Heart, Lung and Circulation (2019) **28,** 1090–1098
1443-9506/04/$36.00
https://doi.org/10.1016/j.hlc.2018.06.1044

ORIGINAL ARTICLE

Long-Term Survival and Health-Related Quality of Life in Adults After Extra Corporeal Membrane Oxygenation

Mark A. Roll, BPhty [a*], Suzanne Kuys, PhD [a,b], James R. Walsh, PhD [a,c], Oystein Tronstad, BPhty [a,d,e], Marc D. Ziegenfuss, MBChB [d], Dan V. Mullany, MBBS [d,e]

[a]Physiotherapy Department, The Prince Charles Hospital, Brisbane, Qld, Australia
[b]School of Physiotherapy, Australian Catholic University, Brisbane, Qld, Australia
[c]School of Allied Health Sciences, Griffith University, Gold Coast, Qld, Australia
[d]Intensive Care Unit, The Prince Charles Hospital, Brisbane, Qld, Australia
[e]Critical Care Research Group, University of Queensland, Brisbane, Qld, Australia

Received 10 October 2017; received in revised form 22 May 2018; accepted 21 June 2018; online published-ahead-of-print 5 July 2018

Background The study aims to determine long-term survival, health-related quality of life (HRQoL) and functional and physical outcomes of adult extra corporeal membrane oxygenation (ECMO) patients as there are limited and conflicting data in this area.

Methods All patients receiving ECMO from April 2009 until June 2014 at The Prince Charles Hospital, Brisbane had Kaplan Meier survival calculated. Quality of life (QoL) was assessed using the Short Form Health Survey (SF-36v2), EQ5D-5L, The Frenchay Activities Index (FAI) and a return to work survey. From December 2011, these measures and 6-minute walk distance (6MWD) were assessed at hospital discharge and 12 months post-discharge.

Results Seventy-seven (77) patients (45 veno-arterial and 32 veno-venous) received ECMO of whom 47/77 (61%) survived to hospital discharge. There were no deaths recorded in those discharged alive from the intensive care unit at median follow-up time 1,011 days (range 227–2,014 days). Mean SF-36 scores (n = 33) and EQ5D were assessed at a median of 606 days after hospital discharge. SF-36 scores were significantly ($p < 0.05$) worse than age-matched norms in all domains except vitality, bodily pain and mental health. Thirteen (13) (39%) participants had persistent problems with mobility and usual activity as measured by EQ5D. At 12 months post-ECMO, 6MWD was 531(IQR:397.3–626.8)m; 72% (IQR:53.2–77.6%) predicted but had improved by 223 m ($p = 0.002$) when compared to baseline. Nineteen (19) of 20 participants who had been employed pre-ECMO had returned to work.

Conclusions All ECMO patients discharged from hospital were alive at follow-up. Despite improvements in physical measures and HRQoL, long-term functional deficits persist when compared to that of aged- and sex-matched norms.

Keywords ECMO • Quality of Life • Outcomes • Survival

*Corresponding author at: Physiotherapy Department, The Prince Charles Hospital, Rode Road, Chermside, 4032 Queensland, Australia. Tel.: +61731394443; fax: +61731396147., Email: mark.roll@health.qld.gov.au

Introduction

Extra corporeal membrane oxygenation (ECMO) is a salvage therapy used in highly selected patients with severe respiratory and/or cardiac failure who have not responded to maximal conventional medical therapy [1]. Veno-arterial (VA) ECMO is used predominantly for severe cardiac dysfunction [1] and veno-venous (VV) ECMO is used for isolated severe respiratory failure [2]. Indications are expanding [3] and use has increased markedly since the Conventional ventilation or ECMO for severe adult respiratory failure (CESAR) trial [4] particularly in patients at high risk of dying [5–7]. There is ongoing debate about whether any form of ECMO is associated with improved outcomes despite its use as a rescue therapy [8].

Between 1989 and July 2016 the Extracorporeal Life Support (ECLS) registry had reported over 22,500 adult ECMO cases worldwide with an overall survival rate of 58% [9]. Adult ECMO support has represented the largest growth over this period [9]. During the 2012–13 financial year, based on Australian Institute of Health and Welfare data, ECMO was used in 193 patients with an average hospital length of stay of 28.3 days for the acute care component [10].

Survivors of critical illness often have impaired long-term functional outcomes which may be broadly categorised as physical (e.g. weakness), cognitive (e.g. memory) and/or psychosocial (e.g. anxiety, depression) [11]. These deficits continue long after the acute illness has resolved [12]. Long-term functional data in adults who receive ECMO is limited and conflicting [13–18]. Persistent physical and social problems have been reported in patients supported by ECMO for both acute respiratory distress syndrome (ARDS) and refractory cardiogenic shock [15,17].

Given patient demographics, increasing use and high costs of ECMO worldwide, it is important to know the extent and severity of any ongoing physical, functional and cognitive impairment [4,15,17,19]. This information may assist in determining an evidence-based approach to patient selection for ECMO, better informed consent and provide information for potential post ECMO rehabilitation strategies. Therefore, the primary aims of this study are to determine survival and health related quality of life (HRQoL) of adult ECMO survivors. Secondary aims include determination of functional outcomes, physical function and return to work status. We hypothesised that there are reduced functional outcomes and HRQoL in ECMO survivors compared to healthy aged and gender-matched controls.

Methods

A single-centre observational study was conducted at the Prince Charles Hospital, Brisbane, Australia. The ECMO service model of care and initial short-term outcomes have previously been published [20]. As similar equipment is used as a temporary ventricular assist device (VAD), ECMO was defined by the presence of an oxygenator in the circuit. Patients receiving ECMO from the commencement of the service on 1 April 2009 until 30 June 2014 were identified. There were two components to this study: actuarial survival for all patients receiving ECMO; and detailed assessment of functional status in survivors. Human Research Ethics Committee (HREC) approval was obtained along with written informed patient consent. For patients less than 18 years old at the time of recruitment, parental/guardian consent was obtained.

Clinical Data

Clinical and demographic data were retrieved from the ECMO and intensive care unit (ICU) databases. Data obtained included mechanical ventilation time, type of ECMO, time on ECMO, ICU and hospital length of stay (LOS), primary diagnosis requiring ECMO, Acute Physiology And Chronic Health Evaluation (APACHE) [21] II and III at ICU admission, and sequential organ failure assessment (SOFA) [22] scores at day 1, 3 and 5 of ICU admission.

Unless otherwise specified ECMO type was defined by the first configuration used as several patients transitioned between configurations. For example, three patients required initial VA ECMO for septic shock with profound myocardial depression due to necrotising pneumonia then transitioned to VV ECMO for ARDS. One patient received preoperative bridge to lung transplantation on VV ECMO, immediate postoperative VA ECMO then VV ECMO with cardiac recovery and ongoing graft dysfunction. Two (2) patients had veno (access)-pulmonary artery (return)-circuit and were included in the VA group.

Long-Term Survival Determination

All patients where ECMO was attempted were included in the survival analysis. One (1) patient died in the operating room without ICU admission and was included as were two patients who died very shortly after the commencement of ECMO-CPR. Survival was calculated from the time of ICU discharge from this hospital to the last date of contact/follow-up. One (1) patient required ECMO as a bridge to long-term left VAD and, after discharge home required subsequent post-cardiac transplant ECMO support for primary graft dysfunction with the first admission only included in the survival and functional analysis. Survival status was determined by medical record and/or from the Hospital-Based Clinical information system (HBCIS) which is linked to the Queensland Births, Deaths and Marriages registry. Additional confirmation of survival status was determined by phone call at time of follow-up. The last interrogation of HBCIS occurred on 30 June 2015 but date of censoring was 1 January 2015 to allow for delays in updating records. In most patients, last determination of survival status occurred well after assessment of QoL measures.

Quality of Life and Functional Status

Patients discharged alive from ICU were eligible for assessment of HRQoL. Patients from January 2012 to June 2014 were consented at ICU discharge and followed prospectively. Patients discharged alive from ICU before December 2011 were assessed once retrospectively at a variable follow-

up time (12–60 months post ECMO) (Figure 1). Patients were contacted via a letter and with a follow-up phone call. Participants who provided written informed consent were sent detailed questionnaires to complete. Return postage-paid envelopes were provided to participants. No other financial incentives were provided.

Health-related quality of life was determined using similar methods previously described [4,15]. Measures including the Short Form 36 version 2 (SF-36v2) the EQ-5D-5L and the Frenchay Activities Index (FAI) were used. The SF-36v2 has been validated for use in critically ill patients and is a widely used measure of health status [23]. The 36 items are divided into eight independent dimensions and the sum of the items from each dimension combine to form a total score of 0–100. Lower scores indicate greater disability. Two summary scores, the Physical Component Score (PCS) and Mental Component Score (MCS), were calculated [24]. A difference of five points for SF-36v2 domain scores has been considered to be clinically important [15]. Australian SF-36v2 age- and sex-matched norms [25] were compared with our patients' mean raw SF-36v2 scores.

The EQ-5D is a standardised, non-disease specific instrument for measuring HRQoL and validated in a critical care population [26,27]. It consists of a questionnaire and visual analogue scale (EQ-VAS). The five domains assessed are mobility, self-care, usual activities, pain/discomfort, and

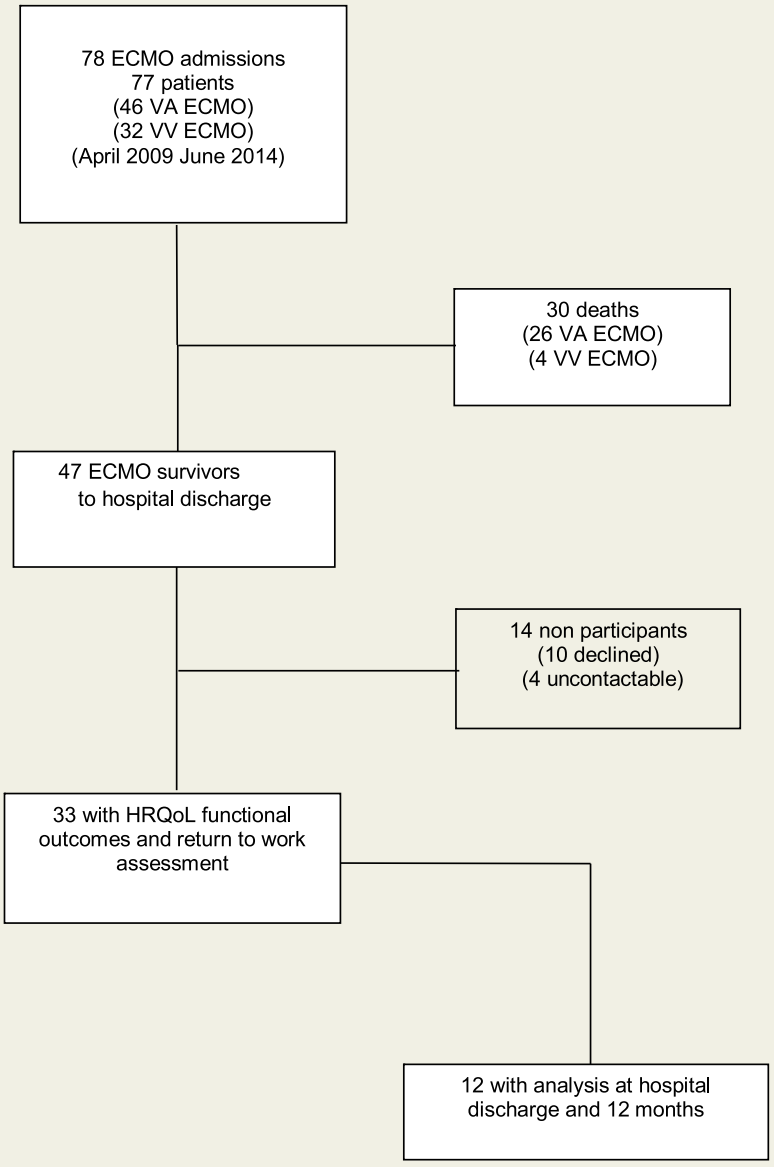

Figure 1 Derivation of the study sample for assessment of long-term survival and health related quality of life for patients in the first 5 years of an adult ECMO service.
Abbreviations: ECMO, adult extra corporeal membrane oxygenation; HRQoL, health-related quality of life; VA, veno-arterial; VV, veno-venous.

anxiety/depression. EQ-5D domains were dichotomised into ''No problems'' Vs ''Any problems'' for this study. The EQ-VAS was used to self-rate heath state on a scale of 0–100 where 0 is worst imaginable health.

The FAI is a tool used to capture complex instrumental activities of daily living including household chores, work status, hobbies and social outings. The FAI has been shown to have good construct validity [28]. A modified scoring system was used in our study [29]. Physical function was measured using 6MWT in the n = 12 subgroup and compared to age- and sex-matched norms [30]. Assessment occurred once at hospital discharge and again at 12 months. The 6MWT is a useful tool for measuring functional capacity in populations with moderately severe impairments [31].

A return to work survey consisting of both closed response and open-ended questions was developed by the study's investigators and from previous literature. Prior to study commencement, the face and content validity of the questionnaire was tested. Patients were asked to indicate possible factors that affected return to work status and feedback was sought regarding the readability of the survey. Assessment was conducted once at a variable follow up time of 12 months to 6 years.

Statistical Analysis

Continuous variables were expressed as mean and standard deviation (SD) and non-normally distributed data summarised as median and interquartile range (IQR) or range. The mean difference between participants and Australian age and sex-matched population norms for SF-36 domains was calculated using a t-test assuming unequal variances. In the subset with functional, HRQoL and 6MWT data at hospital discharge and one year, the median difference was calculated using a Wilcoxon signed-rank test. Actuarial survival was calculated using Kaplan-Meier analysis using (Stata 13.0, Statacorp LLC, College Station, TX, USA). SPSS v22 (Released 2013. IBM Corp. SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA) was used for analysis and statistical significance was $p < 0.05$.

Results

From April 2009 to June 2014, 77 patients had 78 hospital admissions requiring ECMO. Demographic, clinical and severity of illness data are shown in Table 1. Forty-eight (48) admissions (62%) survived to hospital discharge of whom 20 (42%) had received VA ECMO and 28 (58%) had received VV ECMO. Of the 47 the surviving patients, 33 (77%) were recruited for detailed assessment of HRQoL and 12 had their first assessment at hospital discharge (Figure 1).

Actuarial 1-year and 3-year survival for the sample (n = 77) were 0.61 (95% confidence interval 0.48–0.71), 0.41 after VA ECMO (95% confidence interval 0.28–0.54) and 0.88 after VV ECMO (95% confidence interval 0.7–0.95) as there were no deaths in those discharged alive form the ICU. The median time from ICU discharge to last determination of survival status in survivors (n = 47) was 1011 days (range 227–2014 days).

Health-related quality of life measures at long-term follow-up are summarised in Tables 2 and 3. The overall mean PCS and MCS were 46.4 (SD 9.9, range 27.1–67.1) and 48.7 (SD 13.3, range 18.4–64.5) respectively. Extra corporeal membrane oxygenation survivors were statistically significantly worse than age matched norms in all SF-36v2 domains except vitality and bodily pain with mental health difference of borderline statistical significance ($p = 0.058$). Thirteen (13) (39%) respondents reported problems with mobility and usual activity at follow-up reflected in the EQ5D. Seventeen (17) (51%) reported pain and 15 (45%) anxiety. Functional deficits were noted in the Frenchay activities index with a mean score of 29.2 (SD 9.0).

A subgroup of 12 participants undertook a detailed HRQoL and functional assessment at hospital discharge and 12 months (Table 4). Median 6MWD at hospital discharge and 12 months were 308 m and 531 m respectively. This includes a significant improvement in median walk test distance of 223 m ($p = 0.002$). Statistically significant improvements in mobility, ($p = 0.033$), self-care ($p = 0.034$) and usual activity ($p = 0.003$) were noted in the EQ-5D at 12 months.

Assessment of return to work is shown in Table 5. Twenty (20) of the 33 participants (61%) reported employment pre-ECMO decreasing to 19 (58% of sample) at post ECMO follow-up and of those working, 17 (89%) were working a mean of 30.1 (13.7) hours in the same job. Thirteen (13) (39%) reported being on unemployment or disability benefits. Seventeen (17) (52%) were participating in some sort of social or recreational activity at the time of analysis.

Discussion

We have provided detailed functional outcomes data on a heterogeneous sample of adult ECMO patients together with measures of change over time. As with previous ECMO studies long-term (>12 months) QoL and functional limitations persist. Improvement in function was noted from a low baseline at hospital discharge to 12 months and was consistent in most domains except mental health. In this study, there were no recorded deaths at follow-up in patients who were discharged alive from ICU. Unlike the studies by Hodgson et al. and Peek et al., VA ECMO patients were included in this study.

Extra corporeal membrane oxygenation use has increased significantly and costs of care are high. In the United States, between 2006 and 2011, ECMO cases increased from 11.4 to 60.9 cases per million (433%) [7]. A non-significant trend toward improved survival rates ($p = 0.14$) was reported [7]. Maxwell et al. reported on 8753 adult admissions involving ECMO in the US from 1998 to 2009 [6]. The overall hospital length of stay was 18.3 days, compared to 34.5 in our study, slightly higher than the Australian national average of 28.3 days in the 2012–13 period [10]. Total hospital

Table 1 **Demographic, clinical and severity of illness data for the sample.**

Characteristic	Died n = 30	Non-Participants n = 14	All Participants n = 33	Total n = 77
Age years (IQR)	48.5 (34–60.3)	38.5 (32.5–51.3)	42 (26.5–57)	43 (30–57.5)
Males (%)	22 (73.3)	5 (35.7)	19 (57.6)	46 (59.7)
Days from hospital discharge to survey (IQR)	–	–	606 (379–1550)	–
Days in ICU (IQR)	6 (3.2–17.5)	23.5 (19.4–35.6)	29.8 (17.0–45.0)	20.6 (7.3–34.5)
Days in Hospital (IQR)	8.2 (3.6–17.1)	33.6 (26.1–42.8)	48.5 (30.4–55.4)	30.6 (9.4–49.3)
Ventilation Days (IQR)	5.3 (3.2–14.7)	21.9 (12.5–28.4)	24.7 (14.3–41.8)	16.8 (6.1–32.5)
Diagnosis				
ARDS/pneumonia (%)	4 (13.3)	7 (50.0)	10 (30.3)	21 (27.3)
Cardiothoracic surgery (%)	5 (16.7)	1 (7.1)	5 (15.2)	11 (14.3)
Lung +/− other transplant (%)	2 (6.7)	1 (7.1)	5 (15.2)	8 (10.4)
Septic shock (%)	2 (6.7)	1 (7.1)	5 (15.2)	8 (10.4)
Cardiogenic shock (%)	12	3 (21.4)	6 (18.2)	21 (27.3)
Cardiac arrest (%)	5 (16.7)	1 (7.1)	2 (6.1)	8 (10.4)
Type of ECMO				
VA (%)	26 (86.7)	5 (35.7)	14 (42.4)	45 (58.4)
VV (%)	4 (13.3)	9 (64.3)	19 (57.6)	32 (41.6)
Days on ECMO (IQR)	5 (2.2–9.6)	10.6 (7.6–16.1)	8.8 (6.4–21.3)	7 (4.8–15.8)
Median APACHE II score (IQR)	26 (18.5–31)	19.5 (14.8–24)	20 (16–26.5)	22 (17.3–28)
Median APACHE III score (IQR)	92 (61.5–116.5)	62 (56.8–88)	76 (57–92)	79 (58–106.8)
SOFA score day 1 (IQR)	12 (9–14)	8 (7–10.5)	10 (6.5–12)	10 (8–13)
SOFA score day 3 (IQR)	12 (10–16)	8 (4.8–12.3)	9 (7–11)	10 (7.3–13)
SOFA score day 5 (IQR)	11 (8.5–14.3)[a]	8.5 (5.5–14)	8 (6–10)	9 (6.3–11.8)[b]
Discharge destination				
Home	0	9 (64.3)	19 (57.6)	28 (36.4)
Hospital transfer	0	2 (14.3)	4 (12.1)	6 (7.8)
Rehabilitation	0	3 (21.4)	10 (30.3)	13 (16.9)
Died	30 (100)	0	0	30 (39)

[a]n = 14 [b]n = 60. Categorical data expressed as the number of participants n, (%). Continuous data expressed as median (IQR).
Abbreviations: ICU, intensive care unit; ARDS, adult respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; APACHE, Acute Physiological And Chronic Health Evaluation; SOFA, sequential organ failure assessment; IQR, interquartile range; VA, veno-arterial; VV, veno-venous.

Table 2 **Functional outcomes using SF36 compared to age and gender norms at long-term follow-up.**

SF-36 Domain (/100)	All participants (n = 33)	Age adjusted normal values	Mean difference (95% CI)	P
Physical function	65.0 ± 28.5	87.4 ± 6.8	−22.4 (−33.2 to −11.6)	<0.001
Role physical	65.5 ± 30.4	84.0 ± 5.9	−18.5 (−29.4 to −7.6)	0.002
Bodily pain	74.2 ± 26.6	76.5 ± 4.8	−2.3 (−12.2 to 7.6)	0.637
General health	56.7 ± 24.4	70.5 ± 5.2	−13.8 (−22.7 to −4.9)	0.003
Vitality	57.6 ± 25.7	60.3 ± 3.1	−2.7 (−11.8 to 6.4)	0.544
Social functioning	72.7 ± 29.7	84.0 ± 2.9	−11.2 (−22.0 to −0.5)	0.041
Role emotional	77.8 ± 29.8	89.1 ± 1.8	−11.3 (−21.8 to −0.8)	0.036
Mental health	69.7 ± 26.3	78.7 ± 2.7	−9.0 (−18.3 to 0.33)	0.058

Continuous data expressed as mean ± SD.

Table 3 Functional outcomes at long-term follow-up 12 months and 6 years using EQ-5D-5L and Frenchay measures for all participants.

EQ-5D-5L	Mean Score ± SD for all participants	EQ-5D-5L Category	12–24 mnths (n = 17) n, (%)	24 mnths–6 yrs (n = 16) n, (%)	All participants (n = 33) n, (%)
Mobility	1.7 ± 1.0	Any Problems	6 (35.3)	7 (43.7)	13 (39.4)
		No Problems	11 (64.7)	9 (56.3)	20 (60.6)
Self-Care	1.2 ± 0.8	Any Problems	3 (17.6)	1 (6.2)	4 (12.1)
		No Problems	14 (82.4)	15 (93.8)	29 (87.9)
Usual Activity	1.6 ± 1.0	Any Problems	6 (35.3)	7 (43.7)	13 (39.4)
		No Problems	11 (64.7)	9 (56.3)	20 (60.6)
Pain/Discomfort	1.7 ± 0.9	Any Pain	9 (52.9)	8 (50.0)	17 (51.5)
		No Pain	8 (47.1)	8 (50.0)	16 (48.5)
Anxiety/Depression	1.7 ± 1.0	Any Anxiety	8 (47.1)	7 (43.7)	15 (45.5)
		No Anxiety	9 (52.9)	9 (56.3)	18 (54.5)
Mean ± SD EQ-5D Index	0.8 ± 0.2				
Mean ± SD EQ5D VAS/100			70.7 ± 21.6	71.6 ± 18.6	71.1 ± 19.9
Frenchay Activities Index		**12–24 months (n = 17) mean ± SD**		**24 months–6 years (n = 16) mean ± SD**	**All participants (n = 33) mean ± SD**
Domestic Chores (/15)		10.2 ± 5.1		10.3 ± 5.2	10.2 ± 5.1
Leisure/Work (/15)		10.6 ± 3.1		7.9 ± 3.4	9.3 ± 3.5
Outdoors/Other (/15)		10.4 ± 3.2		8.9 ± 3.8	9.7 ± 3.5
Total Score (/45)		31.2 ± 7.8		27.1 ± 10.0	29.2 ± 9.0

charges of $344,009 (2009 USD) were reported compared to $166,636 (2012 AUD) for Australian centres [6,10]. The Extracorporeal Life Support (ECLS) registry 2016 reports an overall 58% survival to hospital discharge after ECMO, a similar short-term survival rate to our study [9].

Muller et al. showed that 6-month survival was highly dependent on age and the degree of organ dysfunction as measured by the prEdictioN of Cardiogenic shock OUtcome foR AMI patients salvaGed by VA-ECMO (ENCOURAGE) score at the time of ECMO insertion for those with cardiogenic shock secondary to acute myocardial infarction [32]. In ECMO for severe adult ARDS, higher age, immunocompromised status, associated extra-pulmonary organ dysfunction, low respiratory compliance and non-influenza diagnosis seem to be the main determinants of poorer long-term survival [33]. A recent study of long-term survival of VA and VV ECMO patients treated for respiratory failure and sepsis reported a high risk of death, 15% within 90 days of hospital discharge increasing to 24% at long-term follow-up at 3 years [34]. The authors noted the requirement for more detailed QoL measures. Similarly a study by Burrell et al. determining long-term survival in VA ECMO patients reported high survival rates of 72% at 3 months, 65% at 12 months and 57% at 2 years [18]. In contrast, de Waha et al. reported 15.7% survival with good functional outcome at 18 months in those with refractory cardiogenic shock requiring ECLS [35]. Survival benefits linked to rehabilitation in ECMO patients have not been published and require further investigation. In contrast to other studies, survival to hospital discharge in our study seems a good indicator of long-term survival post ECMO [34]. Predictors of survival were not analysed in our study. Local selection practices and/or patient management may have contributed to reduced post hospital mortality in our group.

The CESAR trial reported increased survival without disability at 6 months for severe ARDS patients who were referred to an ECMO centre (63%) compared to that of conventional management (47%) (p = 0.03). The cost per quality-of-life years (QALY) of ECMO in 2005 was predicted to be $31,112 (2005 USD) suggesting that referral for ECMO may be more cost effective than conventional management [4]. With the high financial cost of ECMO it is important to not only recognise the potential to survive but the effect ECMO may have on long term QoL and function.

Hodgson et al. studied HRQoL for a median of 8 months post VV ECMO in young patients with predominantly H1N1 related ARDS. They found severe effects on physical and social function, mental health and vitality with only 53% returning to work and 26% returning to previous work levels [15]. Health-related quality of life in ECMO survivors was

Table 4 **Subgroup analysis in those with hospital discharge data and 12 months assessment post ECMO (n = 12).**

Outcomes	Hospital Discharge Scores		12 Months Post Hospital Discharge Score			P
SF-36 (/100)						
Physical function	22.5 (11.3–47.5)		75.0 (50.0–91.3)			0.005
Role physical	15.6 (6.3–31.3)		65.6 (39.1–84.4)			0.007
Bodily pain	67.0 (33.5–87.5)		92.0 (60.5–100.0)			0.092
General health	60.0 (50.0–70.0)		67.5 (45.0–73.8)			0.199
Vitality	50.0 (32.8–62.5)		59.4 (39.1–75.0)			0.165
Social functioning	50.0 (28.1–50.0)		87.5 (28.1–100.0)			0.066
Role emotional	87.5 (29.2–91.7)		95.8 (58.3–100.0)			0.011
Mental health	77.5 (70.0–88.8)		80.0 (47.5–90.0)			0.412
PCS	34.1 (24.8–38.4)		47.7 (40.3–55.5)			0.008
MCS	52.2 (44.3–55.2)		54.9 (46.5–58.7)			0.69
EQ-5D-5L		**N, (%)**	**Median (IQR)**	**N, (%)**	**Median (IQR)**	**P**
Mobility	Any Problems	11 (91.7)	2.0 (2.0–2.0)	3 (25.0)	1.0 (1.0–1.8)	0.33
	No Problems	1 (8.3)		9 (75.0)		
Self-Care	Any Problems	7 (58.3)	2.0 (1.0–2.0)	2 (16.7)	1.0 (1.0–1.0)	0.034
	No Problems	5 (41.7)		10 (83.3)		
Usual Activity	Any Problems	12 (100)	3.0 (2.0–3.0)	3 (25.0)	1.0 (1.0–1.8)	0.003
	No Problems	0 (0)		9 (75.0)		
Pain/Discomfort	Any Pain	8 (66.7)	2.0 (1.0–2.8)	5 (41.7)	1.0 (1.0–2.0)	0.096
	No Pain	4 (33.3)		7 (58.3)		
Anxiety/Depression	Any Anxiety	5 (41.7)	1.0 (1.0–2.0)	5 (41.7)	1.0 (1.0–2.0)	0.546
	No Anxiety	7 (58.3)		7 (58.3)		
Median (IQR) EQ-5D VAS		65.0 (32.5–73.8)		67.5 (50.0–80.0)		0.327
6MWT						
Median 6MWT (m)		308.0 (273.0–435.0)		531.0 (397.3–626.8)		0.002
% Predicted 6MWD		42.9 (32.1–52.5)		72.0 (53.2–77.6)		0.002

Abbreviations: 6MWT, six-minute walk test; (m), metres.
Categorical data expressed as the number of participants n, (%). Continuous data expressed as median (interquartile range, IQR).

Table 5 **Assessment of Return to Work.**

Outcomes	All Participants n = 33	12–24 months n = 17	24+ months post n = 16
Employment pre-ECMO	20 (60.6)	10 (58.8)	10 (62.5)
Same Work as those employed pre-ECMO	17 (85.0)	9 (52.9)	8 (50)
Physically fit enough to work	21 (63.6)	12 (70.6)	9 (56.3)
Mentally fit enough to work	26 (78.8)	15 (88.2)	11 (68.8)
Currently employed of total participants	19 (57.6)	9 (52.9)	10 (62.5)
Current hrs/week	30.1 ± 13.7	32.6 ± 14.0	27.3 ± 13.8
Unemployment benefits	13 (39.4)	7 (41.2)	6 (37.5)
Involved social/recreational activities	17 (51.5)	8 (47.1)	9 (56.3)

Categorical data expressed as the number of participants n, (%). Continuous data expressed as mean, ±SD.
Abbreviation: ECMO, extra corporeal membrane oxygenation.

significantly less than sex and age-matched controls and further research was recommended to determine the physical capacity and rehabilitation needs of survivors [15]. In our study, we found similar results including significant impairments in physical and social function, emotion and general health compared to sex and age-matched norms. Ninety-five per cent (95%) of participants previously employed in our study had returned to work at follow-up and 85% had returned to the same level of work. Potential differences in return to work status compared to the Hodgson study may be explained by longer median time to follow-up 605 vs 261 days and a larger cohort of our survivors attending post ECMO rehabilitation 30% vs 6% [15].

Combes et al. investigated outcomes and long-term QoL at median follow-up of 11 months in patients with cardiogenic shock supported by ECMO. Consistent with our study, satisfactory mental health and vitality were reported amongst long-term ECMO survivors. Persistent physical and social problems were also similar in both studies even at longer median follow-up time in our investigation [17]. Health-related quality of life assessment in our study identified problems with mobility, pain and usual activity consistent with the Hodgson study [15]. Anxiety/depression were also comparable in that both studies reported severe problems. Unlike other studies, we also assessed higher order activities of daily living to determine functional outcomes using the FAI. Long-term problems in the domains of domestic chores, leisure/work and outdoor activities were recorded (Table 3).

We were unable to measure societal costs associated with reduced HRQoL and function. There are currently unmeasured and potentially large economical and societal costs required to care for patients post ECMO. This may include further consumption on the health care system, loss of productivity and anxiety leading to a greater burden on patients and families. Introducing post ECMO follow-up and rehabilitation strategies tested in large multicentre research is necessary to pinpoint the factors that may be inhibiting their potential as contributors to society and allow them to return to a better and more productive QOL.

A subgroup of 12 participants was included in a comparison of functional outcomes at hospital discharge and 12 months. Six-minute-walk-test was used to measure physical function. Few studies have utilised this tool as a physical outcome measure in the adult ECMO population. Hayes et al. assessed physical function in ECMO patients post heart transplant. Six-minute-walk-test distance was measured at hospital discharge and 3 months with a significant improvement in walk test distance of 202 m [19]. Similarly, our study showed a clinically significant improvement ($p = 0.002$) of 223 m over 12 months although final distance was only 72% of aged and sex-matched norms [36]. A review of the literature has reported 14–30 m as the minimally clinical important distance (MCID) for 6MWT in adults with pathology [36]. In our study, identifiable statistically significant improvements in the domains of physical function, role physical and role emotional measured by the SF-36v2 were noted over 12 months. Clinical improvement (>5 point difference) [15] was noted in all domains except mental health. This was also supported by improvements in mobility, self-care and usual activity measured by EQ-5D over the same period. Four (4) of the 12 (33%) of the ECMO subgroup attended rehabilitation post hospital discharge which may have contributed to this trend of improved physical function over 12 months.

Anxiety is the most common mental health condition and even minor symptoms may impact every-day function [37]. High levels of anxiety (41%) were reported in the EQ5D assessment at 12 months along with a non-significant ($p = 0.41$) worsening of the mental health component of the SF-36v2 over the same period. Persistent anxiety may impact on social skill and work performance [37]. A need to return to work creates stress leading to further anxiety and the potential to impact on productivity and even loss of employment [37]. Despite a large number of patients in our study working at time of follow-up 19/33 (57%) it is imperative that appropriate mental health follow-up is offered to all ECMO patients to assess, diagnose and manage any underlying anxiety and mental health related disorders. This may, in turn, lead to greater improvement in function over time. Further investigation is required to determine the best management strategies to address this.

This study is not without limitations. Firstly, this is a single centre study with a small sample size and we were unable to include all patients in HRQoL assessment. Small sample size precluded any comparative functional analysis of VA vs VV ECMO. Compared to other studies, there was a longer follow-up time after hospital admission in those assessed. Despite the small sample size, we were able to demonstrate statistically significant differences with both age and sex-matched normal HRQoL measures at long-term follow-up. Our clinical implications would need to be tested in larger multicentre trials and include an analysis of post-ICU follow-up and rehabilitation strategies. This study was unable to determine whether reduced functional outcomes were attributable to an ECMO effect or critical illness. Other limitations include a lack of detailed investigation into cognitive function and factors contributing to unusual long-term survival rates post hospital discharge. All of which require further analysis.

Conclusion

Extra corporeal membrane oxygenation patients are often young people who have many years' potential as contributors to society. If a treatment exists which not only leads to their survival, but allows them to survive with normal or near-normal functional status they are able to fulfil this potential. The ability to establish survival and functional outcomes for post ECMO patients has the potential to guide future practice and multidisciplinary care for this cohort of patients. Further analysis of structured early rehabilitation during and post ECMO may help to shape a more evidence-based approach to supporting ECMO patients and improve long-term function and QoL. This should include

randomised controlled trials involving greater numbers and across multiple sites. Once this is established, multidisciplinary intervention programs may be developed to enhance their return to a positive, functional and productive life.

Declarations of Interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.hlc.2018.06.1044.

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