The use of extracorporeal membrane oxygenation (ECMO) has grown exponentially for a decade and can now be considered as a viable therapeutic option in numerous clinical situations. Accessibility of mobile ECMO teams and smaller devices have assisted in broadening its indications. The main indication for venovenous (VV) ECMO is for patients with severe acute respiratory distress syndrome (ARDS) with refractory hypoxaemia or who are unable to tolerate volume-limited strategies. It can also now be used as a bridge to lung transplant in patients with end-stage chronic respiratory failure. Promising results obtained in a multicentre randomised controlled trial and observational data obtained during the influenza A(H1N1) pandemic have both contributed to the exponential increase in usage of ECMO in this setting.

The key indications for venoarterial (VA) ECMO are refractory cardiogenic shock after either cardiotomy, acute myocardial infarction (AMI) or fulminant myocarditis. VA ECMO is, therefore, used as a bridge to recovery, implantation of a left ventricular assist device (LVAD) or heart transplantation. More recently, successes have been also reported for VA ECMO use during cardiopulmonary resuscitation (E-CPR), septic shock-induced cardiac dysfunction and life-threatening massive pulmonary embolism.

The growing experience of physicians with ECMO management has been that, although ECMO is beneficial, the numerous and potentially fatal complications such as bleeding, thrombosis, nosocomial infection and cerebral events that can result during ECMO still exist. For these reasons, and because ECMO has a significant physiological and financial cost, several survival prediction models have recently been developed. The purpose of these models is to help clinicians identify patients most likely to survive following initiation of ECMO. These models are numerous, based on heterogeneous studies and are now used in several publications to benchmark outcomes in ECMO population. Therefore, it is worth understanding the basis and relevance of these scores.

This review summarises short- and long-term outcomes of VA or VV ECMO-treated patients and describes the characteristics and performance of the different survival prediction models. We searched the literature using a detailed PubMed query to identify observational studies (retrospective and prospective) on predictive survival model in ECMO between January 2000 and August 2017.

ABSTRACT

Over the past decade, there has been growing interest in extracorporeal membrane oxygenation (ECMO) as a rescue therapy for patients with severe acute respiratory distress syndrome (ARDS) and cardiogenic shock. Although survival of ECMO-treated patients has improved recently, the incidence of ECMO-related complications such as bleeding and nosocomial infections remains unacceptably high. In addition, patients often experience long-term physiological and psychological sequelae. Hence, identifying patients who will most likely benefit from ECMO is crucial. Because the technique exposes patients to complications and is associated with high costs and resource utilisation, prediction models have been developed to assist clinicians in identifying patients that would most likely survive after ECMO treatment. In addition, these prediction models enable comparison of risk-adjusted outcomes, both over time and between centres. Our review explores the latest predictive survival models developed for ECMO-treated severe cardiogenic shock and ARDS patients.

Outcomes of VA or VV ECMO treated patients

Although there are outcome specificities of VA and VV ECMO treated patients, the short-term outcome of these patients may be influenced by several factors, such as (i) timing of initiation, (ii) case-volume of the ECMO centre (a higher case-volume being associated with a lower mortality), and (iii) occurrence of ECMO-related complications such as bleeding (reported in 20%–40% of patients with various severity degrees) and nosocomial infections. In addition, neurological complications account for major morbidity and have a significant impact on quality of life.

VA ECMO-treated cardiogenic shock

Short-term outcome on VA ECMO primarily depends on the aetiology of the cardiogenic shock. The three main
aetiologies for ECMO initiation are acute myocarditis, acute myocardial infarction (AMI) and post-cardiotomy, which display very different outcomes. Consequently, hospital survival rates were 68% and 72% in cohorts of 41 and 56 patients with ECMO-treated fulminant myocarditis, respectively.10,28 By contrast, in patients with post-cardiotomy cardiogenic shock, the overall survival rate in 517 ECMO-treated patients was substantially lower, with only 25% survival.8 Lastly, in the context of cardiogenic shock after AMI, hospital survival rate was reported to be from 47% to 64%.29,30 Greater age (mean age, 63 years [SD, 11 years]), more frequent comorbidities and frequent central cannulation (61%) could explain this poor outcome.

Beyond ICU or hospital survival, few studies have focused on long-term survival and health-related quality of life (HRQoL) of these patients. These studies are summarised in Table 1. All studies9,10,12,23,24 used the 36-Item Short-Form Health Survey (SF-36)31 to assess HRQoL. There was concurrence that VA ECMO survivors present a significantly lower physical component score, but a preserved mental component score, compared with healthy age- and sex-matched controls. Three studies9,10,12 also reported anxiety and depression symptoms using the Hospital Anxiety and Depression (HAD) scale. For example, significant and severe anxiety and depression symptoms were present in 38% and 27% of patients, respectively, and for three, there were 12% and 8% survivors of myocarditis, respectively.10 Similarly to other post-ICU survivors, these patients were at risk for post-traumatic stress disorder (PTSD) (11% to 27% of survivors).32-34

ARDS treated with VV ECMO

A combination of the newly optimised, improved Berlin ARDS definition,35 a better understanding of ventilator-induced lung injury, and the benefits of prone positioning36 and early neuromuscular blockade37 have all contributed to improved outcomes. However, the exact role of VV ECMO for severe ARDS is still unclear. The largest recent registry (2355 patients) extracted from the Extracorporeal Life Support Organization (ELSO) reports 57% hospital survival18.

<p>| Table 1. Studies relating long-term outcomes after VA ECMO for cardiogenic shock and VV ECMO for severe ARDS |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort enrolment</th>
<th>Total population</th>
<th>Aetiology</th>
<th>Follow-up (Population, Median time)</th>
<th>Long-term outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA ECMO for cardiogenic shock</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combes et al.23</td>
<td>2003–2006</td>
<td>81</td>
<td>All cause</td>
<td>28, 11 months</td>
<td>HRQoL (SF-36 score)</td>
</tr>
<tr>
<td>Mirabel et al.10</td>
<td>2002–2009</td>
<td>41</td>
<td>Acute myocarditis</td>
<td>26, 17 months</td>
<td>HRQoL (SF-36 score), anxiety and depression (HAD scale), PTSD (IES)</td>
</tr>
<tr>
<td>Brechot et al.12</td>
<td>2008–2011</td>
<td>14</td>
<td>Septic shock</td>
<td>10, 13 months</td>
<td>HRQoL (SF-36 score), anxiety and depression (HAD scale), PTSD (IES)</td>
</tr>
<tr>
<td>Muller et al.9</td>
<td>2008–2013</td>
<td>138</td>
<td>Acute myocardial infarction</td>
<td>41, 32 months</td>
<td>HRQoL (SF-36 score), anxiety and depression (HAD scale), PTSD (IES)</td>
</tr>
<tr>
<td>Schoenrath et al.24</td>
<td>2005–2014</td>
<td>57</td>
<td>All cause</td>
<td>17, 34 months</td>
<td>HRQoL (SF-36 score and Bartell index)</td>
</tr>
<tr>
<td>VV ECMO for severe ARDS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peek et al.6</td>
<td>2001–2006</td>
<td>68</td>
<td>All cause</td>
<td>52, 6 months</td>
<td>Lung function (PFT), overall health status, HRQoL, depression and anxiety symptoms</td>
</tr>
<tr>
<td>Lindén et al.49</td>
<td>Before 2009</td>
<td>37</td>
<td>All cause</td>
<td>21, 26 months</td>
<td>Lung function (PFT), pulmonary symptoms (SGRQ)</td>
</tr>
<tr>
<td>Hodgson et al.50</td>
<td>2009–2011</td>
<td>34</td>
<td>All cause</td>
<td>15, 9 months</td>
<td>Related-ECMO complications, discharge destination, return-to-work status</td>
</tr>
<tr>
<td>Luyt et al.51</td>
<td>Winter 2009</td>
<td>67</td>
<td>H1N1-related ARDS</td>
<td>12, 12 months</td>
<td>Symptoms and activities since hospital discharge, weight and muscle-strength testing, lung morphology (CT scan), anxiety and depression (HAD scale), PTSD (IES)</td>
</tr>
<tr>
<td>Schmidt et al.14</td>
<td>2008–2012</td>
<td>140</td>
<td>All cause</td>
<td>67, 17 months</td>
<td>HRQoL (SF-36 score), pulmonary symptoms (SGRQ), anxiety and depression (HAD scale), PTSD (IES)</td>
</tr>
<tr>
<td>Li et al.52</td>
<td>2009–2012</td>
<td>29</td>
<td>All cause</td>
<td>8, 12 months</td>
<td>Pulmonary morphology</td>
</tr>
</tbody>
</table>

VA = venoarterial. ECMO = extracorporeal membrane oxygenation. VV = venovenous. ARDS = acute respiratory distress syndrome. HRQoL = health-related quality of life. HAD = hospital anxiety and depression. PTSD = post-traumatic stress disorder. IES = impact of event scale. PFT = pulmonary function tests. SGRQ = St George’s Respiratory Questionnaire. SF-36 = Medical Outcome Short-Form.
ARDS patients, von Bahr and colleagues recently reported 6 months after ICU discharge for 140 ECMO-treated ARDS patients, von Bahr and colleagues recently confirmed these results (66% survival in their cohort of 255 patients). In addition, the latest study provided a long-term follow-up showing that only 47% of these patients treated were still alive after 5 years. To date, only one prospective, randomised controlled trial has evaluated a strategy of conventional ventilation versus ECMO in the modern era. The CESAR trial, which included 180 patients with severe ARDS, with a median age of 40 year, reported 63% survival without severe disability at 6 months in the ECMO arm.

As reported with VA ECMO-treated patients, the HRQoL score of ECMO-treated ARDS survivors was significantly impaired (Table 1). Prolonged ICU stays, frequently exceeding 1 month, and the long-term impact of the disease on respiratory function, could both play key roles. When compared with a control group, no difference in lung capacity at 6 months was shown. Nevertheless, computed tomography scan revealed damage compatible with interstitial fibrosis, moderate obstructive disease (reduced forced expired volume) and a lung diffusion pattern (reduced DLCO). These changes were seen in 65% of ECMO-treated ARDS survivors. As previously described with VA ECMO, the same proportion of survivors showed symptoms compatible with significant-to-severe anxiety and depression, and 41% were considered at risk for PTSD.

Survival prediction models

Characteristics
These scores have been designed to predict survival in patients who are candidates for ECMO, to help inform clinicians and family members of likely outcomes and to benchmark outcomes between centres. Recently, a total of four and seven scores, respectively, were developed for ECMO-treated refractory cardiogenic shock and ARDS. The main characteristics of these scores are summarised in Table 2 and Figure 1. The risk factors considered in these models can be divided into four domains: 1) demographic characteristics and comorbidities, 2) pre-ECMO acute organ dysfunction, 3) initial diagnosis, and 4) characteristics and management of respiratory failure (only for the ARDS predictive survival model).

Survival prediction scores for refractory cardiogenic shock

Demographic characteristics and comorbidities
All scores but one included demographic characteristics. Older age and higher weight or body mass index were consistently associated with lower survival. Further, the Survival After Venoarterial ECMO (SAVE) score takes account of the fact that chronic renal failure and pre-ECMO cardiac arrest were both independently associated with mortality (odds ratio [OR], 0.42 [95% CI, 0.28–0.68] and OR, 0.75 [95% CI, 0.65–0.86], respectively).

Acute pre-ECMO organ dysfunction
Pre-ECMO organ dysfunction, such as kidney failure, neurological failure or liver failure were present in all VA ECMO prediction models. In addition, pre-ECMO severity of cardiac dysfunction (as shown by lower pulse pressure) was part of the SAVE-score. The performance of the SAVE-score seemed superior when the model was augmented with pre-ECMO arterial lactate.

Initial diagnosis
The aetiology of cardiogenic shock is of major importance as it indicates likelihood of cardiac recovery. Thus, this parameter was present in all scores (except de facto in the ENCORAGE score, which was based on post-AMI cardiogenic shock). Peigh and colleagues found post-cardiotomy cardiogenic shock to be associated with a worse outcome than all other diagnoses (AMI and E-CPR), but the SAVE and the modified SAVE-scores suggest that myocarditis, heart or lung transplants, and refractory electrical storm were independently associated with a better survival (OR, 1.58 [95% CI, 1.18–2.13], 1.52 [95% CI, 1.16–2] and 1.34 [95% CI, 1.09–1.64], respectively).

Survival prediction scores for severe ARDS

Demographic characteristics and comorbidities
First, all models identified older age as an independent risk factor for mortality. In the PRESERVE scores, being aged under 45 years was associated with a better prognosis, and being aged over 60 years led to an increased mortality risk. In four of the scores, immunocompromised status was linked with poorer outcome and underlying lung disease (ie, chronic obstructive pulmonary disease, interstitial lung disease, lung cancer) was identified as an independent risk factor for mortality (OR, 12.2 [95% CI, 1.2–122.2]; \( P = 0.033 \)).

Acute pre-ECMO organ dysfunction
Perhaps not surprisingly, the number of organs with pre-ECMO dysfunction had a substantial negative impact on survival. This point might be well assessed with the SOFA score if neurological evaluation is accurate despite frequent heavy sedation.

Cause of respiratory failure
The optimal survival figures for patients requiring VV ECMO are seen in patients with the diagnosis of influenza-related ARDS, in a similar relationship that acute myocarditis has
to VA ECMO. Influenza was consistently associated with better outcome in the Roth and colleagues, PRESERVE and RESP scores (70%, 83% and 70% survival, respectively). This better outcome was not highlighted with other ARDS causes. The limited power of the actual scores may explain the lack of other association.

**Characteristics and management of respiratory failure**

The relative infrequency of pre-ECMO management strategies such as neuromuscular blockers, nitric oxide or use of prone positioning reported in the published scores preclude assessment of their impact on predicted survival. The variability in data collected in the ECMO databases also

---

**Table 2. Survival predictive models for patients on VA ECMO for cardiogenic shock and VV ECMO for severe ARDS**

<table>
<thead>
<tr>
<th>Predictive models</th>
<th>Centres, Patients, Enrolment period</th>
<th>Inclusion criteria</th>
<th>Score items</th>
<th>AUROC Validation</th>
<th>AUROC Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scores for VA ECMO</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple cardiac ECMO score; Peigh et al.</td>
<td>1</td>
<td>73</td>
<td>2010–2014</td>
<td>Refractory cardiogenic shock</td>
<td>Post-cardiotomy, lactate &gt; 2 mmol/L, RIFE score injury or above</td>
</tr>
<tr>
<td>SAVE score; Schmidt et al.</td>
<td>280</td>
<td>3846</td>
<td>2003–2013</td>
<td>Refractory cardiogenic shock</td>
<td>Age, weight, chronic renal failure, pre-ECMO acute organ failures, diagnosis, pre-ECMO cardiac arrest, pre-ECMO diastolic blood pressure, pre-ECMO pulse pressure, bicarbonate levels, peak inspiratory pressure</td>
</tr>
<tr>
<td>Modified SAVE score; Chen et al.</td>
<td>1</td>
<td>154</td>
<td>2009–2014</td>
<td>VA ECMO within 24h of admission in ED</td>
<td>SAVE score, + lactate &gt; 7.5 mmol/L</td>
</tr>
<tr>
<td>ENcourAge score; Muller et al.</td>
<td>2</td>
<td>138</td>
<td>2008–2013</td>
<td>Refractory cardiogenic shock post-AMI</td>
<td>Age, sex, body mass index, Glasgow coma score. Creatininemia, serum lactate, prothrombin activity</td>
</tr>
<tr>
<td><strong>Scores for VV ECMO</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECMOnet score; Pappalardo et al.</td>
<td>14</td>
<td>60</td>
<td>2009</td>
<td>A(H1N1) influenza-related ARDS</td>
<td>Pre-ECMO LOS, bilirubin, creatinine Haematocrit level, mean arterial pressure</td>
</tr>
<tr>
<td>PRESERVE score; Schmidt et al.</td>
<td>3</td>
<td>140</td>
<td>2008–2012</td>
<td>Severe ARDS</td>
<td>Age, body mass index, immunocompromised, SOFA score Days of MV, prone positioning, PEEP, plateau pressure</td>
</tr>
<tr>
<td>RESP score; Schmidt et al.</td>
<td>280</td>
<td>2,355</td>
<td>2000–2012</td>
<td>Acute respiratory failure</td>
<td>Age, immunocompromised, days of MV, diagnosis, central nervous system dysfunction, acute associated non-pulmonary infection. Neuromuscular blockade agents, nitric oxyde use, bicarbonate infusion, cardiac arrest, PaCO₂, peak inspiratory pressure</td>
</tr>
<tr>
<td>Roch et al.</td>
<td>1</td>
<td>85</td>
<td>2009–2013</td>
<td>ARDS brought to a referral center</td>
<td>Age, SOFA score, influenza</td>
</tr>
<tr>
<td>Enger et al.</td>
<td>1</td>
<td>284</td>
<td>2008–2013</td>
<td>ARDS</td>
<td>Age, immunocompromised, minute ventilation Haemoglobin, lactate</td>
</tr>
<tr>
<td>VV ECMO mortality score; Cheng et al.</td>
<td>1</td>
<td>116</td>
<td>2007–2015</td>
<td>Severe ARDS</td>
<td>Immunocompromised, SOFA score, days of MV</td>
</tr>
<tr>
<td>Liu et al.</td>
<td>1</td>
<td>18</td>
<td>2009–2014</td>
<td>ARDS</td>
<td>Barotrauma, underlying lung disease</td>
</tr>
</tbody>
</table>

VA = venoarterial. ECMO = extracorporeal membrane oxygenation. VV = venovenous. ARDS = acute respiratory distress syndrome. AUROC = area under receiver operating characteristic curve. RIFE = risk, injury, failure, loss of kidney function, end-stage kidney disease. SAVE = survival after venoarterial ECMO. ED = emergency department. ENCOURAGE = prediction of cardiogenic shock outcome for AMI patients salvaged by VA ECMO. AMI = acute myocardial infarction. LOS = length of stay. PRESERVE = predicting death for severe ARDS on VV ECMO. SOFA = sequential organ failure assessment. MV = mechanical ventilation. PEEP = positive end-expiratory pressure. RESP = respiratory extracorporeal membrane oxygenation survival prediction. a. Validation on a cohort of 161 patients with cardiogenic shock. b. Validation on the cohort of Chen et al. c. Validation on the cohort of Muller et al. d. Validation on a cohort of 74 patients with A(H1N1) influenza-induced ARDS. e. Validation on the cohort of Enger et al. f. Validation on the cohort of Huang et al. g. Validation on the cohort of Kleinzing et al. h. Validation on the PRESERVE cohort of Schmidt et al. i. Barotrauma prior to ECMO was defined as pneumothorax, pneumomediastinum, pneumatoceles or subcutaneous emphysema.
Strengths and limitations of these predictive survival models

ECMO predictive survival models consistently showed better performance than classical ICU severity scores, such as the SOFA, SAPSII or APACHE scores. In other words, the area under the receiver operating characteristic curve (AUROC) for the ECMO models were higher than for the SOFA, SAPSII or APACHE models. However, these better performances should be analysed in light of the time these scores were performed (ie, ICU admission versus day of ECMO cannulation). Obviously, it is easier to predict survival on ECMO at the time of cannulation rather than at ICU admission, which may be several days before. As expected, all VA ECMO scores had a higher AUROC when compared with the SOFA score. Similarly, the SAVE score had an AUROC of 0.9, and the SOFA score had an AUROC of 0.71 and 0.79 at admission and cannulation, respectively.

The APACHE II score also showed worse performance compared with the SAVE score (AUROC, 0.58) or to the simple cardiac score (AUROC, 0.60 v 0.77).

Nevertheless, these models have several limitations that ECMO-stakeholders must consider. First, the cohorts from which these models have been constructed are heterogeneous in terms of studied population and data collected. Some survival models have been designed for specific populations such as H1N1-induced severe ARDS, ECMO-retrieved patients and acute myocardial infarction-related cardiogenic shock. Because the initial diagnosis has a strong impact on the prognosis, caution should be exercised when considering these specific models in another ECMO population.

In addition, variation in data collected in the ECMO databases influences the composition of the score. For example, prone positioning before ECMO, which was a significant protective factor for 6-month mortality, was not a factor that was available in the ELSO database used to create the RESP score. Duration of mechanical ventilation before ECMO initiation is also a major point to consider, as delayed initiation of more than 7 days had a negative impact on outcome in several predictive models.

Last, although it has not been considered in recent predictive survival models for ECMO, the Murray score, which already combines PaO2/FiO2 ratio, positive end-expiratory pressure, lung compliance and number of quadrants with infiltration on chest x-ray, showed good correlation with the rate of ECMO-treated patients with severe ARDS discharged alive from the intensive care unit. However, its performance in predicting short-term survival after ECMO in patients with severe ARDS warrants further investigations.

Figure 1. Pre-ECMO factors associated with survival on VA and VV ECMO, according to published predictive survival models

* Models for cardiogenic shock and ARDS.
neurological events and septic shock), despite favourable pre-ECMO score-based predicted survival. Consequently, this scoring system should never be considered as a substitute for clinical judgment.

Conclusion

“Which patients are more likely to survive on ECMO?” is a key question, as its ECMO management is costly and its complications potentially fatal. After failure of conventional management, survival-prediction models might be considered to identify which patients are more likely to survive with ECMO, as the performances of the models appear much better than classical ICU severity scores. On the basis of the large development cohort, external validation and easily available web calculators (www.respscore.com and www.save-score.com), we recommend the use of the RESP and the SAVE scores to benchmark outcomes, interpret variation in practice, and to inform clinicians and families of likely outcomes for patients treated with ECMO for severe respiratory failure and refractory cardiogenic shock, respectively.

However, further research in this topic is warranted. External validation of these predictive survival models with comparison of their performance between each other in a population of patients who had not yet received ECMO could be a first step forward. In the interim, the burning question, “When, how and for whom should we provide ECMO?” remains open and unanswered. Results from the ongoing randomised controlled EOLIA trial (ECMO for severe ARDS) are eagerly anticipated to provide some answers. Finally, this article must be seen in the context of a dedicated issue that explores multiple aspects of answers. Finally, this article must be seen in the context of a dedicated issue that explores multiple aspects of answers. Finally, this article must be seen in the context of a dedicated issue that explores multiple aspects of answers. Finally, this article must be seen in the context of a dedicated issue that explores multiple aspects of answers. Finally, this article must be seen in the context of a dedicated issue that explores multiple aspects of answers.

Acknowledgement

Santiago Montero was funded by a 2016 Clinical Training Grant from the European Society of Cardiology.

Competing interests

None declared.

Author details

Sacha Rozencwajg
John Fraser
Santiago Montero
Alain Combes
Matthieu Schmidt

1 Medical Intensive Care Unit, Institute of Cardiometabolism and Nutrition, Hôpital de la Pitié-Salpêtrière, Assistance Publique, Hôpitaux de Paris, Paris, France.
2 Critical Care Research Group, University of Queensland; and Adult Intensive Care Unit, Prince Charles Hospital, Brisbane, QLD, Australia.
3 Acute and Intensive Cardiovascular Care Unit, Department of Cardiology, Hospital de la Santa Creu i Sant Pau, Biomedical Research Institute (IIB Sant Pau), Barcelona, Spain.

Correspondence: matthieu.schmidt@aphp.fr

References

12 Bréchot N, Luyt C-E, Schmidt M, et al. Venoarterial extracorporeal membrane oxygenation support for refractory


