO cannulation was 1.3 (0.3–3.8) days. Overall ECMO weaning and hospital survival rates were 57.4% and 48.5%, respectively. Median duration of ECMO support was 7.5 (4.7–13.3) days.

Table 1. Baseline Characteristics

	Patients With VV-ECMO on Day 3 (n = 272)
Demographic characteristics	
Age (y)	56 (44–64)
Sex (male)	182 (66.9%)
BMI (kg/m²)	24.5 (23.4–29.4)
Preexisting conditions	
COPD	24 (8.8%)
Asthma	17 (6.3%)
Lung fibrosis	26 (9.6%)
Cystic fibrosis	7 (2.6%)
Nicotine abuse	94 (34.6%)
Arterial hypertension	93 (34.2%)
Diabetes mellitus	34 (12.5%)
CAD	33 (12.1%)
Chronic renal failure	20 (7.4%)
Immunosuppression*	81 (29.8%)
Pre-cannulation parameters	
FiO_2 (%)	100 (80–100)
Horowitz index (mm Hg)	74.3 (61–103.1)
$D(A\text{-}a)O_2$ (mm Hg)	549 (416.5–596)
Duration of MV before ECMO (d)	1.3 (0.3–3.8)
Prone positioning before ECMO	69 (25.4%)
Acute renal failure	87 (32%)
Causes of ARDS	
Pneumonia	202 (74.3%)
Aspiration	19 (7%)
Other	51 (18.8%)
Scores	
SOFA score	12 (10 to 15)
RESP score	1 (–1 to 3)

Continuous variables are presented as median (25th–75th percentile), categorical variables as numbers and percentages.

*Detailed definition of immunosuppression in the online data supplement (http://links.lww.com/ASAIO/B142).

ARDS, acute respiratory distress syndrome; BMI, body-mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; D(A-a)O2, alveolar-arterial gradient of oxygen concentration; ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; MV, mechanical ventilation; PEEP, positive end-expiratory pressure.

Catecholamine/vasopressor support on day 3 was low (norepinephrine 0.1 [0–0.2] µg/kg/min) but fluid balance was highly positive (6,111 [2,305.5–12,020.3] ml, see Table S1, http://links.lww.com/ASAIO/B142 in the online data supplement, http://links.lww.com/ASAIO/B142). The settings for ventilatory support were within the target range of a lung-protective strategy (median PEEP 14 [10–15] cmH_2O, median driving pressure 10 [8–13.4] cmH_2O and median plateau pressure 24 [21–26] cmH_2O). Median ECMO blood flow on day 3 was 3.5 (2.8–4.1) l/min, median ECMO sweep gas flow was 3.4 (2.1–4.9) l/min, and ECMO FiO_2 (%) was 100 (100–100) %.

Primarily, from the baseline characteristics age, lung fibrosis, and immunosuppression were considered for inclusion in the score generation. Moreover, the preselected variables hemoglobin, bilirubin, lactate, norepinephrine, cumulative fluid balance, ventilator FiO_2 as well as ECMO blood flow and ECMO sweep gas flow on day 3 after ECMO cannulation were examined for association with mortality. The absolute and ideal body-weight adjusted tidal volumes as well as other ventilation parameters were not considered because these are strongly dependent on respirator settings and the individual concept of the ECMO center.

Continuous candidate variables were plotted against hospital mortality (see Figure S1, http://links.lww.com/ASAIO/B142–Figure S3, http://links.lww.com/ASAIO/B142 in the online data supplement, http://links.lww.com/ASAIO/B142). After multivariate analysis, five independent predictors for mortality could be determined (Table 2) and included in the PREDICT VV-ECMO score. The score consists of three categorical items before ECMO cannulation (age ≥60 years, lung fibrosis, and immunosuppression) and two continuous items during ongoing ECMO support on day 3 (cumulative fluid balance and ECMO sweep gas flow, Table 3). The score ranges from 0 to 132, whereas a higher score value corresponds to an increasing probability of death (Figure 1). An online calculator for determining the PREDICT VV-ECMO score in individual patients was designed and is freely available at www.PREDICT-VV-ECMO.org.

In the derivation cohort, the PREDICT VV-ECMO score showed a reasonable discrimination of patient outcome (AUC 0.76 [95% CI, 0.71–0.82], see supplement Figure S4, http://links.lww.com/ASAIO/B142). The cross-validated mean AUC was 0.78 (95% CI, 0.68–0.80, supplemental Figure S5, http://links.lww.com/ASAIO/B142). The predicted mortality of the four risk classes of the PREDICT VV-ECMO score (I ≤ 30, II 31–60, III 61–90, and IV, ≥ 91) are 28.2%, 56.2%, 84.8%, and 96.1%, respectively (Table 3). The observed mortality is shown in Figure 2.

The external validation cohort (Monza, Italy) included 180 patients (age 51 [43–59] years, 62.2% male, supplement Table S2, http://links.lww.com/ASAIO/B142) and showed a high ECMO weaning and hospital survival rate (73.9% and 72.2%). The external validation of the PREDICT VV-ECMO score showed a favorable level of discrimination (AUC 0.74 [95% CI 0.67–0.82], supplement Figure S2, http://links.lww.com/ASAIO/B142). Because no patients with lung fibrosis were

Table 2. Odds Ratio and Beta Coefficient of Score Parameters

Parameter	Odds Ratio (95% CI)	Beta Coefficient (95% CI)	*p* Value
Age ≥60 years	2.74 (1.55–4.87)	1.01 (0.44–1.58)	0.001
Lung fibrosis	11.02 (2.46–49.39)	2.40 (0.90–3.90)	0.002
Immunosuppression	2.58 (1.41–4.73)	0.95 (0.34–1.55)	0.002
Cumulative fluid balance* (ml) day 3	1.18 (1.00–1.39)	0.166 (0.00–0.33)	0.045
Sweep gas flow (L/min)* day 3	1.26 (1.08–1.48)	0.24 (0.08–0.39)	0.003
Constant	0.14 (0.07–0.30)	–1.95 (–2.69 to 1.21)	<0.001

Remaining variables after backward selection of candidate variables associated with hospital mortality.

*Graduation of variables as shown in Table 3.

CI, confidence interval.

Table 3. The PREDICT VV-ECMO Score

Parameters		Score
Age ≥60 years		20
Lung fibrosis		48
Immunosuppression		19
Cumulative fluid balance (ml) day 3		
0–2,499		3
2,500–4,999		6
5,000–7,499		9
7,500–9,999		12
≥10,000		15
Sweep gas flow (L/min) day 3		
1–1.9		5
2–2.9		10
3–3.9		15
4–4.9		20
5–5.9		25
≥6		30
Total score		0–132
Risk Classes	Score Range	Predicted Mortality
Risk class I	<30	28.2%
Risk class II	31–60	56.2%
Risk class III	61–90	84.8%
Risk class IV	91–132	96.1%

treated in the external validation cohort, no patients showed the highest risk category (IV, Figure 2). Moreover, patients in this validation cohort were younger and few of them were immunosuppressed. In contrast to the derivation cohort, 36 out of 180 patients in the external validation cohort developed ARDS as a result of a COVID-19 infection.

Compared to the RESP and SOFA scores pre-ECMO cannulation (AUC RESP 0.60 [95% CI 0.53–0.66] and SOFA 0.52 [95% CI 0.45–0.59], supplement Figure S1, http://links.lww.com/ASAIO/B142), the PREDICT VV-ECMO score showed a higher level of discrimination.

Discussion

Estimating prognosis in patients with severe ARDS under ECMO support is challenging but essential in daily clinical practice. We developed the PREDICT VV-ECMO score as a mortality prediction model to provide guidance for treatment decisions in patients with severe ARDS and VV-ECMO based on age, status of immunosuppression and lung fibrosis as well as cumulative fluid balance and sweep gas flow on day 3 after ECMO cannulation (www.PREDICT-VV-ECMO.org). The strength of this score is its strong predictive power as well as its easy applicability, as only a few clinically relevant and routinely available parameters are needed for the calculation.

In our analysis, the cumulative fluid balance on day 3 of VV-ECMO support revealed a highly significant prognostic value for the prediction of in-hospital mortality with high values being associated with increased mortality. The cumulative fluid balance can be considered as an indirect marker for inflammation, capillary leakage, and the level of hemodynamic instability. In contrast, the predictive value of norepinephrine support or lactate levels were low. Interestingly, ECMO sweep gas flow was found to be relevant for the prediction of mortality, but FiO_2 on ventilator and ECMO as well as ECMO blood flow on day 3, were not significantly associated with in-hospital mortality and therefore not included in the score. This observation suggests a minor role of the required level of oxygenation support in the prognostic assessment. In contrast, the level of ECMO sweep gas flow, as a surrogate parameter for decarboxylation, seems to be more important. These findings are in line with the results of the RESP and PRESERVE score.[11,12] In these analyses pre-ECMO cannulation the level of oxygenation support was not associated with patient survival, but the CO_2 levels and the magnitude of ventilatory pressures required for achieving decarboxylation, respectively.

Currently, there is no other thoroughly validated score for mortality prediction in patients with severe ARDS during ECMO support. Other well-established scores like the RESP or PRESERVE score[11,12] were created for survival prediction before initiation of ECMO as a decision support for or against ECMO. These scores are not designed for assessing the probability of death once ECMO support has been started. Other common intensive care outcome scores, like the SOFA score[34] were created before the ECMO era, and thus their isolated predictive value is limited.[12] This was also demonstrated in our analyses. The PREDICT VV-ECMO score may therefore improve the outcome estimation of VV-ECMO patients during ECMO support in addition to these established and widely used scores. This can be particularly useful in a "bridge to decision" situation where ECMO support has been initiated to re-evaluate the patient's prognosis when a definitive assessment was not possible at the time of cannulation.

For validation of the PREDICT-VV-ECMO score, we assessed its reliability in an independent validation cohort treated at the University of Monza, Italy, which showed a high predictive value of the score. Nonetheless, it is important to mention that significant differences existed between the derivation and external validation cohorts (younger age, lower mortality, lower rate of immunosuppression, and no patients with lung fibrosis in the external validation cohort). Despite the observed consistent mortality distribution across the score levels, this disparity between the two cohorts constitutes a

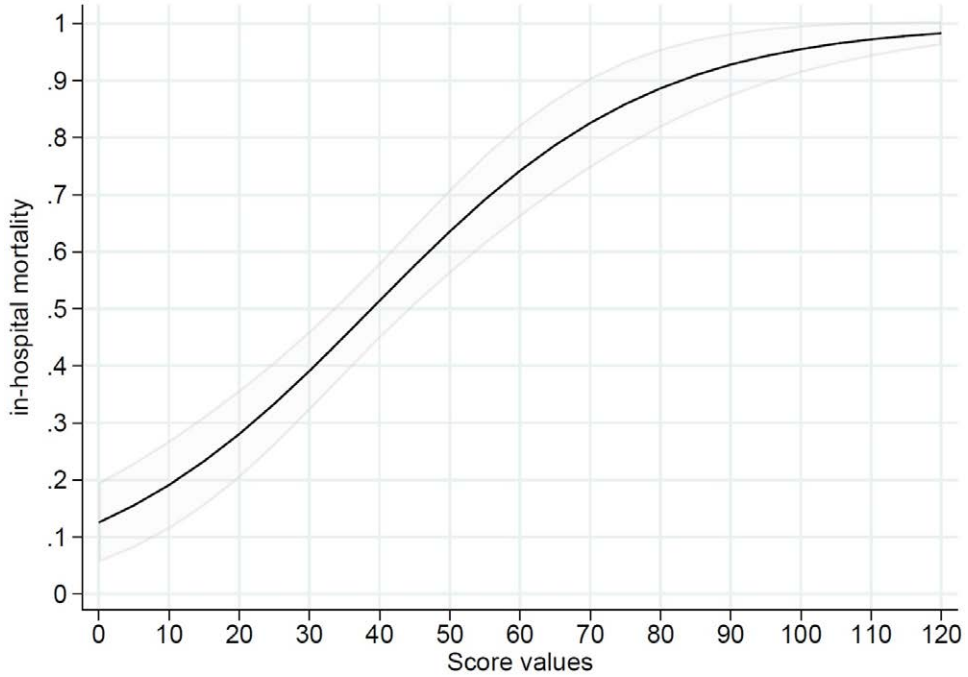

Figure 1. PREDICT VV-ECMO score—predicted mortality as a function of the score value (95% CI). CI, confidence interval.

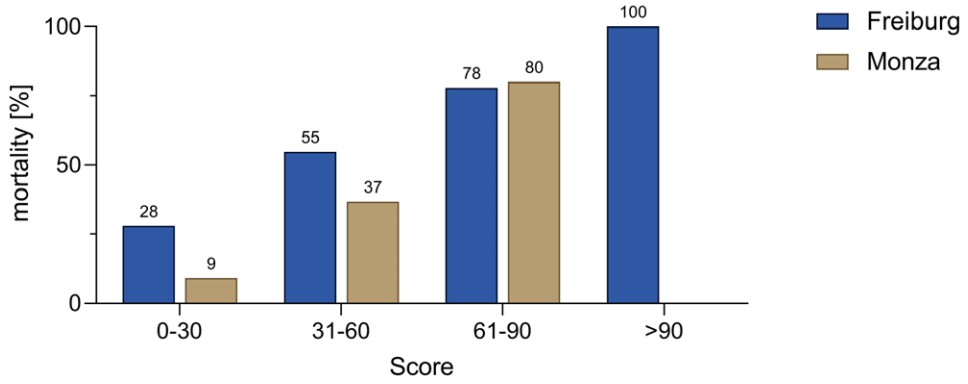

Figure 2. Observed mortality rates in the risk classes of the PREDICT VV-ECMO score in the original cohort and external validation cohort. None of the patients within the external validation cohort (Monza) appeared to be in the highest risk group (score >90).

notable limitation. Hence, in the future, the score should be evaluated in cohorts encompassing a diverse range of clinical characteristics. Furthermore, in the derivation cohort, due to the pronounced severity of illness among patients with a high proportion of immunosuppression and lung fibrosis, there was an above-average mortality rate. Therefore, despite the comparable results in the validation cohort, further evaluations of the score should be conducted to enhance its generalizability.

Limitations

The score was generated on a retrospective data set of a single ECMO center and therefore contains the risk of selection and reporting bias. Moreover, even though the score showed a favorable result in an external validation cohort, specific processes in patient selection and treatment may challenge the generalizability to other cohorts.

Conclusions

This is the first model to predict mortality under ongoing VV-ECMO support in patients with severe ARDS derived from a large retrospective single-center cohort. The PREDICT VV-ECMO score consists of five easy-to-access parameters and provides a strong prediction of hospital mortality.

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