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Long-term health-related quality of life of adult patients treated with extracorporeal membrane oxygenation (ECMO): An integrative review

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ABSTRACT

Background: Extracorporeal membrane oxygenation (ECMO), a rescue treatment for patients with severe pulmonary and/or cardiac dysfunction, is increasingly being used worldwide. A better understanding of long-term health-related quality of life (HRQOL) is needed. *Objective:* To synthesize research on long-term (at least 6 months post-ECMO) HRQOL of adults treated with ECMO. *Methods:* In this integrative review, we searched 3 electronic databases and did a hand search of relevant journals for articles published 2000–2019, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. *Results:* Thirty-one studies, representing 913 patients treated with ECMO, were included. Long-term HRQOL was slightly better for patients treated with veno-venous ECMO than veno-arterial ECMO, and mental health outcomes tended to be better than physical ones. Survivors frequently experienced physical complications, functional limitations, anxiety, depression, and post-traumatic stress symptoms, although improvements were observed over time. *Conclusions:* Early identification and management of physical and mental health problems may improve HRQOL outcomes.

Introduction

Extracorporeal membrane oxygenation (ECMO) is a complex rescue treatment for patients with severe, but potentially reversible pulmonary and/or cardiac dysfunction.[1] ECMO may be configured to provide temporary organ support to the lungs (veno-venous, or VV ECMO) or the heart and lungs (veno-arterial, or VA ECMO), or to augment conventional cardiopulmonary resuscitation efforts (ECPR).[1] Goals of ECMO treatment are often described as "bridges" (i.e., bridge to decision, recovery, a more long-term mechanical circulatory device, e.g., left ventricular assist device [LVAD], or heart or lung transplant).[1] Table 1 includes indications for and clinical applications of ECMO.[2–7] Survival rates to hospital discharge or transfer are 59%, 42%, and 29% for adults treated with VV ECMO, VA ECMO, and ECPR, respectively.[8] The most frequent short-term complications are acute kidney injury, bleeding, and infection, with complications varying by ECMO configuration (Table 2).[9,10]

Health-related quality of life (HRQOL) is a multidimensional construct that describes the perceived impact of health status on aspects of daily life.[11,12] Dimensions include biological and physiological variables, symptoms, functional status, and health perceptions, which are influenced by and interact with individual characteristics (e.g., personality, values, preferences), environmental characteristics (e.g., psychological, social, and economic sources of support), and nonmedical considerations.[11] Although these dimensions may be assessed in isolation, a full evaluation of HRQOL incorporates all of them.[12]

Data from a growing body of literature on long-term outcomes of adult patients treated with ECMO suggest that survivors often experience varying levels of diminished HRQOL. Wilcox and colleagues[13] conducted a systematic review of long-term HRQOL after ECMO for acute respiratory failure and found significantly worse HRQOL in ECMO survivors compared with those treated with conventional mechanical ventilation (CMV) alone. However, ECMO survivors experienced significantly less psychological morbidity. The authors

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Table 1
Indications for and clinical applications of ECMO initiation in adult patients.

VV ECMO	VA ECMO
Indications[2]	**Indications**[3,4]
1. Hypoxemic respiratory failure from any cause - Consider if ≥50% mortality risk - Indicated if ≥80% mortality risk 2. CO_2 retention on mechanical ventilation despite high plateau pressures (>30 cm H_2O) 3. Severe air leak syndromes 4. Need for intubation in a patient on lung transplant list 5. Immediate cardiac or respiratory collapse	1. Inadequate tissue perfusion manifested as hypotension and low cardiac output despite adequate intravascular volume 2. Shock persists despite volume administration, inotropes, vasoconstrictors, and intraaortic balloon pump counterpulsation if appropriate 3. To aid cardiopulmonary resuscitation in patients who had reversible event and have had excellent CPR
Applications[2,5,6]	**Applications**[3,5–7]
1. Acute respiratory distress syndrome 2. Airway obstruction 3. Alveolar proteinosis 4. Aspiration syndromes 5. Bridge to lung transplant 6. Chronic obstructive pulmonary disease exacerbation 7. Pneumonia, severe (viral, bacterial) 8. Primary graft failure after lung transplantation 9. Pulmonary contusion 10. Pulmonary hemorrhage or massive hemoptysis 11. Smoke inhalation 12. Status asthmaticus	1. Acute myocardial infarction 2. Anaphylaxis, acute 3. Bridge to decision, ventricular assist device support, or transplant 4. Cardiac tamponade 5. Cardiomyopathy (chronic, peripartum) 6. Chronic heart failure, decompensated 7. Congenital heart disease 8. Drug overdose/toxicity with profound cardiac depression 9. Hypothermia (severe) 10. Isolated cardiac trauma 11. Myocarditis 12. Organ retrieval 13. Peri-procedural support for high-risk percutaneous cardiac interventions 14. Post-cardiotomy shock (inability to wean from cardiopulmonary bypass machine) 15. Pulmonary embolism 16. Septic with profound cardiac depression

CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; VA, veno-arterial; V V, veno-venous

included 6 studies of exclusively VV ECMO samples, published between 1998 and 2013, that incorporated only the 36-Item Short Form Health Survey (SF-36).

Considerable research undertaken in recent years has provided more details on outcomes for diverse patient populations, all configurations of ECMO, and longer durations from treatment to follow-up.

Table 2
Short-term complications of ECMO in adult patients identified by meta-analyses.

VV ECMO[9] Complication	Average point estimate (95% CI)
Bleeding	29.3% (20.8–39.6)
Significant bleeding	10.4% (5.6–18.7)
Cannula infections	9.9% (4.2–21.5)
Cannula bleeding	9.3% (5.3–15.6)
Other bleeding	9.3% (4.9–16.9)
Pulmonary bleeding	6.4% (3.2–12.4)
Pneumothorax	5.7% (1.1–24.2)
Intracranial hemorrhage	5.4% (2.7–10.3)
Deep vein thrombosis/Pulmonary embolism	4.6% (2.2–9.2)
VA ECMO[10] Complication	**Pooled estimate rate (95% CI)**
Acute kidney injury	55.6% (35.5–74.0)
Renal replacement therapy	46.0% (36.7–55.5)
Re-thoracotomy for bleeding or tamponade (postcardiotomy)	41.9% (24.3–61.8)
Major or significant bleeding	40.8% (26.8–56.6)
Significant infection	30.4% (19.5–44.0)
Lower extremity ischemia	16.9% (12.5–22.6)
Neurologic complications	13.3% (9.9–17.7)
Fasciotomy or compartment syndrome	10.3% (7.3–14.5)
Stroke	5.9% (4.2–8.3)
Lower extremity amputation	4.7% (2.3–9.3)

CI, confidence interval; ECMO, extracorporeal membrane oxygenation; VA, veno-arterial; VV, veno-venous

Given the extensive resources dedicated to these patients, potential for morbidity, and the increasing use of ECMO worldwide, a better understanding of long-term HRQOL outcomes is needed.

The purpose of this integrative review was to synthesize research on long-term HRQOL outcomes of adults treated with ECMO. Specific aims were to:

1) Describe long-term HRQOL outcomes, as evaluated by HRQOL-specific self-report instruments, of adults treated with ECMO.
2) Examine additional long-term outcomes (mental health, cognitive, physical, functional, social, and return to home and work), as evaluated by measures other than HRQOL-specific instruments, of adults treated with ECMO.

Methods

We conducted an integrative review to include research with diverse methods and to provide a comprehensive understanding of a phenomenon of interest.[14] We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15] The National Heart, Lung and Blood Institute quality assessment measures for observational and randomized controlled studies were used to assess the internal validity of the studies.[16]

Search method

A medical librarian who specializes in literature reviews was consulted before the literature search was performed. We searched the following databases for relevant studies: MEDLINE (OvidSP 1946-March 6, 2016), Embase (OvidSP 1974-March 6, 2016), and Cochrane Library (Wiley Online through March 6, 2016). The databases were searched using both controlled vocabulary words and synonymous free text words that covered the topic of interest: extracorporeal membrane oxygenation. The search strategies were adjusted for the

syntax appropriate for each database/platform. The search was limited to humans and adults 18 years or over. Further studies were identified through subsequent searches (last search on May 2, 2019). (See Supplement 1 for the full OVID Embase search strategy). We also examined the reference lists of included articles, reviewed publications of experts in the field, and hand-searched relevant journals.

Inclusion and exclusion criteria

Two authors (KAK and CMG) assessed each study for inclusion using Covidence systematic review software.[17] Articles were included if they met the following criteria: 1) population: adult patients, 2) intervention: treated with ECMO, and 3) outcome: description of long-term (at least 6 months after treatment with ECMO) HRQOL outcomes, measured with HRQOL-specific instruments. Studies must have been peer-reviewed and written in English. Given the technological advancements and substantial evolution in clinical management of adults undergoing ECMO, the search was limited to studies published in or after the year 2000.

Results

Study quality

Most studies were determined to have good quality (Table 3), with minimal risks of internal bias. Studies with fair quality were subject to some bias or reported confusing and contradictory results, but none sufficient to undermine their conclusions.

Study characteristics

In total, the literature searches generated 6,778 articles (Fig. 1). Thirty-one were included in this analysis. The selected articles were published between 2008 and 2019 and included one randomized controlled trial[37] and 30 observational studies (26 cross-sectional, 4 longitudinal).[18–36,38–48] Study samples included predominant/exclusive use of VV ECMO,[23,24,26,30–32,37,40,41,48] VA ECMO,[19,20,22,25,28,33–36,42,45,47] ECPR,[18,43] and mixed VV and VA ECMO.[21,27,29,38,39,44,46] The most common clinical indications for ECMO were severe acute respiratory distress syndrome (ARDS), shock (cardiogenic, post-cardiotomy, septic), peri/post cardiac arrest, and bridge to LVAD or transplant. Included studies were conducted in Australia,[26,38,44] China,[47,48] Finland,[28] France,[18,19,22,25,32,33,35,41] Germany,[20,39,43] Italy,[23,24,34,40] Lithuania,[36] Netherlands,[30] Sweden,[31,46] Switzerland,[42] Taiwan,[21,27] the United Kingdom,[37] and the United States.[29,45] Characteristics shared by most included studies were data obtained from a single center, lack of pre-ECMO illness quality of life data, small sample size, and moderate to high response rate. See Table 3 for details of included studies.

Sample demographic and clinical characteristics were reported in different ways, both in content (e.g., some authors reported hospital length of stay, some did not) and descriptive statistics (e.g., mean vs. median). Some authors described their samples as a whole (including non-survivors), whereas others compared survivors versus non-survivors, and still others reported only the data from survivors included in long-term analysis. As the purpose of this analysis is to focus on outcomes of survivors of ECMO, we report characteristics that most closely represent long-term survivors (at least 6 months after treatment with ECMO). Most studies included long-term follow-up data only from patients treated with ECMO; 8 compared those data with patients with similar diagnoses not treated with ECMO.[24,29,30,36,37,42,45,48]

Data are reported for 913 patients treated with ECMO. The average (mean or median) sample size was 29.5 (range 7 to 100) participants. Average duration from treatment with ECMO to follow-up assessment of HRQOL ranged from 6 months to 9 years and tended to be shorter for VV samples (most between 6 and 17 months) and longer for VA samples (all 11 months and longer). Twenty-six (84%) of the included studies had samples that were comprised of predominantly males. The average age of participants was ≤40 years, 41–49 years, and ≥50 years in 29.0%, 32.3%, and 38.7% of studies, respectively. The average duration of ECMO treatment ranged from 3 to 19 days. The average lengths of stay ranged from 5 to 37 days in the intensive care unit (ICU) and 21 to 79 days in the hospital.

Variables and instruments

All studies reported HRQOL measured with at least one HRQOL-specific instrument. Some studies include additional long-term health outcomes (specific to mental health, cognition, physical health, functional status, and social outcomes) that were assessed using measures other than HRQOL-specific instruments (Table 4). Survivor employment status was evaluated by survey or interview. Details of long-term HRQOL outcomes of ECMO survivors are presented in Supplement 2.

Long-term HRQOL outcomes, as evaluated by HRQOL-specific instruments

Types of instruments

HRQOL-specific instruments measure generic or disease-specific HRQOL. Generic HRQOL instruments included the SF-36, the 12-Item Short Form Health Survey (SF-12), and the EuroQol (EQ)–5D instrument. Disease-specific HRQOL instruments included the St. George's Respiratory Questionnaire (SGRQ), Airways Questionnaire 20-Revised (AQ20-R), and the Kansas City Cardiomyopathy Questionnaire (KCCQ).

Most studies incorporated generic HRQOL instruments. Some reported their findings as specific scores, whereas others compared their results with findings from other studies using only graphs without specific scores. For example, 22 studies included results from the SF-36, but only 15 reported domain scores.[18,22,24,27,32,35–38,40–43,46,48] The highest overall scores (indicating better HRQOL) were observed in domains of bodily pain, role-emotional, and social function; the lowest were seen in role-physical, general health, and vitality. Fourteen studies included Physical Component Summary (PCS) and Mental Component Summary (MCS) scores, either by the SF-36[18,21,22,27,32,35,36,40–42,46,48] or the SF-12.[29,34] Norm-based standardized mean scores for the PCS and MCS are 50 (SD 10).[50] MCS scores for included studies ranged from 44 to 79, with 54% ≤50; PCS scores ranged from 42 to 72, with 85% ≤50. In 79% ($n = 11$) of these studies, MCS scores were equal to or higher than PCS scores.

Eight studies reported specific EQ-5D dimension scores and scores ranged widely.[20,23,26,30,37–39,48] On average, three-quarters of survivors reported no problems with self-care, and 50–58% reported no problems with usual activities, anxiety/depression, and mobility. Only 40% of survivors reported having no pain/discomfort. If problems did exist, they were most likely to be reported as "severe" or "extreme" in the dimensions of anxiety/depression (6.9%) and usual activities (11.4%). EQ-5D visual analogue scale (VAS) scores were reported in 12 studies[20,23,25,26,28,30,37–39,44,45,48]; average VAS scores ranged from 65 to 81.5, on a scale of 0–100 (with higher scores indicating better HRQOL).

Scores were reported from 3 disease-specific instruments. HRQOL is often measured in people with obstructive airway disease and congestive heart failure with the SGRQ and AQ20-R, and the KCCQ, respectively. Five studies with VV samples reported SGRQ data; total scores ranged from 10.5 to 23 (range 0–100, with higher scores representing worse HRQOL).[24,31,37,41,46] Clinically important improvements were found using the AQ20-R before and 6 months after lung transplantation with ECMO bridge.[29] Statistically significant improvement was noted in KCCQ overall summary scores between

Table 3
Details of included studies.

Author, Date Years of Data Collection	Study Design	ECMO Configuration, Indication, Duration of Treatment (Days)	# of Patients in Long-term Follow-up Evaluation	Sex (% Male)	Age (years)	ICU LOS (days)	Hospital LOS (days)	Duration from ICU to Follow-up	Included Measures	Study Quality[d]
Anselmi[18,a] 2015 2005-13	Cross-sectional	ECPR Cardiac arrest N/A	18	72.2	44.9 ± 17.3*	N/A	79.2 ± 97.6*	15.6 ± 19.2 months*	SF-36[49,50]	Good
Brechot[19,a] 2013 2008-11	Cross-sectional	VA Cardiogenic & septic shock 5.5^; Range 2-12	10	33.3	40.0 ^; Range 28-59	17.5^; Range 8-51	N/A	13 months^; Range 3-43 months	SF-36[49,50] HADS[57] IES[60]	Good
Camboni[20,a] 2017 2006-15	Cross-sectional	VA Cardiogenic shock N/A	82	65	56 ± 17*	N/A	N/A	983 ± 682 days*; IQR 252-1478	EQ-5D[51–53]	Good
Chen[21,a] 2018 2012-14	Longitudinal	Mixed VV & VA 34% VV 66% VA Cardiogenic shock & respiratory failure 8.0 ± 5.9*	32 34% respiratory 60% cardiac 6% ECPR	84	52 ± 12*	17.4 ± 9.7*	48.1 ± 41.7*	3, 6, 9, 12 months	SF-36[49,50] SSS[72] FSQ[70] CES-D[59]	Good
Combes[22,b] 2008 2003-06	Cross-sectional	VA Cardiogenic shock 7 (5-10)^	28	71	46 ± 17*	21 (12-31)^	N/A	11 (6-23) months^; Range 3-39 months	SF-36[49,50]	Good
Galazzi[23,a] 2018 2013-15	Cross-sectional	VV ARDS 19 (15-33)^	17	70	49 (38-55)^	37 (20-79)^	N/A	17 (14-25) months^	EQ-5D[51–53]	Good
Grasselli[24,b] 2019 2013-15	Cross-sectional	VV ARDS 9 (6-13) ^ N/A	18 w/ECMO 19 w/o ECMO	70 62	54 (41-63) ^ 54 (45-70) ^	24 (15-36) ^ 11 (5-25) ^	33 (19-48) ^ 23 (12-45) ^	12 months	SF-36[49,50] SGRQ[54] IES[60]	Good
Guihaire[25,b] 2017 2005-14	Cross-sectional	VA Postcardiotomy 7.9 ± 0.9*	28	76.5	56.8 ± 15.5*	24.8 ± 14.3*	N/A	20.9 ± 32.8 months*	EQ-5D[51–53]	Good
Hodgson[26,b] 2012 2009-11	Cross-sectional	VV ARDS 10.6 (3.6-15.8)^	15	48	36.3 ± 12.1*	20.7 (14.9-28.6)^	28.4 (18.5-37.7)^	8.4 (6-16) months^	SF-36[49,50] EQ-5D[51–53]	Good
Hsieh[27,a] 2017 2009-11	Cross-sectional	Mixed VV & VA 26% ARDS 63% Cardiac 11% Other 8.9 ± 10.8*; Range 1-59	100	70	49.0 ± 14.8*; Range 23-81	25.2 ± 21.2*; Range 3-113	52.6 ± 44.4*; Range 8-260	Range 9-51 months	SF-36[49,50] BI[68] IADL[67] NHP-II[73]	Good
Jäämaa-Holmberg[28,a,b] 2019 2007-16	Cross-sectional	VA Cardiogenic shock 6 (5)^	49	71	56 (18)^	18 (19) ^	N/A	1.9 (3.2) years^	SF-36[49,50] EQ-5D[51–53]	Good
Kolaitis[29,a] 2018 2010-17	Longitudinal	Mixed VV & VA 53% VV 47% VA All required lung transplant N/A N/A N/A	17 w/ECMO 48 w/o ECMO, inpatients 124 w/o ECMO, outpatients	47 50 58	46.1 ± 16.6* 52.9 ± 9.0* 51.8 ± 11.6*	N/A	N/A	Baseline, 3, 6, 12 months	SF-12[50] EQ-5D[51–53] AQ20-R[55] GDS[58]	Good

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Table 3 (*Continued*)

Author, Date Years of Data Collection	Study Design	ECMO Configuration, Indication, Duration of Treatment (Days)	# of Patients in Long-term Follow-up Evaluation	Sex (% Male)	Age (years)	ICU LOS (days)	Hospital LOS (days)	Duration from ICU to Follow-up	Included Measures	Study Quality[d]
Lansink-Hartgring[30,b] 2017 2010-14	Cross-sectional	VV Pulmonary disease requiring lung transplant 10 (6-12)^ N/A	7 w/ECMO 121 w/o ECMO	67 54	44 (19-55)^ 52 (42-58)^	25 (9-68)^ 7 (4-18)^	66 (40-114)^ 42 (29-62)^	12 months	EQ-5D[51–53]	Good
Linden[31,b] 2009 62-month period, before 2009	Cross-sectional	VV ARDS 14.4*; Range 2.7-51.6	21 15 completed HRQOL measure	57	40*; Range 21-65	N/A	N/A	26 months^; Range 12-50 months	SGRQ[54]	Good
Luyt[32,a] 2012 2009-10	Cross-sectional	VV ARDS (H1N1) 9.5 (7.5-17)^ N/A	12 w/ECMO 25 w/o ECMO	42 52	35.5 (30-39)^ 42 (33-51)^	37.5 (19 -67)^ 19 (12-27.5)^	N/A	12.5 (10.9-12.8) months^ 12.4 (11.1-13.2) months^	SF-36[49,50] HADS[57] IES[60]	Good
Mirabel[33,b] 2011 2002-09	Cross-sectional	VA Myocarditis 6.2 ± 21.2*	26	42.9	38.1 ± 12.7*	32.3 ± 29.0* 26 (13-46)^	79.4 ± 74.0* 63 (31-88)^	525 (305-1496) days^; Range 92-2400 days	SF-36[49,50] HADS[57] IES[60]	Good
Mojoli[34,b] 2013 2008-11	Cross-sectional	VA Cardiogenic shock 37% ECPR 3.0 (1.9-6.0)^	7	75	51 (45-55)^	22 (10-26)^	N/A	46 (36-54) months^	SF-12[50]	Fair
Muller[35,b] 2016 2008-13	Cross-sectional	VA Acute MI w/ cardiogenic shock 8 (5-12)^	41	85	53 (44-60)^	N/A	21 (12-40)^	32 (18-54) months^	SF-36[49,50] HADS[57] IES[60]	Good
Norkiene[36,a] 2019 2009-14	Cross-sectional	VA Postcardiotomy 4.9 (3.7-6.4)^	15	60	59.6 ± 13*	15 (11-31)^	38 (28-82)^	70.6 ± 10 months*	SF-36[49,50] IES[60]	Good
Peek[37,c] 2009 2001-06	RCT	VV ARDS 9.0 (6.0-16.0)^ N/A	Full data in: 52 w/ECMO 32 w/o ECMO	57 59	39.9 ± 13.4* 40.4 ± 13.4*	24.0 (13.0-45.0)^ 13.0 (11.0-16.0)^	35.0 (15.6-74.0)^ 17.0 (4.8-45.3)^	6 months	SF-36[49,50] EQ-5D[51-53] SGRQ[54] HADS[57] MMSE[62]	Good
Roll[38,a] 2018 2009-14	Longitudinal	Mixed VV & VA 58% VV 42% VA Mixed diagnoses 8.8 (6.4-21.3)^	33	57.6	42 (26.5-57.0)^	29.8 (17.0-45.0)^	48.5 (30.4-55.4)^	606 days^	SF-36[49,50] EQ-5D[51–53] FAI[68]	Good
Ruckert[39,c] 2017 2009-14	Cross-sectional	Mixed VV & VA (Majority VV) ARDS & cardiogenic shock 12.0 (7.5-17.0)^	27	58	56 (47.0-66.0)^	21.0 (11.5-46.5)^	22.0 (11.5-48.5)^	31 months^	EQ-5D[51–53] MMSE[62] DemTect[63] TE4D-Cog[64] KPS[71]	Good
Sanfilippo[40,a] 2019 2009-16	Cross-sectional	VV ARDS 10 (7-15)^	33	73	41.3 ± 9.8*	N/A	N/A	2.7 (2.8) years^	SF-36[49,50] HADS[57] IES-R[60] CES-D[59]	Good
Schmidt[41,b] 2013 2008-12	Cross-sectional	VV ARDS (5% VA ECMO) 15 (8-30)^	67	55	37 (28-47)^	46 (29-74)^	63 (38-95)^	17 months^; Range 11-28 months	SF-36[49,50] SGRQ[54] HADS[57] IES[60] IADL[67]	Good

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Table 3 (*Continued*)

Author, Date Years of Data Collection	Study Design	ECMO Configuration, Indication, Duration of Treatment (Days)	# of Patients in Long-term Follow-up Evaluation	Sex (% Male)	Age (years)	ICU LOS (days)	Hospital LOS (days)	Duration from ICU to Follow-up	Included Measures	Study Quality[d]
Schoenrath[42,b] 2016 2005-14	Cross-sectional	VA RV failure w/cardiogenic shock 5.6 (2.2-7.7)^	16 Includes 4 bridged to OHT	63	43.7 ± 15*	N/A	N/A	34 months^; Min: > 1 year Max: 8.3 years	SF-36[49,50] BI[69]	Fair
Spangenberg[43,a] 2018 2014-16	Cross-sectional	ECPR Cardiac arrest N/A	17	80	57.6 ± 12.8*	N/A	N/A	≥6 months	SF-36[49,50]	Good
Tramm[44,a] 2017 2013-14	Longitudinal	Mixed VV & VA 29% VV 71% VA Mixed diagnoses 6 (3-7.5)^	24 8% attrition rate over time	75	42*	16 (11.5-22.7)^	32.5 (23.8-43.3)^	3, 6, 12 months	SF-36[49,50] EQ-5D[51–53] HADS[57] IES-R[60] TICS[65–66]	Good
Unai[45,b,e] 2017 2008-14	Cross-Sectional	VA Bridge to LVAD 11 ± 6.2* N/A	7 w/ECMO 73 w/o ECMO	82 81	54 ± 12* 58 ± 12*	N/A	35 ± 27* 23 ± 24*	11 ± 11 months*	EQ-5D[51–53] KCCQ[56]	Good
von Bahr[46,a] 2019 1995-2009	Cross-sectional	Mixed VV & VA 71% VV 29% VA Mixed diagnoses 11 (7-23)^	38	63	38 (24-52)^	37 (23-57)^	54 (30-114)^	9.0 years^; Range 3.1-17.1 years	SF-36[49,50] SGRQ[54] HADS[57] TSQ[61]	Good
Wang[47,b] 2009 2004-08	Cross-sectional	VA Postcardiotomy 2.5 ± 1.5* N/A	32 w/ECMO 85 w/o ECMO	51.6 51.8	51 ± 15* 58 ± 12*	5.2 ± 3.8* N/A	44.3 ± 17.6* N/A	2.3 ± 1.5 years* Max: 4 years	SF-36[49,50]	Good
Wang[48,a] 2017 2012-14	Cross-sectional	VV ARDS 6.0 ± 2.3* N/A	24 w/ECMO 48 w/o ECMO	75 69	38.0 ± 15.1* 44.3 ± 15.6*	13.0 (9.8-22.3)^ 11.0 (8.0-18.0)^	25.5 (16.5-31.3)^ 26.0 (15.0-56.3)^	12.7 months* 14.8 months*	SF-36[49,50] EQ-5D[51–53]	Good

AQ20-R, Airways Questionnaire 20-Revised; ARDS, acute respiratory distress syndrome; BI, Barthel Index; CES-D, The Center for Epidemiologic Studies Depression Scale; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; EQ-5D, Eurol-Qol-5D; FAI, Frenchay Activities Index; FSQ, Functional Status Questionnaire; GDS, Geriatric Depression Scale; H1N1, H1N1 flu virus; HADS, Hospital Anxiety and Depression Scale; HRQOL, health-related quality of life; IADL, Instrumental Activities of Daily Living; ICU, intensive care unit; IES, Impact of Events Scale; IES-R, Impact of Events Scale-Revised; IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; KPS, Karnofsky Performance Scale Index; LOS, length of stay; LVAD, left ventricular assist device; MI, myocardial infarction; MMSE, Mini Mental State Examination; N/A, data not available; NHP-II, Nottingham Health Profile-Part II; OHT, orthotopic heart transplant; RCT, randomized controlled trial; RV, right ventricular; SD, standard deviation; SF-12, 12-Item Short Form Healthy Survey; SF-36, 36-Item Short Form Health Survey; SGRQ, St. George's Respiratory Questionnaire; SSS, Social Support Scale; TE4D-Cog, Test for the Early Detection of Dementia; TICS, Telephone Interview for Cognitive Status; TSQ, Trauma Screening Questionnaire; VA, veno-arterial ECMO; VV, veno-venous ECMO; w/, with; w/o, without.

* Data are expressed as mean ± SD.

^ Data are expressed as median (IQR).

[a] Reported data reflect only survivors who completed HRQOL follow-up measures.

[b] Reported data reflect survivor group (not all of whom completed HRQOL follow-up measures).

[c] Reported data reflect survivors and non-survivors.

[d] National Heart, Lung and Blood Institute quality assessment tool

[e] 191 patients implanted with LVAD without ECMO; of these baseline characteristics reported for 21 patients and HRQOL data reported post-LVAD for 73 patients. Characteristics reported for all 22 patients bridged to LVAD with ECMO; of these, HRQOL data reported for 7 patients.

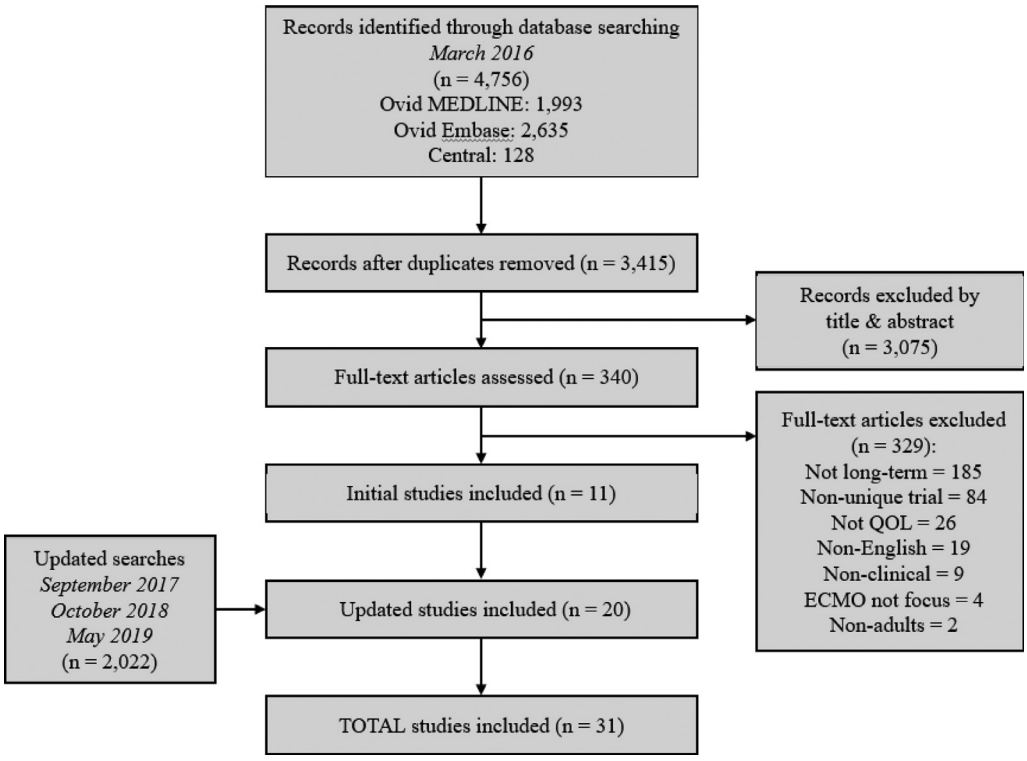

Fig. 1. Flow diagram
ECMO, extracorporeal membrane oxygenation; QOL, quality of life.

pre- and post-LVAD implantation (mean 11 months post-LVAD) for patients who had undergone ECMO.[45]

ECMO by configuration

Overall scores (by SF-36 or SF-12 PCS and MCS and EQ-5D VAS) were slightly better in samples treated with VV ECMO, compared with VA ECMO. The highest SF-36 domain scores were bodily pain (indicating less pain) for ECPR, mixed, and VA samples; role-emotional for mixed, VA, and VV samples; and social function for mixed, VA, and VV samples. Across all ECMO configurations, the worst SF-36 domain scores were reported in role-physical, vitality, and general health.[18,22,27,32,35–38,40–43,46,48]

Outcomes following bridge to heart transplant

In 2 studies, researchers reported SF-36 data that compared HRQOL outcomes between ECMO survivors who were bridged to heart transplant and those who were not bridged to transplant. In one study, HRQOL was comparable between groups[42]; in the other, HRQOL was better for transplant recipients.[22] Results from both studies suggest that the biggest difference between groups was in the role-emotional domain (better in transplant recipients).

Comparisons with non-ECMO populations

Most studies included in this analysis compared HRQOL outcomes of ECMO survivors with other non-ECMO populations. Fourteen studies compared HRQOL results with age-matched or age- and sex-matched reference populations[18,19,22,28,31–33,35,41–43,46–48]; in 13 of these studies HRQOL scores were better in reference populations. Eight studies compared long-term HRQOL of ECMO survivors with survivors of other acute illness states, such as ARDS, myocardial infarction, heart failure, hemodialysis, and cardiothoracic surgery.[19,22,26,31,33,35,41,46] In most cases, HRQOL was better for ECMO survivors.

Results were mixed among studies that included patients within their own sample who had similar underlying diagnoses but did or did not require ECMO as a bridge. Most studies that compared long-term outcomes of ARDS patients treated with or without ECMO showed better HRQOL for ECMO survivors, but statistical significance was not consistently reported.[24,32,37,48] HRQOL outcomes were comparable between patients who underwent lung transplant or LVAD implantation, with or without ECMO as a bridge.[30,45] In one study, people who underwent cardiac surgery with ECMO bridge had significantly worse SF-36 domains of vitality and mental health than those in the non-ECMO group.[47]

Changes in HRQOL over time

HRQOL outcomes tended to improve over time. HRQOL instruments were administered at multiple time points in 4 studies. At 6 months post-discharge, minimal clinically important differences from pre-ECMO were found using the SF-12 (particularly in PCS), EQ-5D, and AQ20-R.[29] An overall trend of improving SF-36 and EQ-5D scores was seen up to 12 months post-hospital discharge,[21,38,44] with some evidence suggesting that the increase in PCS is most robust in the period between 9 and 12 months.[21] Statistically significant improvements between hospital discharge and 12 months later were reported in SF-36 domains (physical function, role-physical, role-emotional), SF-36 PCS, and EQ-5D dimensions (self-care and usual activities).[38]

Four additional studies used cross-sectional designs but stratified their samples into sub-groups (< and ≥325 days[22]; < and ≥503 days[41]; < and ≥945 days[35]; <2 years, 2–3 years, and ≥3 years[27] post-ECMO, based on duration between times of ECMO treatment and follow-up assessment. Statistically significant improvements were observed in PCS ($n = 1$ study) and SF-36 domains of physical function ($n = 2$), role-physical ($n = 3$), general health ($n = 2$), social function ($n = 2$), role-emotional ($n = 2$), bodily pain ($n = 1$), and vitality ($n = 1$).

Table 4
Details of included measures.

Outcome/Dimension	Measure	Purpose	Components	Details & Scoring	Study that Included Measure
Generic HRQOL	36-Item Short Form Health Survey (SF-36)[49,50]	Measure generic health status	36 items 8 domains: Physical function Role-physical Bodily pain General health Vitality Social function Role-emotional Mental health 2 summary scores: Physical component summary (PCS) Mental component summary (MCS)	Sum of items from each dimension forms total score 0-100. Higher score indicates better health status. Domains aggregated to 2 summary measures (PCS, MCS). Norm-based T scores for each scale: mean = 50, SD = 10. MCID = 5 Physical function: Limitations in daily life due to health problems Role-physical: Role limitations due to physical health problems Pain: Frequency & interference with usual roles General health: Perceptions of general health Vitality: Levels of energy & fatigue Social function: Extent to which ill health interferes with social activities Role-emotional: Role limitations due to emotional problems Mental health: Psychological distress To calculate PCS, highest weights given to domains of physical function, role-physical, bodily pain, & general health. To calculate MCS, highest weights given to vitality, social functioning, role-emotional, & mental health	Anselmi *et al.*[18] Brechot *et al.*[19] Chen *et al.*[21] Combes *et al.*[22] Grasselli *et al.*[24] Hodgson *et al.*[26] Hsieh *et al.*[27] Jäämaa-Holmberg *et al.*[28] Luyt *et al.*[32] Mirabel *et al.*[33] Muller *et al.*[35] Norkiene *et al.*[36] Peek *et al.*[37] Roll *et al.*[38] Sanfilippo *et al.*[40] Schmidt *et al.*[41] Schoenrath *et al.*[42] Spangenberg *et al.*[43] Tramm *et al.*[44] von Bahr *et al.*[46] Wang *et al.*[47] Wang *et al.*[48]
	12-Item Short Form Health Survey (SF-12)[50]	Measure generic health status	8 domains, PCS, MCS as in SF-36	Adaptation of SF-36 that includes only 12 questions. Details & scoring as in SF-36. Typically only PCS & MCS are reported.	Kolaitis *et al.*[29] Mojoli *et al.*[34]
	EuroQol-5D (EQ-5D)[51-53]	Measure generic health status	5 items + VAS 5 dimensions: Mobility Self-care Usual activities Pain/discomfort Anxiety/depression	Responses reported in descriptive system as health states, w/3 levels (EQ-5D-3 L; no/some/severe problems) or 5 levels (EQ-5D-5 L; none/slight/moderate/severe/ extreme). Health states of EQ-5D-5 L may be converted to weighted health state index (useful in calculation of QALYs). Scores range from 0 (dead) to 1 (full health). Also includes VAS as measure of overall self-rated health status; scores range from range from 0 (worst health) to 100 (best health). Higher score indicates better HRQOL. MCID = 0.06.	Camboni *et al.*[20] Galazzi *et al.*[23] Guihare *et al.*[25] Hodgson *et al.*[26] Jäämaa-Holmberg *et al.*[28] Kolaitis *et al.*[29] Lansink-Hartgring *et al.*[30] Peek *et al.*[37] Roll *et al.*[38] Rückert *et al.*[39] Tramm *et al.*[44] Unai *et al.*[45] Wang *et al.*[48]
Disease-Specific HRQOL	St. George's Respiratory Questionnaire (SGRQ)[54]	Measure HRQOL in obstructive airway disease	76 items 3 sections: Symptoms Restrictions of activity Impact of daily life caused by the disease	Scores range from 0 to 100. Higher score indicates worse HRQOL.	Grasselli *et al.*[24] Linden *et al.*[31] Peek *et al.*[37] Schmidt *et al.*[41] von Bahr *et al.*[46]
	Airways Questionnaire 20 -Revised (AQ20-R)[55]	Measure HRQOL in obstructive airway disease	20 items	Modification of original AQ20 instrument. Response options of yes/no/unable/not applicable. Higher scores indicate worse HRQOL.	Kolaitis *et al.*[29]
	Kansas City Cardiomyopathy Questionnaire (KCCQ)[56]	Measure HRQOL in heart failure	23 items 5 sections: Physical limitations Symptoms	OSS provided. Scores range from 0 – 100. Higher score indicates better health status. Improvement of >10 points in OSS indicates	Unai *et al.*[45]

(*continued on next page*)

Table 4 (*Continued*)

Outcome/Dimension	Measure	Purpose	Components	Details & Scoring	Study that Included Measure
			QOL Social interference Self-efficacy	moderately large clinically significant difference in health status.	
Mental Health	Hospital Anxiety & Depression Scale (HADS)[57]	Assess anxiety & depression	14 items 2 subscales: Anxiety (7 questions) Depression (7 questions)	Scores range on 4-point Likert scale from 0 (none) to 21 (severe) for each subscale. Subscale scores of ≥ 8 indicate clinically significant symptoms (borderline anxiety or depression). Scores of ≥ 11 indicate severe psychological distress.	Brechot *et al.*[19] Luyt *et al.*[32] Mirabel *et al.*[33] Muller *et al.*[35] Peek *et al.*[37] Sanfilippo *et al.*[40] Schmidt *et al.*[41] Tramm *et al.*[44] von Bahr *et al.*[46]
	Geriatric Depression Scale (GDS)[58]	Assess depressive symptoms over last week	15 yes/no items	Scores range from 0 to 15. Higher scores reflect more depressive symptoms.	Kolaitis *et al.*[29]
	The Center for Epidemiologic Studies Depression Scale (CES-D)[59]	Measure current level of depressive symptomatology	20 items 6 scales: Depressed mood Feelings of guilt and worthlessness Feelings of helplessness and hopelessness Psychomotor retardation Loss of appetite Sleep disturbance	Scores range from 0 to 60. Higher score represents more severe depressive symptoms. Traditional cutoff score indicating major depression is ≥16.	Chen *et al.*[21] Sanfilippo *et al.*[40]
	Impact of Events Scale & Impact of Events Scale-Revised (IES & IES-R)[60]	Assess subjective distress caused by traumatic events	IES: 15 items, 2 diagnostic clusters IES-R: 22 items, 3 diagnostic clusters Diagnostic clusters: Intrusion (IES & IES-R) Avoidance (IES & IES-R) Hyperarousal (IES-R only)	IES: Total score ranges from 0 (no symptoms) to 75 (severe symptoms). IES-R: 5-point Likert scale. Total scores range from 0 (no symptoms) to 88 (severe symptoms). Cutoff scores indicating high risk for PTSD vary on nature of traumatic event. Most studies in this analysis indicate score of ≥ 30. Tramm uses cutoff of ≥ 33.	Brechot *et al.*[19] Grasselli *et al.*[24] Luyt *et al.*[32] Mirabel *et al.*[33] Muller *et al.*[35] Norkiene *et al.*[36] Sanfilippo *et al.*[40] Schmidt *et al.*[41] Tramm *et al.*[44]
	Trauma Screening Questionnaire (TSQ)[61]	Screen for symptoms of PTSD over last week	10 items (5 intrusion, 5 hyperarousal)	Scores range from 0 to 10. Scores ≥6 indicate possible PTSD.	von Bahr *et al.*[46]
Cognition	Mini Mental State Examination (MMSE)[62]	Assess cognitive status	11 items 5 areas of cognitive function: Orientation Registration Attention & calculation Recall Language	Scores range from 0 to 30. Score of ≤ 23 indicates cognitive impairment.	Peek *et al.*[37] Rückert *et al.*[39]
	DemTect[63]	Screen for mild cognitive impairment (MCI) & early dementia	5 tasks: Word list Number transcoding Word fluency Digit span reverse Delayed recall of word list	5 tasks cover immediate & delayed verbal recall, working memory, language & number processing, executive functioning). Maximum total score of 18. Indicates adequate cognitive performance for age (13-18 points), or suspected MCI (9-12 points) or dementia (≤ 8 points).	Rückert *et al.*[39]
	Test for the Early Detection of Dementia (TE4D-Cog)[64]	Screen for early detection of dementia	8 items 6 subscales: Immediate recall Semantic memory Clock drawing test	Cutoff score 35 (from maximum score 45) indicates possible early dementia.	Rückert *et al.*[39]

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Table 4 (*Continued*)

Outcome/Dimension	Measure	Purpose	Components	Details & Scoring	Study that Included Measure
			Category fluency Orientation to time Ideomotor praxis		
	Telephone Interview for Cognitive Status (TICS)[65,66]	Assess global cognitive functioning	11 items including: Word list memory Orientation Attention Repetition Conceptual knowledge Nonverbal praxis	Max score 41. Total scores reported as ranges of qualitative impairment. 41 to 33: Unimpaired 32 to 26: Ambiguous 25 to 21: Mild impairment ≤20: Severe impairment	Tramm *et al.*[44]
Functional Status	Instrumental Activities of Daily Living Scale (IADL)[67]	Assess complex independent living skills	8 items: Telephone use Shopping Food preparation Housekeeping Laundry Mode of transportation Medication use Financial management	Rated with summary score, ranging from 0 to 8. Higher scores indicate higher levels of independence.	Hsieh *et al.*[27] Schmidt *et al.*[41]
	Frenchay Activities Index (FAI)[68]	Assess complex instrumental ADL	15 items 3 subscales: Domestic (5 items) Leisure/work (5 items) Outdoors (5 items)	Roll *et al.* used a modified scoring system: 0-3 points per item. Summed score range 0 – 45. Higher scores indicate higher levels of functioning.	Roll *et al.*[38]
	Barthel Index (BI)[69]	Measure extent of functional independence in ADL & need for assistance in care	10 activities: Feeding Bathing Grooming Dressing Bowel & bladder control Toileting Chair transfer Ambulation & stair climbing	Scores range from 0 to 100. Higher scores indicate higher functioning.	Hsieh *et al.*[27] Schoenrath *et al.*[42]
	Functional Status Questionnaire (FSQ)[70]	Assess functional status	9 items in 2 parts 2 parts: Basic activities of daily living (3 items) Intermediate activities of daily living (6 items) Categories of function: Physical Psychological Social/role	Scores for each item range from 0 to 4. Summary score includes scale score for each part along with single item scores. Higher scores indicate greater functional ability.	Chen *et al.*[21]
	Karnofsky Performance Scale Index (KPS)[71]	Assess symptom-related functional limitation	3 subscales: Activity Self-sufficiency Self-determination	Scores range from 0 (death) to 100 (perfect health).	Rückert *et al.*[39]
Social Support	Social Support Scale (SSS)[72]	Determine perception of effective social support received by participants	14 items 4 types of functional assistance: Emotional (4 items) Appraisal (3 items) Informational (4 items) Tangible (3 items)	Scores for each item range from 0-4. Higher scores indicate greater perception of effective social support.	Chen *et al.*[21]

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Table 4 (*Continued*)

Outcome/Dimension	Measure	Purpose	Components	Details & Scoring	Study that Included Measure
	Nottingham Health Profile – part II (NHP-II)[73]	Measure subjective health status related to social functioning	7 yes/no items Life areas affected: Work/occupation Housework Social life Home/family life Sexual function Interests & hobbies Vacations	In the Hsieh paper, participants asked about these functional areas before & after treatment with ECMO.	Hsieh *et al.*[27]

ADL, activities of daily living; ECMO, extracorporeal membrane oxygenation; HRQOL, health-related quality of life; MCID, minimal clinically important difference; MCS, mental component summary score; OSS, overall summary score; PCS, physical component summary score; PTSD, posttraumatic stress disorder; SD, standard deviation; QALY, quality-adjusted life year; QOL, quality of life; VAS, visual analogue scale.

Additional long-term outcomes, as evaluated by measures other than HRQOL-specific instruments

Additional long-term outcomes of ECMO survivors included mental health, cognitive, physical, functional, social, and return to home and work. Details of these additional long-term outcomes are presented in Supplement 3.

Mental health outcomes

Results from 12 studies revealed high rates of mental health symptoms, including anxiety, depression, and post-traumatic stress post-ECMO. Nine studies included data from the Hospital Anxiety and Depression Scale with subscale scores reported for anxiety and depression.[19,32,33,35,37,40,41,44,46] The proportion of patients reporting clinically significant symptoms of anxiety and depression ranged from 33% to 50% and 11% to 28%, respectively. Proportions with scores consistent with severe anxiety and depression ranged from 8% to 27% and 4% to 18%, respectively. Scores tended to improve over time,[35,41,44] but only one study reported a statistically significant change (a decrease in depression).[35] One study reported clinically important improvement in depressive symptoms between baseline and 6 months post-hospitalization, using the Geriatric Depression Scale.[29] Within a sample of long-term survivors (median duration from ECMO to follow-up: 9 years), 38% were "medically" treated for depression or anxiety after hospital discharge, and of these, half were still being treated at the time of follow-up.[46] Rates of anxiety and depression were similar or slightly lower in survivors of VV ECMO compared with those treated with CMV only.[32,37]

Nine studies reported data from the Impact of Events (IES) or Impact of Events-Revised (IES-R) instruments, with 5% to 41% of patients at high risk for developing posttraumatic stress disorder (PTSD).[19,24,32,33,35,36,40,41,44] Another study, using data from the Trauma Screening Questionnaire, found symptoms of post-traumatic stress in 14% of survivors.[46] Scores did not change significantly over time, although one study reported a peak in posttraumatic stress symptoms at the 6-month point of recovery.[44] In survivors of ARDS, IES scores were better in patients treated with ECMO vs. CMV in 1 study,[24] but similar in another.[32] Some survivors sought psychological support/counseling services during their recoveries.[19,44]

Cognitive outcomes

Long-term cognitive outcomes, captured in 3 studies[37,39,44] using 4 instruments, were predominantly normal. The vast majority of patients were found to have normal cognition as measured by the Mini-Mental State Examination, DemTect, and Test for the Early Detection of Dementia. In one study, global cognitive functioning remained consistent over time; at 12 months post-discharge, 9% of patients' scores indicated mild cognitive impairment.[44]

Physical outcomes

Numerous long-term physical complications were reported. The most common were problems at the site of ECMO cannula insertion, which was most often the groin (e.g., late wound healing, femoral artery aneurysm requiring surgical repair)[20,22] and nerve injury attributed to ECMO cannulation (e.g., numbness, paresthesia, foot drop).[22,23,26,33,44] Two survivors had amputations, the result of persistent ischemia during their ECMO illnesses (1 patient required amputation of all 4 extremities).[19,33] In 1 study, 30% of survivors required pulmonary medications[41]; in another, 18% took medications daily for pain.[23] At the time of long-term follow-up, few patients required home oxygen therapy.[23,24,26,31,32,41,46]

Average long-term pulmonary function was addressed in 8 studies and most often was normal or mildly impaired when evaluated by spirometry.[24,31,32,37,39,46,48] Evidence of mild interstitial fibrosis (e.g. reticular patterns, ground glass opacities, parenchymal distortion) was determined in 42%–81% of patients by computed

tomography scans of the chest.[24,31,32,46,48] Total mean extent of pathological parenchyma ranged between 7 and 10%.[31,46] While mean exercise testing performance was in the lower normal range in one study,[31] in other studies approximately 75% of survivors had normal 6-minute walk test (6MWD) results[38,46,48] and distances walked significantly improved over time.[38] Findings from spirometry tests, computed tomography scans of the chest, exercise testing, and 6MWD were comparable between ECMO and non-ECMO groups.[24,32,37,48]

Functional outcomes

Long-term functional outcomes were captured in 6 studies using 5 instruments. Overall, most patients were able to perform daily activities independently.[27,35,42] When assistance was required, it was most often to aid with stair climbing and dressing.[27,42] Physical activity increased significantly from baseline to 12 months post-hospital discharge.[21] However, important functional limitations were also reported in up to one-quarter of survivors, particularly in domestic chores, leisure/work, medication use, outdoor activities, and transportation.[27,38,41] These scores did not change over time.[27,41] Patients' capacity to drive improved over time, but 25% of survivors in one study were unable to drive 12 months after hospital discharge.[44] Severe functional limitations were observed in 3% of participants in another study.[27]

Social outcomes

Survivors frequently reported that participation in several aspects of life was more difficult after their ECMO experience. The most common life areas affected reported in one study were occupation (29% pre- and 44% post-ECMO), sexual function (25% pre- and 41% post-ECMO), housework (18% pre- and 31% post-ECMO) and hobbies (31% post-ECMO).[27] Further, greater impact of illness on life was associated with worse mental and physical aspects of HRQOL.[27] Survivors relied heavily on informal caregivers, but in another study, up to 13% of patients reported not having enough social or physical support.[44] Greater levels of perceived social support were associated with higher levels of education and being married.[21]

Return to home and work

In two studies, 57–92% of patients returned home and the remainder were transferred either to rehabilitation facilities or other hospitals.[38,48] Another study found that all patients had returned home at the time of follow-up (median 1.9 years).[28] Multiple studies evaluated work status at follow-up, finding that the majority of patients who were employed before their illnesses returned to the workforce.[19,20,23,24,26,27,31–34,38,41,44,46,48] Twenty-six to 85% resumed their previous work.[26,31,34,38,41] Most survivors returned to work between 4 and 12 months following hospital discharge.[32,44,46,48]

Discussion

This integrative review is the first to our knowledge to synthesize research results on long-term HRQOL and additional outcomes of adults treated with ECMO for both pulmonary and cardiac indications. Long-term HRQOL was worse for ECMO survivors when compared to matched reference populations but tended to be better than survivors of other acute illnesses. Mental health outcomes were often better than physical ones, although survivors frequently experienced deficits in both dimensions. Among people treated with and without ECMO from within the same sample, those treated with ECMO tended to have slightly better HRQOL, comparable pulmonary function, and similar incidence of mental health problems.[24,30,32,37,45,47,48] Survivors treated with VV ECMO tended to have slightly better HRQOL than those who had VA ECMO. Regardless of the configuration of ECMO or time periods measured, improvements in HRQOL can be seen from the relative short-term (6 months) to more than 3 years post-ECMO treatment, particularly in domains involving physical function. A majority of survivors returned to work by the time of long-term follow-up.

One-third to one-half of survivors experienced anxiety and/or depression, and a substantial proportion of those survivors reported severe or extreme symptoms. These findings are consistent with other research that suggested that as many as half of adult survivors of ECMO developed psychiatric problems, including anxiety, depression, and PTSD.[74,75] ECMO patients are routinely and widely exposed to almost all known PTSD risk factors specific to the ICU, including prolonged mechanical ventilation and exposure to certain medications, particularly opioids, benzodiazepines, and catecholamine drugs.[76] Further, our findings are consistent with recent research on survivors of various types of critical illness who experience new or worsening physical, cognitive, and mental health impairments following critical illness that persist into long-term recovery. This phenomenon, known as post-intensive care syndrome, has recently gained much attention in the field of critical care.[77,78]

SF-36/SF-12 physical function component scores tended to be worse than mental health component scores among patients with all ECMO configurations. Consistently low (poor) scores in domains of vitality, role-physical, and general health, suggest that survivors often experienced worse levels of energy and fatigue, higher rates of role limitations due to physical health problems, and diminished perceived states of health. Patients recovering from illnesses requiring ECMO commonly faced profound physical deconditioning and high rates of morbidity,[79] including problems at the site of cannula insertion, neurovascular injury, and mild pulmonary dysfunction.[19,20,22–24,26,31–33,37–39,44,46,48,80] Further, a substantial proportion of patients treated with ECMO for cardiac indications later are implanted with LVADs. For those survivors, generic measures of HRQOL may not fully capture the impact that LVAD-specific factors (e.g., driveline management and carrying equipment) might have had on long-term outcomes (e.g., challenges with bathing, driving, and sexual activities).[45,81,82]

Worse self-reported HRQOL by survivors of critical illness was associated with inability to return to original place of residence.[83] We found that about half of patients were hospitalized or required out-of-home rehabilitation services for periods longer than 30 days. Additionally, participation in social activities and returning to work are important elements in perceived quality of life.[27,83] Survivors may avoid social activities, preferring instead to focus on improving their health by prioritizing wound care, limb rehabilitation, and nutrition.[84] Work is frequently associated with elements of social integration, including development and maintenance of interpersonal relationships and a sense of accomplishment. Survivors who were employed before treatment with ECMO typically took 3 to 4 months or longer to return to work, but many were not able to continue their original work. Data on patients' ability to drive following treatment with ECMO is limited but suggests that inability to drive may play a role in not resuming previous work and social activities.[27,44]

We also found a trend of slightly higher HRQOL scores for patients treated with VV ECMO compared with VA ECMO. This is especially interesting because the average duration of follow-up for survivors of VV ECMO was shorter than VA ECMO, allowing less time for healing between treatment and study enrollment. A number of factors may contribute to this finding. First, in the studies reviewed, patients treated with VA ECMO tended to be older. Second, differences in cannulation strategies have important implications in patient management. The most common vascular access for VA ECMO is via the femoral vessels. VV ECMO cannulas may also be placed via the femoral vein but are frequently inserted instead into the internal jugular vein.[85] Historically, ambulation of patients with femoral vessel cannulation was considered to be especially risky, and concern for cannula dislodgement precluded patients from walking.[86] Further, peripheral femoral cannulation in VA ECMO involves delivering

oxygenated blood to the aorta in retrograde fashion. In certain clinical scenarios, this retrograde flow can result in upper body hypoxemia (e.g., watershed phenomenon, Harlequin syndrome),[87] and it is unknown whether these events influence HRQOL outcomes, including long-term cognitive ability.[47,85]

Implications for practice

Our findings suggest that persistent difficulties resulting in diminished HRQOL are common, but in our clinical experience, routine screening for these problems is lacking. Assessment of HRQOL may provide important insights into the perceived health and well-being of ECMO survivors. It is important to improve screening for anxiety, depression, and PTSD, and to refer survivors for mental health counseling as needed. Long-term care of these patients should also include strategies to maximize physical rehabilitation and provide adequate management of pain and discomfort.[38] Provision of long-term, comprehensive healthcare for these survivors may be accomplished as part of an interdisciplinary (e.g., nurses, physicians, social workers, clinical pharmacists, chaplains) post-ICU clinic.[88]

Implications for research

Further investigations of long-term HRQOL are necessary to inform clinical practice. Data are particularly lacking in patients who are older, women, or treated with ECPR. Studies with larger sample sizes are needed for more meaningful statistical analyses. Longitudinal studies, especially those including baseline HRQOL data, can provide insights into how pre- and post-ECMO illness HRQOL differ. Little is known about how long-term HRQOL compares among patients bridged with ECMO to recovery, LVAD, or transplant. Future analyses could illuminate our understanding of long-term HRQOL by controlling for severity of illness while comparing outcomes of survivors of ECMO with patients with similar diagnoses. Further research is needed to identify factors associated with better HRQOL. Although several survival prediction models for ECMO in adults have recently been proposed,[35,41,89–96] anticipating the long-term prognosis of ECMO patients is difficult. Rückert and colleagues[39] identified several factors associated with both hospital mortality and HRQOL; predictors of adverse outcomes included worse severity of illness (as measured using the Acute Physiology and Chronic Health Evaluation II score), ventilation time before ECMO implantation, higher lactate level at the time of ECMO implantation, and female gender. Recently, core outcome measures were proposed for the first time to evaluate outcomes in ECMO patients and include: adverse events (i.e., intracranial hemorrhage and major bleeding), mortality, and life impact (i.e., HRQOL, neurologic recovery, disability, activities of daily living, and return to work).[97] We strongly endorse standardization of outcome reporting for this population, as it is useful to facilitate sharing of data across studies and increase generalizability of findings.

Limitations

This review has several limitations. First, despite careful literature review strategies, it is possible that we may have missed relevant studies. Second, potentially valuable research may not have been included because we limited our review to studies published in English, although included studies took place in 13 different countries. Third, currently available studies offer data that are, while important and interesting, highly heterogeneous (e.g., variability in use of outcome measures, timing of follow-up evaluation, overall quality). Fourth, most studies had small samples, often not powered to address differences. Fifth, it is not surprising that a single center may need several years to accumulate an adequate sample size, given the relatively small number of adult patients treated per year with ECMO. However, as clinical strategies and technology are rapidly advancing, it is possible that modifications in patient management over that time could affect long-term HRQOL. Sixth, most of these studies lacked baseline HRQOL data. Although improvements in HRQOL may be observed during the recovery period, it remains unknown how patients' post-ECMO HRQOL data compare with their pre-ECMO HRQOL. Seventh, several researchers reported outcomes that accounted for varying clinical courses, but it remains a challenge to tease out the effects of ECMO from the consequences of critical illness, or the experiences of those treated with ECMO when those same patients were eventually bridged to LVAD or transplant. Lastly, although the response rates in these included studies was moderate to high, there is potential for survival bias that could skew the true magnitude of long-term impairments in mental and physical health.[98,99]

Conclusion

Rather than considering survival rates in isolation, clinicians and researchers have begun to emphasize the importance of long-term HRQOL as an indicator of the usefulness of ECMO for adult patients. Survivors frequently experienced physical complications, anxiety, depression, and post-traumatic stress symptoms, although improvements in HRQOL were observed over time. Early identification and management of physical and mental health problems may improve the lives of survivors of this complex rescue treatment.

Declaration of Competing Interest

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Supplementary materials

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