Journal of Critical Care 73 (2023) 154215

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Health-related quality of life, one-year costs and economic evaluation in extracorporeal membrane oxygenation in critically ill adults

Annemieke Oude Lansink-Hartgring, MD PhD [a,*], Dinis Dos Reis Miranda, MD PhD [b], Loes Mandigers, MD PhD [b], Thijs Delnoij, MD PhD [c], Roberto Lorusso, MD PhD [d], Jacinta J. Maas, MD PhD [e], Carlos V. Elzo Kraemer, MD PhD [e], Alexander P.J. Vlaar, MD PhD [f], S. Jorinde Raasveld, MD [f], Dirk W. Donker, MD PhD [g,h], Erik Scholten, MD PhD [i], Anja Balzereit, MD PhD [j], Judith van den Brule, MD PhD [k], Marijn Kuijpers, MD [l], Karin M. Vermeulen, PhD [m], Walter M. van den Bergh, MD PhD [a], On behalf of the Dutch ECLS Study group

[a] Department of Critical Care, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[b] Adult Intensive Care Unit, Erasmus Medical Center, Rotterdam, the Netherlands
[c] Department of Intensive Care, Maastricht University Medical Center, Maastricht, the Netherlands
[d] Department of Cardio-Thoracic Surgery, Maastricht University Medical Centre, Maastricht, the Netherlands
[e] Adult Intensive Care Unit, Leiden University Medical Center, Leiden, the Netherlands
[f] Department of Intensive Unit, Amsterdam University Medical Centers, Academic Medical Centers, Amsterdam, the Netherlands
[g] Department of Critical Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[h] Cardiovascular and Respiratory Physiology Group, TechMed Centre, University of Twente, Enschede, the Netherlands
[i] Department of Intensive Care, St. Antonius Hospital, Nieuwegein, the Netherlands
[j] Department of Critical Care, Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands
[k] Department of Intensive Care, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands.
[l] Department of Intensive Care, Isala Klinieken, Zwolle, the Netherlands
[m] Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

ARTICLE INFO

Available online xxxx

Keywords:
Cost analysis
Critical care
Extracorporeal life support
Hospital costs
Outcome
Quality of life

ABSTRACT

Purpose: This study reports on survival and health related quality of life (HRQOL) after extracorporeal membrane oxygenation (ECMO) treatment and the associated costs in the first year.
Materials and Methods: Prospective observational cohort study patients receiving ECMO in the intensive care unit during August 2017 and July 2019. We analyzed all healthcare costs in the first year after index admission. Follow-up included a HRQOL analysis using the EQ-5D-5L at 6 and 12 months.
Results: The study enrolled 428 patients with an ECMO run during their critical care admission. The one-year mortality was 50%. Follow up was available for 124 patients at 12 months. Survivors reported a favorable mean HRQOL (utility) of 0.71 (scale 0–1) at 12 months of 0.77. The overall health status (VAS, scale 0–100) was reported as 73.6 at 12 months. Mean total costs during the first year were $204,513 ± 211,590 with hospital costs as the major factor contributing to the total costs. Follow up costs were $53,752 ± 65,051 and costs of absenteeism were $7317 ± 17,036.
Conclusions: At one year after hospital admission requiring ECMO the health-related quality of life is favorable with substantial costs but considering the survival might be acceptable. However, our results are limited by loss of follow up. So it may be possible that only the best-recovered patients returned their questionnaires. This potential bias might lead to higher costs and worse HRQOL in a real-life scenario.

* Corresponding author at: Hanzeplein 1, 9700 RB Groningen, the Netherlands.
E-mail address: a.oudelansink@umcg.nl (A. Oude Lansink-Hartgring).

https://doi.org/10.1016/j.jcrc.2022.154215

List of abbreviations

ARDS	acute respiratory distress syndrome
ECMO	extracorporeal membrane oxygenation
ECPR	extracorporeal cardiopulmonary resuscitation
HRQOL	health-related quality of life
QOL	quality of life
RESP	Respiratory ECMO Survival Prediction
SAVE	Survival after veno-arterial ECMO
VA	veno-arterial
VAS	visual analogue scale
VV	veno-venous

1. Background

Extracorporeal membrane oxygenation (ECMO) is the use of mechanical support to temporarily support heart or lung function during cardiopulmonary failure when conventional treatments have failed towards recovery or permanent device or organ transplantation. According to the international guideline of the Extracorporeal Life Support Organization (ELSO), ECMO should be considered when the estimated mortality risk is about 50% and is indicated in most circumstances when mortality risk approaches 80% [1]. This recommendation has been incorporated into the Dutch ECMO guideline [2]. Between 2008 and 2019 the use of ECMO increased exponentially with a total of 130,000 reported runs in the international ELSO registry, with a reported hospital survival of 60% for patients with a pulmonary indication, 44% for a cardiac indication, and 29% in case of extracorporeal cardiopulmonary resuscitation (ECPR) [3].

The CESAR trial was the first trial performed to compare costs between ECMO and mechanical ventilation for severe acute respiratory distress syndrome (ARDS) [4]. This trial provided data concerning the subgroup of patients with severe ARDS suitable for veno-venous ECMO (VV ECMO) comparing referral to a single center that offered ECMO with conventional management at the original center. Mean health care costs per patient were more than twice as high for patients allocated to consideration for ECMO than for those allocated to conventional management. A systematic review combining the only two randomized controlled trials in severe ARDS showed significantly lower 90-day mortality with ECMO therapy (36%) compared with conventional management (48%) [5]. Based on these numbers a subsequent model-based cost-utility analysis in VV ECMO for severe ARDS rendered it plausible that ECMO for this indication is cost-effective [6].

Several studies in the field of ECPR postulated the cost-effectiveness of ECMO based on an assumed beneficial effect, while in other indications, e.g., post-cardiotomy, this information is lacking and the benefit of ECMO therapy is therefore under debate [7-10]. The next step in assessing the cost-effectiveness of ECMO therapy is to proceed with an economic evaluation in which a broad appreciation of costs and effects, including a societal perspective, is considered. More knowledge about outcome variables such as survival as well as quality of life (QOL) needs to be gathered in a prospective manner. In this context, it is well known that psychiatric and cognitive symptoms and QOL among ECMO survivors are very relevant outcome measures. Even more than a year after discharge patients display cognitive and psychiatric symptoms, as well as significant physical deficits that impact QOL [11]. Long-term health-related QOL (HRQOL) assessment after ECMO treatment is necessary to determine whether patients actually benefit from ECMO treatment after which costs of ECMO treatment can be placed in context. For that purpose, we conducted a multicenter prospective observational cohort study in the Netherlands with the aim to assess survival and HRQOL after ECMO treatment and the associated costs in the first year.

2. Material and methods

We performed a prospective cohort study in ten intensive care units in the Netherlands between August 2017 and July 2019. This study was assessed and approved by the institutional review board of the University Medical Center Groningen (METc 2017/196) and approved by the ethical committees of the other participating hospitals. Written informed consent was obtained from all patients or their legal representatives. The trial is registered at https://clinicaltrials.gov/ (NCT02837419). The study protocol has been published previously [12]. The results are reported in accordance with the CHEERS guidelines [13]. The primary outcome was HRQOL assessed with the EQ-5D-5L instrument one year after initiation of ECMO treatment. Secondary outcomes were one-year survival, EQ-5D-visual analog scale (VAS) score, and costs.

2.1. Study population

All consecutive adult patients on ECMO were included in the study. Patients in whom ECMO was used to bridge a procedure like a high-risk percutaneous coronary intervention or during surgery were excluded. We collected demographic data such as physiological data concerning ventilator settings, hemodynamics, arterial blood gasses, and the determinants of the APACHE IV score [14]. In addition, Sequential Organ Failure Assessment on the day of ECMO initiation was collected [15]. The Respiratory ECMO Survival Prediction (RESP)-Score or the Survival after veno-arterial ECMO (SAVE)-score was collected to predict survival for patients undergoing ECMO for respiratory or cardiac failure [16,17]. Subgroups were created to categorize patients into support mode: veno-venous (VV), veno-arterial (VA), or ECPR.

HRQOL is a multidimensional construct that describes the perceived impact of health status on aspects of daily life. The patient's HRQOL was measured with EQ-5D-5L at six and 12 months after initiation of ECMO. The EQ-5D-5L instrument consists of a descriptive system with five domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with five possible levels on each which can be converted into a single summary index score, which represents the societal perspective on QOL, and a score on a visual analog scale, which represents the patient's perspective on QOL, where 0 is “the worst imaginable” and 100 “the best imaginable”. The same questionnaire, retrieving the health status one month prior to ICU admission, was retrospectively completed by the patient if awake on admission to the ICU or if necessary, by their relatives. Questionnaires were sent by ordinary mail or email at the patient's request. In case of no response, reminders were sent twice.

The quality adjusted life year (QALY) is a concept created to measure the outcome of a healthcare intervention, combining (expected) life years gained by a given intervention with the QOL experienced by the patient. We calculated the QALYs by multiplying each patient's expected life years gained with the individual health summary score from the EQ-5D-5L survey based on the Dutch tariff [18]. Patients who died during the index hospitalization did not gain any QALYs.

To test the robustness of our data we performed a sensitivity analysis with adding a worst case scenario for the 12 month data. When the patient returned the questionnaire at 6 months, but was missing at 12 months we used the 6 months results. For the remaining non-responders we discounted 25% from the approximated score (within the support type) to take into account the possibility that not returning the survey would relate to poorer HRQoL.

2.2. Cost analysis

Hospital costs were acquired from our previous study in which we used a microcosting bottom-up method [19]. In the current study, we measured all relevant healthcare costs in the first year following the index hospitalization including admissions in hospital, outpatient clinic visits, primary care costs, and medication use. Costs of resource use outside the hospital, such as absenteeism, productivity losses, or traveling expenses have been collected using the relevant parts of the iMTA cost questionnaires [20]. All costs were expressed in 2019 US dollars. For converting the different currencies to 2019 US dollars (USD) we used the method of purchasing power parities.

2.3. Economic evaluation

Since we performed a prospective cohort study, a reference group representing usual care was not part of the study. Therefore, we assumed all life years and QALYs to be gained by ECMO treatment, and the life expectancies of the one-year survivors to equal the age, sex and year-matched population-based life expectancies [21]. However, for survivors after ECPR we choose to apply a 50% reduction in the population-based life expectancy based on previous research [9]. In addition, costs per QALY were computed for the ECMO treatment, assuming a lifetime perspective. Cost/QALY allows comparison with other therapies that are used in other diseases and this ratio facilitates decision making. To include the costs that were made for patients who did not survive in hospital, the effective costs per hospital survivor were calculated by adding up the in-hospital costs of all ECMO patients divided by the number of survivors. Subsequently effective costs per QALY were computed as well. In the According to the Dutch guidelines, we used, different discount rates costs and effects. Costs were discounted at a constant discount rate of 4% and future effects at 1.5% [20].

2.4. Statistical analyses

Descriptive statistics are used for all data. Continuous variables are presented as mean with standard deviation if normally distributed, other distributions are presented as median with interquartile range (IQR). To calculate alternative confidence intervals surrounding the estimates of mean costs, bootstrapping was performed to generate 500 replications of the original data set. Based on the 2.5th and the 97.5th percentile score, the confidence interval was determined. We used Kaplan–Meier survival curves to describe 1-year survival. Data was analyzed using SPSS software version 23 (SPSSInc., Chicago, USA).

2.5. Planned sample size

Predicted mortality in standard care was assumed to be 80% and 38% in patients with ECMO. To compensate for a 5% underestimation of mortality and 5% drop-outs, we planned to enroll 210 patients.

3. Results

Between August 2017 and July 2019 we included 428 consecutive patients treated with ECMO in the ten participating hospitals. Patient characteristics are shown in Table 1. The study flow is depicted in Fig. 1. The median age was 57 (IQR 47–65) years, and 64% of patients were male. The primary indication for ECMO support was respiratory failure in 143 (33%), cardiac failure in 203 (47%) patients and 82 (20%) underwent ECMO within the context of ECPR. The median hospital length of stay was 16 (IQR 5.5–35) days, and 198 (46%) patients died in the hospital. One-year mortality was 50%.

In the 143 patients with respiratory failure, the diagnosis leading to ECMO treatment was pneumonia/ARDS in 82 patients (57%), bridge to lung transplantation in 16 patients (11%), primary graft dysfunction after lung transplantation in 14 patients (10%), status asthmaticus in 12 patients (8%), and other reasons in 19 patients (14%). The mean pH prior to start ECMO was 7.20 ± 0.13, the median P/F-ratio was 82 (IQR 62–138), worst lactate was median 1.5 mmol/L (IQR 1.1–3.1).The median RESP score in patients with respiratory failure was 1.0, which correlates with an estimated hospital survival of 57% [16]. In our cohort survival for this patient category was 61%.

Table 1
characteristics according to support type.

Patients, No	All patients	Respiratory support	Cardiac support	ECPR
	$N = 428$	$N = 143$	$N = 203$	$N = 82$
Age, years, median (IQR)	57 (47–65)	55 (47–62)	63 (50–70)	52 (44–63)
Age ≥ 70 years, n (%)	62 (14%)	7 (5%)	49 (24%)	6 (7%)
BMI (kg/m^2), median (IQR)	26.3 (23.7–29.3)	25.3 (22.3–28.3)	26.8 (24.2–30.0)	26.0 (24.3–29.4)
Sex, male, n (%)	276 (64%)	92 (64%)	128 (63%)	56 (68%)
Apache IV, median (IQR)	80 (59–108)	75 (57–101)	78 (42–98)	115 (88–137)
Overall health 1 month prior to ICU admission	0.88	0.88	0.88	0.88
SOFA score, median (IQR)	10 (8–13)	9 (7–12)	11 (8–13)	11 (9–14)
Pre ECMO cardiac arrest, yes, n (%)	163 (38%)	12 (9%)	69 (34%)	82 (100%)
ECMO mode, n (%)				
VA	291 (68%)	12 (8%)	197 (97%)	82 (100%)
VV	126 (29%)	126 (88%)		
Combined	11 (3%)	5 (4%)	6 (3%)	0
ECMO duration, days, median (IQR)	4 (1.8–9)	9 (4–16)	4 (2–7)	1 (0–4)
Hospital LOS, days, median (IQR)	16 (5.5–35)	22 (12–51)	17 (7–32)	4 (1−11)
Hospital mortality, n (%)	198 (46%)	56 (39%)	87 (43%)	55 (67%)
One year mortality, n (%)	215 (50%)	65 (45.5%)	93 (45.8%)	57 (69.5%)

BMI: body mass index.
ICU: intensive care unit.
SOFA: sequential organ failure assessment.
ECMO: extracorporeal membrane oxygenation.
LOS: length of stay.

In the 203 patients with cardiac failure the diagnosis leading to VA ECMO was post-cardiotomy in 95 patients (47%), myocardial infarction in 40 patients (20%), myocarditis in ten patients (5%), postoperative after lung transplantation in ten patients (5%), VT/VF storm in nine patients (4%), pulmonary embolism in eight patients (4%), and other reasons in 31 patients (15%). At cannulation the mean pH was 7.18 ± 0.17, the median lactate was 4.7 mmol/L (IQR 2.5–8.0), and the median arterial pressure was 60 mmHg (IQR 52–72). The SAVE score in patients with cardiac failure was median −5.0, which correlates with an estimated survival of 30% [17]. In our cohort survival for this patient category was 58%. In ECPR patients the mean pH prior to ECPR initiation was 6.9 ± 0.2, and the lactate was median 12.9 mmol/L (IQR 8.2–16.0). Hospital survival was 33%. Kaplan–Meier survival curves are

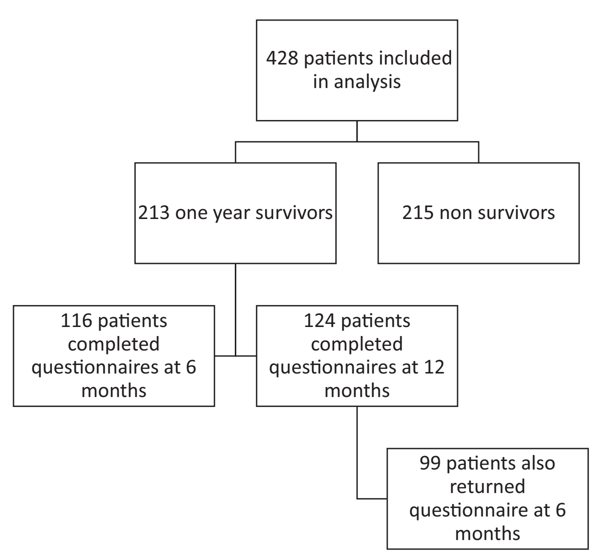

Fig. 1. Study flow diagram.

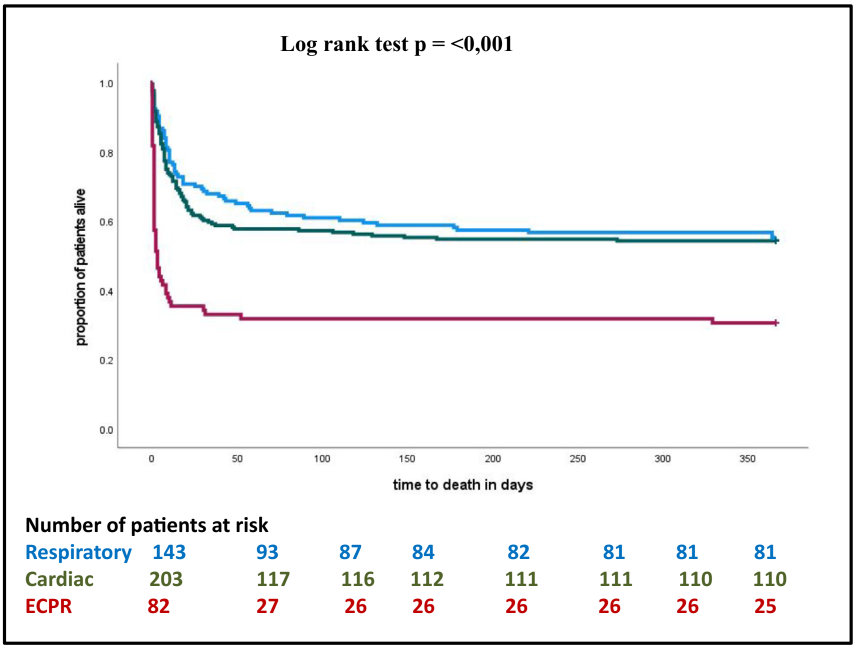

Fig. 2. Kaplan–Meier curves depicting survival in the first year following Extra Corporeal Membrane Oxygenation among critically ill adult patients ($n = 428$).

displayed in Fig. 2 and demonstrate a decline in survival over the first 50 days following ECMO initiation, followed by a relative plateauing of mortality rates. Patients' characteristics according to survival status are depicted in Supplemental Digital Content – Table 1.

The results for the overall HRQOL (utility) one month prior to ICU admission were available for 203 patients (47%). This cohort reported an overall HRQOL (utility) of 0.88 which is comparable to the average score of 0.86 of the Dutch population [18]. Of the 213 one-year survivors

Table 2
Health related quality of life (EQ5D-5 L) at 6 months.

Patients, categories	All patients	Respiratory support	Cardiac support	ECPR
EQ-5D information available	N = 116	N = 43	N = 59	N = 14
Problems with mobility				
None	43,0	41,9	44,1	35,7
Slight	19,8	11,6	30,5	7,1
Moderate	28,9	37,2	18,6	42,9
Severe	7,4	9,3	6,8	7,1
Extreme	0,8	0,0	0,0	7,1
Problems with self-care				
None	70,2	62,8	78,0	71,4
Slight	16,5	18,6	13,6	21,4
Moderate	9,9	11,6	6,8	7,1
Severe	1,7	4,7	0,0	0,0
Extreme	1,7	2,3	1,7	0,0
Problem with usual activities				
None	28,9	23,3	32,2	28,6
Slight	26,4	25,6	32,2	14,3
Moderate	28,1	27,9	27,1	35,7
Severe	11,6	16,3	6,8	14,3
Extreme	5,0	7,0	1,7	7,1
Pain or discomfort				
None	34,7	39,5	33,9	21,4
Slight	27,3	16,3	32,2	42,9
Moderate	27,3	279	27,1	21,4
Severe	9,9	14,0	6,8	14,3
Extreme	0,8	2,3	0,0	0,0
Anxiety or depression				
None	64,5	58,1	69,5	57,1
Slight	20,7	23,2	18,6	21,4
Moderate	9,1	9,3	10,2	7,1
Severe	5,0	7,0	1,7	14,1
Extreme	0,8	2,3	0,0	0,0
Overall health status (VAS 0–100)	68,6	64,7	71,3	68,7
Overall health (Utility)	0,71	0,66	0,76	0,64

Table 3
Health related quality of life (EQ5D-5 L) at 1 year.

Patients, categories	All patients	Respiratory support	Cardiac support	ECPR
EQ-5D information available	N = 124	N = 44	N = 63	N = 17
Problems with mobility				
None	44,2	45,5	42,9	41,2
Slight	30,2	34,1	30,2	23,5
Moderate	17,8	15,9	20,6	11,8
Severe	6,2	4,5	4,8	17,6
Extreme	1,6	0,0	1,6	5,9
Problems with self-care				
None	73,6	68,2	76,2	76,5
Slight	16,3	22,7	15,9	0,0
Moderate	7,8	6,8	6,3	17,6
Severe	0	0,0	0,0	0,0
Extreme	2,3	2,3	1,6	5,9
Problem with usual activities				
None	34,9	38,6	31,7	35,3
Slight	34,9	36,4	36,5	23,5
Moderate	20,2	18,2	22,2	17,6
Severe	7,8	6,8	7,9	11,8
Extreme	2.3	0,0	1,6	11,8
Pain or discomfort				
None	39,5	36,4	44,4	23,5
Slight	38,8	40,9	33,3	58,8
Moderate	19,4	20,5	20,6	11,8
Severe	2.3	2,3	1,6	5,9
Extreme	0	0,0	0,0	0,0
Anxiety or depression				
None	69,0	79,5	65,1	47,1
Slight	19,4	13,6	23,8	23,5
Moderate	7,8	4,5	9,5	11,8
Severe	2,3	0,0	1,6	11,8
Extreme	1,6	2,3	0,0	5,9
Overall health status (VAS 0–100)	73,6	77,5	72,8	66,0
Overall health (Utility)	0,77	0,80	0,78	0,64

169 individual patients returned the EQ-5D-5L questionnaire at 6 and/or 12 months. The results of the EQ-5D-5L are shown in Tables 2 and 3. Moderate to extreme mobility problems were reported by 36.6% of the patients at six months, which decreased to 24% at one year. Moderate to extreme symptoms of anxiety or depression were reported by 14.9% of the patients at 6 months and only slightly decreased at 12 months (11.7%). The overall health utility was 0.71 at six months and increased to 0.77 at 12 months. The overall health status (VAS, scale 0–100) was reported as 68.6 at six months which increased to 73.6 at 12 months. For patients with respiratory failure the overall health status at 12 months on the VAS was 77.5 ± 12.6, for patients with cardiac failure 72.8 ± 17.1, and for ECPR patients was 66.0 ± 25.1 (Table 3). In the worst case scenario in patients with respiratory failure the utility decreased to 0.72 and the VAS to 66. For patients in cardiac failure the utility decreased to 0.69 and the VAS to 65. For ECPR patients the utility decreased to 0.57, and the VAS to 61.

Costs in the year following hospital admission for ECMO were available for the same total of 129 patients who returned the EQ-5D-5L questionnaire (Table 4). Of the 48 responders younger than 65 year36% reported having returned to a paid job 12 months after ECMO treatment. They worked a median of 28 h/week. Mean costs of absenteeism were $7317, lowest in the cardiac support group possibly due to the older age of this group. Mean costs for follow up care (outpatient care/rehabilitation/homecare) were $53,752. In addition to the hospital cost of $143,443, which was calculated in our previous study [19], the total mean societal costs were $204,513 in the first year following ECMO treatment. For patients with respiratory failure, total mean societal costs were the highest ($253,189), followed by $152,498 for cardiac failure, and the lowest costs of $132,082 were for ECPR patients. The effective costs, per hospital survivor for the cohort were $349,304. The total and effective costs at one year per QALY according to support type are highest for patients with respiratory failure. For the lifetime horizon of the cohort the costs per QALY were calculated based on gained life years expected, gained QALYs and expected costs in these coming years. The costs per QALY gained for the cohort were $17,065. By including the costs of the non-survivors the effective costs per QALY were $24,913 (Table 5).

Table 5
Lifetime horizon.

	All patients	Respiratory support	Cardiac support	ECPR
QALY	0.74	0.72	0.76	0.64
Life years expected	30.9	32.3	29.4	16.9
Total QALYs expected	18.45	18.58	18.18	9.68
Total costs at 1 year	204,513	253,189	152,498	132,082
Effective costs at 1 year	349,304	411,752	231,265	253,742
Expected costs in coming years	110,351	112,017	123,842	123,136
Costs / QALY	17,065	19,655	15,199	26,365
Effective costs/QALY	24,913	28,189	19,532	38,933

QALY: quality-adjusted life year.
ECPR: extracorporeal cardiopulmonary resuscitation.
for the ECPR category the life years expected is calculated with a 50% reduction compared to the general population.

4. Discussion

In our multicenter prospective observational cohort study in the Netherlands, we found that HRQOL at 12 months after ECMO was 0.77, compared to the average score of 0.86 of the Dutch population, so ECMO treatment resulted in only a limited reduction in HRQOL [18]. The one year survival of our cohort was 50%, with an overall HRQOL on a VAS of 73.8. The associated societal costs in the first year were significant, $204,513, varying between approximately $130,000–250,000 depending on the patient category, with hospital costs as the major factor contributing to the total costs in all categories, varying between 56 and 76%.

Our results on HRQOL support the findings of a recent literature review of QOL in ECMO treatment in adults, revealing higher scores in VV ECMO patients compared with VA ECMO [22]. For respiratory patients, our results are comparable to several smaller cohort studies [4,23-25]. In a study from Germany in patients requiring ECMO to support cardiogenic shock, the EQ-5D indices of patients with and without cardiac surgery during the index admission were similar to our results although the QOL was significantly lower than the normative age-matched population in Germany [25]. For ECPR patients, studies vary greatly for the questionnaires used for HRQOL and concerning the use of neurological outcome scales converted to estimate QOL. Our HRQOL (VAS) results of 66 are in line with the mean index score of 67 (SD 0.25) for ECPR patients in a Finnish study [10]. In a small cohort of 32 ECPR patients, the Health Utilities Index Mark 2 (scale 0–1.0) was applied to evaluate HRQOL. The mean score of the 15 survivors in that study was 0.44 [7].

In a retrospective study from Finland in patients with cardiogenic shock or cardiac arrest which included complete costs of the index hospitalization followed by the complete hospital-related and the hospital outpatient clinic costs of the subsequent year, the reported one-year costs were $208,735 [10]. However, this study did not include primary care costs, patients' social security reimbursements (e.g., medication after discharge, sick allowances), and costs from other hospital districts. This is 28% more than the one-year costs in our cohort of cardiac patients ($152,498), with a comparable length of hospital stay. The difference might be explained by fewer outpatient visits because of the presence of many post-cardiotomy patients in our cohort compared to patients after heart transplant or LVAD implantation in the Finnish study. In a retrospective study using the health administrative databases in Ontario, Canada to examine the total and sector-specific direct healthcare costs accumulated in the first year following the date of the index hospital admission (including the admission itself) were mean $114,407 [26]. 70% of total costs were accounted for by the index hospital admission, comparable to our findings. This Canadian study uses

Table 4
Mean one-year costs following admission of adults patients requiring ECMO in index hospital admission.

Patients, categories	All patients	Respiratory support	Cardiac support	ECPR
	N = 129	N = 51	N = 62	N = 16
Hospital costs	143,443 ± 129,498	190,276 ± 150,095	93,165 ± 52,891	70,188 ± 53,850
Follow up costs*	53,752 ± 65,051 (42,165-63,842)	53,140 ± 62,451 (35,104-66,646)	54,447 ± 68,785 (39,841-75,432)	52,958 ± 61,714 (20,991-75,956)
Costs of absenteeism	7317 ± 17,036 (4608–10.108)	9772 ± 20,484 (4636-15,632)	4885 ± 13,722 (1821-8400)	8935 ± 16,261 (1939-17,572)
Total costs	204,513 ± 211,590 (17,5547-204,575)	253,189 ± 233,031 (234,891-270,094)	152,498 ± 135,399 (138,283-175,051)	132,082 ± 131,826 (98,677-159,056)

Costs are represented as mean (95% confidence interval).
ECPR: extracorporeal cardiopulmonary resuscitation.
ECMO: extracorporeal membrane oxygenation.
* Follow up costs consists of all relevant healthcare costs in the first year following the index hospitalization including admissions in hospital, outpatient clinic visits, primary care costs, medication use.

robust population-level data on costs but misses the costs paid by patients privately, costs associated with productivity losses, and more importantly, the relation with QOL. The costs for absenteeism from work in our cohort are low both in absolute and relative numbers. This is probably due to the relatively old age of our study population with the cardiac support group being almost 10 years older than the respiratory and ECPR patients. This is in line with a German study in patients with cardiac failure where one-quarter of the population returned to work or school but 50% were older than 60 years and already retired [25].

Although costs for ECMO during the first year are high, other treatments generate costs year after year. For instance, the total annual costs for hemodialysis in the Netherlands are $ 116,351 per patient [27]. On the contrary to ECMO, these costs are repeatedly generated year after year. For patients on long-term mechanical circulatory support, the median total costs after one year of therapy are $247,208 [28].

As far as we know, there are only three studies that provide cost-utility analyses, two for ARDS and one for VA ECMO patients. For patients with respiratory failure, the multicenter randomized trial on the use of VV ECMO showed a lifetime predicted additional cost-effectiveness ratio of $32,649, an amount well within the range regarded as cost-effective by health technology assessment organizations [4]. The hypothetical study from Brazil using epidemiological data and a Markov model showed a negative cost per QALY ratio with a reduction in ICU stay associated with ECMO in a scenario with a 40% survival. [29]. In a study from Finland in patients with VA ECMO median costs per QALY were $9389 with the highest costs per QALY for patients post-heart transplant. However, only hospital costs were included [10]. This amount is lower than in our cardiac cohort, but we estimate that if rehabilitation costs and social security reimbursement would have been included, their costs would more or less equal to the costs per QALY we found.

To our knowledge, our study is the largest study up till now concerning costs and HRQOL of ECMO treatment. The costs are determined bottom-up and realistic and include costs in the societal domain as well. The benefits have been measured on the patient and the societal level. As such, our study provides relevant information for patients, health care professionals, and policymakers. Our findings are also relevant to other countries although indications, referrals, reimbursement will vary between countries. Our study was limited by the observational design and limited to the Dutch health care system. A significant number of patients did not complete the HRQOL and questionnaires on costs. Completing the questionnaires by email or by phone is time-consuming and takes some effort, so it may be possible that only the best-recovered patients returned their questionnaires. This potential bias might lead to higher costs and worse HRQOL in a real-life scenario. Ideally, costs per QALY gained are based on incremental cost-effectiveness ratios. As the current study was a prospective cohort study, no reference group receiving usual care, was included. Therefore we had to make a number of assumptions to estimate the costs per QOL. Furthermore, in the estimation of the life years gained, we did not adjust for the possibility of remaining symptoms due to critical illness after ECMO. However cardiovascular disease is commonly present in the age matched population. The risk of death among hospital survivors of ICU admission is highest in the first year, but may still be increased in the years thereafter compared with the general population. Age and comorbidity are major determinants of long-term survival after ICU [30]. In our analysis, and in concordance with the literature, we only applied a reduction in life years expected for ECPR patients and not for the other groups of patients because estimation of the reduction for the other categories is difficult. This should be taken into account when interpreting the results.

5. Conclusions

ECMO treatment in the Netherlands carries high costs per individual patient in the first year with hospital costs accounting for the majority of costs, but survivors reported a HRQOL one year after ECMO treatment comparable to the general Dutch population, although our results are limited by loss of follow up. The costs per QALY gained are potentially acceptable for the ECMO cohort as a whole as for the different support types (respiratory, cardiac, and ECPR). Our results can be used to calculate cost-effectiveness if future randomized trials on efficacy in different indications for ECMO treatment are published.

Declarations

Ethics approval and consent to participate: This study was assessed and approved by the institutional review board of the University Medical Center Groningen (METc 2017/196) and approved by the ethical committees of the other participating hospitals. Written informed consent was obtained from all patients or their legal representatives.

Consent for publication: not applicable

Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

Walter van den Bergh received a ZonMw grant.

CRediT authorship contribution statement

Annemieke Oude Lansink-Hartgring: Formal analysis, Data curation, Writing – original draft, Visualization. **Dinis Dos Reis Miranda:** Writing – review & editing. **Loes Mandigers:** Writing – review & editing. **Thijs Delnoij:** Writing – review & editing. **Roberto Lorusso:** Writing – review & editing. **Jacinta J. Maas:** Writing – review & editing. **Carlos V. Elzo Kraemer:** Writing – review & editing. **Alexander P.J. Vlaar:** Writing – review & editing. **S. Jorinde Raasveld:** Writing – review & editing. **Dirk W. Donker:** Writing – review & editing. **Erik Scholten:** Writing – review & editing. **Anja Balzereit:** Writing – review & editing. **Judith van den Brule:** Writing – review & editing. **Marijn Kuijpers:** Writing – review & editing. **Karin M. Vermeulen:** Methodology, Formal analysis, Data curation, Writing – review & editing, Supervision. **Walter M. van den Bergh:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

Dirk W. Donker received speaker fee from Getinge-Maquet and Xenios NovaLung Fresenius. Dirk W. Donker has research cooperation's with Getinge-Maquet and Xenios NovaLung Fresenius. Roberto Lorusso is consultant for Medtronic, LivaNova, and Getinge. He is part of the Medical Advisory Board of Eurosets and Xenios. All honoraria are paid to the university for research funding. Dinis dos Reis Miranda received speaking fees from Xenios. The remaining authors have disclosed that they do not have any conflicts of interest.

Acknowledgements

We would like to thank the research nurses and research coordinator from the critical care department of the UMCG for their support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2022.154215.

References

[1] ELSO. General Guidelines version 1.4 Published August 2017. Accessed through www.elso.org. Accessed august 1. ; 2021..

[2] Oude Lansink A, van den Brule J, van Dijk D, et al. Extracorporeal life support for cardiac and respiratory failure in adults in the intensive care unit in the Netherlands indications for ECLS and requirements for an ECLS centre. Neth. J Crit Care. 2016;4:24–7.

[3] Extracorporeal Life Support Organization. Extracorporeal Life Support Organization ECMO Registry Report Overall Outcomes. https://www.elso.org/Registry/Statistics/Reports.aspx#SummaryJuly2020; 2019.

[4] Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet. 2009;374(9698):1351–63. https://doi.org/10.1016/S0140-6736(09)61069-2. [Epub 2009 Sep 15].

[5] Combes A, Peek GJ, Hajage D, et al. ECMO for severe ARDS: systematic review and individual patient data meta-analysis. Intensive Care Med. 2020;46(11):2048–57. https://doi.org/10.1007/s00134-020-06248-3. [Epub 2020 Oct 6].

[6] Barrett KA, Hawkins N, Fan E. Economic evaluation of Venovenous extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. Crit Care Med. 2019;47(2):186–93. https://doi.org/10.1097/CCM.0000000000003465.

[7] Bharmal MI, Venturini JM, Chua RF, et al. Cost-utility of extracorporeal cardiopulmonary resuscitation in patients with cardiac arrest. Resuscitation. 2019;136:126–30. https://doi.org/10.1016/j.resuscitation.2019.01.027. [Epub 2019 Feb 1].

[8] Dennis M, Zmudzki F, Burns B, et al. Cost effectiveness and quality of life analysis of extracorporeal cardiopulmonary resuscitation (ECPR) for refractory cardiac arrest. Resuscitation. 2019;139:49–56. https://doi.org/10.1016/j.resuscitation.2019.03.021. [Epub 2019 Mar 26].

[9] Kawashima T, Uehara H, Miyagi N, et al. Impact of first documented rhythm on cost-effectiveness of extracorporeal cardiopulmonary resuscitation. Resuscitation. 2019;140:74–80. https://doi.org/10.1016/j.resuscitation.2019.05.013. [Epub 2019 May 18].

[10] Jaamaa-Holmberg S, Salmela B, Suojaranta R, et al. Cost-utility of venoarterial extracorporeal membrane oxygenation in cardiogenic shock and cardiac arrest. Eur Heart J Acute Cardiovasc Care. 2020;31. https://doi.org/10.1177/2048872619900090. 2048872619900090.

[11] Khan IR, Saulle M, Oldham MA, et al. Cognitive, psychiatric, and quality of life outcomes in adult survivors of extracorporeal membrane oxygenation therapy: a scoping review of the literature. Crit Care Med. 2020;48(10):e959–70. https://doi.org/10.1097/CCM.0000000000004488.

[12] Oude Lansink-Hartgring A, Dos Reis Miranda D, Donker DW, et al. Cost-effectiveness in extracorporeal life support in critically ill adults in the Netherlands. BMC Health Serv Res. 2018;18(1):172. https://doi.org/10.1186/s12913-018-2964-6.

[13] Fayanju OM, Haukoos JS, Tseng JF. CHEERS reporting guidelines for economic evaluations. JAMA Surg. 2021;156(7):677–8. https://doi.org/10.1001/jamasurg.2021.0540.

[14] Zimmerman JE, Kramer AA, McNair DS, et al. Acute physiology and chronic health evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. Crit Care Med. 2006;34:1297–310.

[15] Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on Sepsis-related problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22:707–10.

[16] Schmidt M, Bailey M, Sheldrake J, et al. Predicting survival after ECMO for severe acute respiratory failure: the respiratory ECMO survival prediction (RESP)-score. Am J Respir Crit Care Med. 2014;189(11):1374–82. https://doi.org/10.1164/rccm.201311-2023OC.

[17] Schmidt M, Burrell A, Roberts L, et al. Cardiogenic shock: the survival after venoarterial predicting survival after ECMO for refractory -ECMO (SAVE)-score. Eur Heart J. 2015;36(33):2246–56. https://doi.org/10.1093/eurheartj/ehv194. [Epub 2015 Jun 1. PMID: 26033984].

[18] Versteegh MM, Vermeulen KM, Evers SM, et al. Dutch tariff for the five-level version of EQ-5D. Value Health. 2016;19(4):343–52. https://doi.org/10.1016/j.jval.2016.01.003.

[19] Oude Lansink-Hartgring A, van den Hengel B, van der Bij W, et al. Hospital costs of extracorporeal life support therapy. Crit Care Med. 2016;44(4):717–23. https://doi.org/10.1097/CCM.0000000000001477.

[20] Guideline for conducting economic evaluations in health care. Accessed through. http://www.zorginstituutnederland.nl; 2016.

[21] https://www.volksgezondheidenzorg.info/.

[22] Knudson KA, Gustafson CM, Sadler LS, et al. Long-term health-related quality of life of adult patients treated with extracorporeal membrane oxygenation (ECMO): an integrative review. Heart Lung. 2019;48(6):538–52. https://doi.org/10.1016/j.hrtlng.2019.08.016. [PMID: 31711573].

[23] Hodgson CL, Hayes K, Everard T. Long-term quality of life in patients with acute respiratory distress syndrome requiring extracorporeal membrane oxygenation for refractory hypoxaemia. Crit Care. 2012;16(5):R202. https://doi.org/10.1186/cc11811.

[24] Tramm R, Ilic D, Sheldrake J, et al. Recovery, risks, and adverse health outcomes in year 1 after extracorporeal membrane oxygenation. Am J Crit Care. 2017;26(4):311–9.

[25] Camboni D, Philipp A, Rottenkolber V, et al. Long-term survival and quality of life after extracorporeal life support: a 10-year report. Eur J Cardiothorac Surg. 2017;52(2):241–7. https://doi.org/10.1093/ejcts/ezx100.

[26] Fernando SM, Qureshi D, Tanuseputro P, et al. Mortality and costs following extracorporeal membrane oxygenation in critically ill adults: a population-based cohort study. Intensive Care Med. 2019;45(11):1580–9. https://doi.org/10.1007/s00134-019-05766-z. [Epub 2019 Sep 16].

[27] Mohnen SM, van Oosten MJM, Los J, et al. Healthcare costs of patients on different renal replacement modalities – analysis of Dutch health insurance claims data. PLoS ONE. 2019;14(8):e0220800.

[28] Chung JJ, Stetson R, Gordon J, et al. Better with time: an economic assessment of long-term mechanical circulatory support in a population surviving at least 1 year with a left ventricular assist device. Semin Thorac Cardiovasc Surg. 2020;32(4):738–46. https://doi.org/10.1053/j.semtcvs.2018.09.029. [Epub 2018 Oct 9].

[29] Park M, Mendes PV, Zampieri FG, et al. The economic effect of extracorporeal membrane oxygenation to support adults with severe respiratory failure in Brazil: a hypothetical analysis. Rev Bras Ter Intensiva. 2014;26(3):253–62. https://doi.org/10.5935/0103-507x.20140036.

[30] Williams TA, Dobb GJ, Finn JC, et al. Determinants of long-term survival after intensive care. Crit Care Med. 2008;36(5):1523–30. https://doi.org/10.1097/CCM.0b013e318170a405.