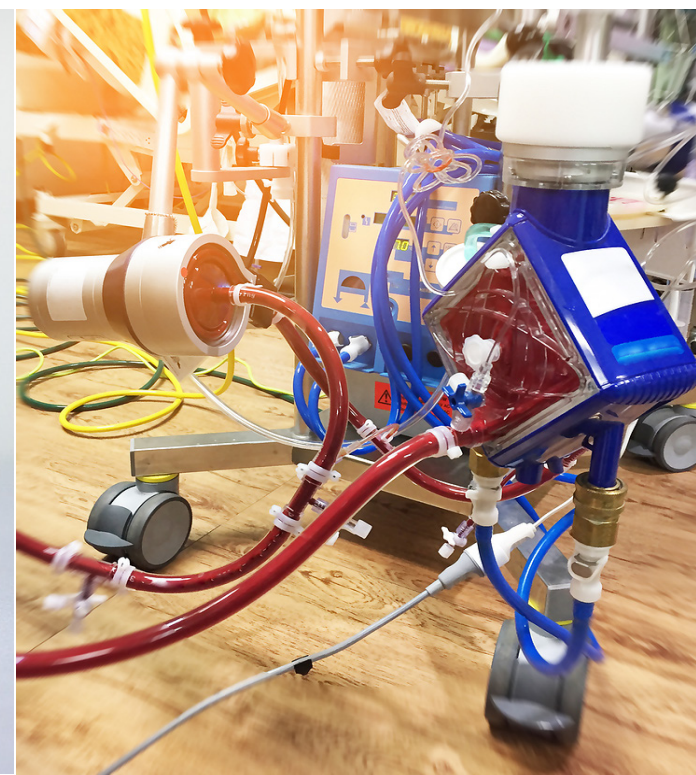


USE AND ORGANISATION OF ECMO IN BELGIUM



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■ TABLE OF CONTENTS

■	SCIENTIFIC REPORT.....	13
1	INTRODUCTION AND SCOPE	13
1.1	BASIC DESCRIPTION OF ECMO	13
1.2	HISTORY	14
1.3	ECMO TECHNIQUES	14
1.3.1	Configurations of ECMO	14
1.3.2	Indications of ECMO	17
1.3.3	Complications of ECMO.....	18
1.4	REPORTED OUTCOMES AND REGISTRIES	18
1.4.1	Background	18
1.4.2	The ELSO registry.....	18
1.5	SCOPE OF THIS REPORT	20
2	USE OF ECMO IN BELGIUM: PERIOD 2016-2019.....	21
2.1	DATA SOURCE.....	21
2.2	METHODS.....	22
2.3	RESULTS	24
2.3.1	Distribution of overall patient population (n=2543)	26
2.3.2	Geographic distribution of adult population according to ECMO type (n=1801)	29
2.3.3	Demographics	31
2.3.4	Clinical information	34
2.3.5	Intervention billing: timing (n=1801).....	36
2.3.6	Blood products consumption (n=1801)	37



	2.3.7	Survival analysis (n=1319).....	37
2.4		LIMITATIONS	40
3		USE OF ECMO IN BELGIUM DURING SARS-COV-2 PANDEMIC: PERIOD 2020-2022.....	41
3.1		DATA SOURCE.....	41
	3.1.1	Clinical Hospital Surveillance (CHS).....	41
3.2		METHODS.....	41
3.3		RESULTS	43
	3.3.1	Number of patients receiving ECMO	43
	3.3.2	Patient and admission characteristics.....	43
	3.3.3	Clinical parameters	54
	3.3.4	Ventilation	58
	3.3.5	Treatment.....	62
3.4		LIMITATIONS	63
4		REVIEW OF LITERATURE: EFFECTIVENESS AND SAFETY OF ECMO	64
4.1		INTRODUCTION	64
4.2		METHODS.....	64
4.3		RESULTS	66
	4.3.1	Veno-venous ECMO	66
	4.3.2	Veno-arterial ECMO for cardiac arrest (extracorporeal cardiopulmonary resuscitation) and cardiogenic shock	72
	4.3.3	More recent evidence.....	84
4.4		DISCUSSION	84
	4.4.1	Main findings	84
	4.4.2	Limitations of available evidence	85



4.4.3	Limitation of this review	86
4.4.4	Perspectives and ongoing studies	86
5	REVIEW OF LITERATURE: ORGANIZATION OF ECMO SERVICES	89
5.1	INTRODUCTION	89
5.2	RESEARCH QUESTION AND METHODS	89
5.3	RESULTS	90
5.3.1	Evidence retrieved from HTA agencies	90
5.3.2	Evidence retrieved from literature	91
5.3.3	International guidelines and experts position	97
5.4	DISCUSSION AND MAIN FINDINGS	100
6	PATIENT PERSPECTIVES AND ETHICAL ASPECTS WITH ECMO USE	102
6.1	INTRODUCTION	102
6.2	METHODS	102
6.3	RESULTS	102
7	INTERNATIONAL COMPARISON ON THE USE AND THE FUNDING OF ECMO	104
7.1	INTRODUCTION	104
7.2	METHODS	105
7.3	RESULTS	106
7.3.1	Countries with a centralisation of ECMO services	106
7.3.2	Countries without centralised ECMO services	110
7.4	DISCUSSION	119
8	SYSTEMATIC LITERATURE REVIEW OF COSTING STUDIES	120
8.1	INTRODUCTION	120
8.2	METHODS	120



8.2.1	Search strategy	120
8.2.2	Selection procedure	120
8.2.3	Selection criteria.....	120
8.2.4	Results:	121
8.3	OVERVIEW OF COSTING STUDIES ON ECMO.....	124
8.3.1	Type of cost analysis.....	125
8.3.2	Perspective	125
8.3.3	Time frame of analyses and discounting	125
8.3.4	Type of ECMO and Population	126
8.3.5	Comparator	126
8.3.6	Cost and outcome inputs	126
8.3.7	Results	127
8.3.8	Discussion and limitations.....	131
8.4	KEY POINTS	133
9	SURVEY OF BELGIAN HOSPITALS ON COSTS OF ECMO	133
9.1	INTRODUCTION	133
9.2	METHODS.....	133
9.3	RESULTS	134
9.3.1	Overall number of ECMO machines and patients on ECMO 2019-2021	134
9.3.2	Costs of ECMO	135
9.4	OVERALL COSTS PER ECMO TREATMENT	138
9.5	SENSITIVITY ANALYSIS	139
9.6	LIMITATIONS	143
9.7	KEY POINTS	145



10	CONCLUSIONS AND GENERAL DISCUSSION	145
■	REFERENCES	148



LIST OF FIGURES

Figure 1 – Schematic representation of VA (A) and VV-ECMO (B) ¹¹	16
Figure 2 – Extracorporeal support registry report for the year 2021 ⁵	20
Figure 3 – Number of stays per hospital by type of hospital	28
Figure 4 – Number of ECMOs per hospital sites	30
Figure 5 – ECMO patient population pyramid (2016-2019).....	32
Figure 6 – Patient population pyramid for VA and VV-ECMO	33
Figure 7 – Elapsed days between hospital admission and first ECMO	36
Figure 8 – In-hospital mortality per type of ECMO	38
Figure 9 – In-hospital mortality according to age.....	40
Figure 10 – COVID-19 waves by hospital admission dates.	42
Figure 11 – Percentage of ECMO patients per COVID-19 wave.	43
Figure 12 – Number of hospitals by category of number of ECMO patients.	43
Figure 13 – Number of ECMO patients by hospital region and wave.	43
Figure 14 – Number of ECMO patients by hospital type and wave.....	44
Figure 15 – Cumulative percentage of ECMO patients by length of stay and wave.	45
Figure 16 – Cumulative percentage of ECMO patients by length of stay in ICU and wave.	46
Figure 17 – Age distribution of ECMO patients by sex.....	47
Figure 18 – Age distribution of ECMO patients by sex and wave (Interwave 1 and Wave 5 not shown due to less than five patients in at least one stratum).	48
Figure 19 – Age distribution of ECMO patients by hospital region.....	49
Figure 20 – Age distribution of ECMO patients transferred from another hospital or not.	50
Figure 21 – Age distribution of ECMO patients by hospital type.	51
Figure 22 – Number of ECMO patients alive or deceased at discharge (grey represents unknown).	52
Figure 23 – Age distribution of ECMO patients alive or deceased at discharge.	53



Figure 24 – Age distribution of ECMO patients alive or deceased at discharge by ECMO hospital volume.	54
Figure 25 – Proportion of ECMO patients by pre-existing condition (full period available questions; grey bar represents unknown status).	55
Figure 26 – Proportion of ECMO patients by COVID-19 complication (2020–2021 period).	56
Figure 27 – Cumulative percentage of ECMO patients by SOFA score and wave (2020–2021 period; Interwave 1 and Wave 5 not shown due to less than five patients in at least one stratum).	58
Figure 28 – Cumulative percentage of ECMO patients by length of non-invasive ventilation and wave (2020–2021 period; Interwave 1 and Wave 5 not shown due to less than five patients).	59
Figure 29 – Cumulative percentage of ECMO patients by length of invasive ventilation and wave (2020–2021 period; Interwave 1 and Wave 5 not shown due to less than five patients).	60
Figure 30 – Cumulative percentage of ECMO patients by length of ECMO and wave (Wave 5 not shown due to less than five patients).	61
Figure 31 – Cumulative percentage of ECMO patients by hospital category of number of ECMO patients.	62
Figure 32 – Proportion of ECMO patients receiving treatments (2020–2021 period).	63
Figure 33 – Expenditures associated with nomenclature billing codes for VA and VV-ECMO over time for patients ≥ 16 years old	115
Figure 34 – Numbers of nomenclature billing codes over time for patients ≥ 16 years old.....	116
Figure 35 – Flow-Chart Selection Process Costing Studies ECMO for respiratory and cardiac failure.....	123
Figure 36 – Tornado diagram for ECMO costs in Belgium.....	142



LIST OF TABLES

Table 1 – Indications of ECMO ^{5, 13-15}	17
Table 2 – List of selection codes	22
Table 3 – Selection applied per analysis type	24
Table 4 – Extraction results	25
Table 5 – Distribution of patient population (total)	26
Table 6 – ECMO stays characteristics per hospital and per year	27
Table 7 – Number of ECMO per type of cardiac care programme hospitals (2016-2019).....	31
Table 8 – Number of ECMO fees by type.....	33
Table 9 – Top 20 Principal diagnosis (first 3 digits from ICD-10 codes): veno-arterial (VA) and): veno-venous (VV) approach	34
Table 10 – Origin of adult patients getting ECMO by type of hospital (2016-2019)	37
Table 11 – In-hospital mortality per type of ECMO.....	38
Table 12 – Hazard ratio adjusted and unadjusted.....	39
Table 13 – PICO strategy- inclusion criteria	65
Table 14 – Inclusion and exclusion criteria of the report from the National Institute of Excellence in Health and Social Services (INESSS) ²⁶	66
Table 15 – Studies included in the report from the National Institute of Excellence in Health Care and Social Services (INESSS).....	68
Table 16 – Most recent systematic reviews on VV-ECMO.....	70
Table 17 – Primary studies from the SR by Zhu F et al.....	70
Table 18 – Pooled analysis of the mortality in RCTs included in the SR by Zhu F et al. ⁴⁰	71
Table 19 – Pooled analysis of the mortality in observational studies included in the SR by Zhu F et al. ⁴⁰	71
Table 20 – Inclusion and exclusion criteria of the report from the Ontario HTA.....	73
Table 21 – Studies on cardiac arrest included in the report from Ontario HTA.....	74
Table 22 – Studies on cardiogenic shock included in the report from Ontario HTA.....	76



Table 23 – Most recent systematic reviews on VA-ECMO for cardiac arrest	78
Table 24 – Results from the meta-analysis undertaken in the report from Ontario HTA (use of ECMO for cardiac arrest)	80
Table 25 – Results from the Ontario HTA on the use of ECMO for cardiogenic shock	82
Table 26 – General conclusions	83
Table 27 – Ongoing studies of interest	87
Table 28 – PICO strategy- inclusion criteria	90
Table 29 – Description and results of included studies	93
Table 30 – Guidelines from Extracorporeal Life Support Organization (ELSO) on the organisation of ECMO centres ⁵	98
Table 31 – Summary of international experts consensus on the organisation of ECMO services for respiratory failure, included in ELSO guidelines ⁹²	98
Table 32 – Summary of international experts consensus on the organisation of ECMO services for cardiac failure ⁹³	99
Table 33 – International comparison of ECMO management and funding in Belgium, France, Italy, the Netherlands and the UK.	105
Table 34 – Key-factors in the recognition as adult ECMO centres across the UK ¹¹¹	107
Table 35 – Summary table on main characteristics of the organisation of ECMO in each country	117
Table 36 – Selection criteria for costing studies	121
Table 37 – Characteristics of selected costing studies.....	124
Table 38 – ECMO type and population sample in selected studies	125
Table 39 – ECMO costs captured on included studies.....	128
Table 40 – Outcomes in the included studies.....	129
Table 41 – Mean Costs per patient of VV and VA-ECMO from the literature	132
Table 42 – Mean personnel costs for cannulation/placement of ECMO	137
Table 43 – Mean daily costs of monitoring for ECMO (VV and VA).....	138



Table 44 – Mean costs of ECMO (February 2022).....	139
Table 45 – Variables and values tested on sensitivity analysis for ECMO costs in Belgium	140
Table 46 – Mean incremental hospital costs of ECMO (per patient) compared to current reimbursement in Belgium	144



LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ACLS	Advanced Cardiac Life Support
AEs	Adverse Events
ARDS	Acute respiratory distress syndrome
CCA	Cost-consequences Analysis
CEA	Cost-effectiveness analyses
CMA	Cost-minimisation Analysis
CO ₂	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CPR	Cardiopulmonary resuscitation
CUA	Cost-utility Analysis
ECCO ₂ R	Extracorporeal CO ₂ removal
ECG	Electrocardiogram
ECLS	Extracorporeal life support
ECMO	Extracorporeal membrane oxygenation
ECPR	Extracorporeal cardiopulmonary resuscitation
ED	Emergency Department
ELSO	Extracorporeal Life support Organization
HF	Heart Failure
HTA	Health and technology assessment
HTx	Heart Transplant
IABP	Intra-aortic balloon pump
ICER	Incremental Cost Effectiveness Ratio
ICU	Intensive Care Unit



LoS	Length of Stay
LVAD	Left Ventricular Assist Device
LYG	Life Years Gained
MA	Meta Analysis
MICU	Mobile intensive care unit
NHDI	National Institute for Health and Disability Insurance
OR	Odds Ratio
PaCO ₂	Arterial Partial Pressure of Carbon Dioxide
PECLA	Pumpless extracorporeal lung assist
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RD	Royal decree
RCT	Randomized controlled trial
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SOFA	Sequential Organ Failure Assessment
SR	Systematic review
VA-ECMO	Veno-arterial Extracorporeal membrane oxygenation
VAD	Ventricular assist device
VV-ECMO	Veno-venous Extracorporeal membrane oxygenation



■ SCIENTIFIC REPORT

1 INTRODUCTION AND SCOPE

1.1 Basic description of ECMO

Extracorporeal membrane oxygenation (ECMO), is part of the so called extracorporeal life support (ECLS) techniques that are used to temporarily provide cardiac and/or respiratory support to patients whose heart and lungs are unable to ensure an adequate amount of gas exchange (respiratory failure) and/or deliver oxygen to the human tissues (haemodynamic or circulatory failure).¹

It is a lifesaving technique that can be used both in adults and children (most often in neonates with severe cardiopulmonary problems at birth). It is considered when the patient's condition is potentially reversible but temporarily unresponsive to conventional management. Hence, ECMO allows to stabilize patients with respiratory and/or circulatory failure until the situation is resolved (bridge to recovery) or until lung or heart transplantation is performed (bridge to transplant). However, due to its potential complications and the underlying condition of the patient, it is associated with high mortality and morbidity.¹⁻⁴

Briefly, ECMO is a mechanical device withdrawing deoxygenated blood from the venous system through a drainage cannula and pumping it through a gas-exchange membrane (oxygenator) where gas exchanges occur (oxygenation and carbon dioxide removal). The blood is afterwards pumped back into the venous (veno-venous ECMO) or arterial (veno-arterial ECMO) circulation through a reinfusion cannula. The choice of ECMO configuration (veno-venous or veno-arterial), depends on the need for haemodynamic or respiratory support. Veno-venous ECMO (VV-ECMO) compensates failing lungs while veno-arterial ECMO (VA-ECMO) provides both respiratory and circulatory support (See below in section 1.3.1 for more details).³

ECMO has become increasingly used over the past decades to support patients with cardio-respiratory failure. The international voluntary registry held by the Extracorporeal Life Support Organization (ELSO) has shown that the number of ECMO centers has been increasing in the last decade (See below in section 1.4).⁵ Currently 166 913 patients have been recorded in the



ELSO registry including 88 104 adult patients. Furthermore, ECMO has been largely used since the beginning of the SARS-CoV-2 pandemic.

1.2 History

ECMO derives from the 'heart-lung machine' used in open-heart surgery and was developed by John Gibbon.^{4, 6, 7} His device allowed the first successful cardiac operation in the 1950s by oxygenating blood during cardiopulmonary bypass. Subsequently, C. Walton Lillehei and Richard De Wall further clinically developed the techniques of oxygenation (bubble oxygenator). Afterwards, many further developments on those machines evolved to the current ECMO techniques. One of the main improvement was the synthesis of silicone rubber in 1957 by Kammermeyer, which provided a strong enough material to withstand hydrostatic pressure, while being permeable to gas transfer.⁷

J. Donald Hill reported the first use of ECMO outside the operating room. A patient with a post-traumatic acute respiratory syndrome, who survived after being supported by VA-ECMO for 75 hours.⁶

Concurrently, Robert Bartlett was the first to implement ECMO in neonates and children for cardiac surgery. Later, in 1975 he successfully used ECMO in a newborn with respiratory failure due to meconium aspiration.⁶

The first controlled trial, conducted on patients with respiratory failure, was published in 1979 by Warren M. Zapol. This trial, that compared VA-ECMO versus standard therapy, showed a poor survival (approximately 10%), and no difference between groups^a. Thereby, clinicians were reluctant to use ECMO in adult patients for many years.^{4, 6, 7} Nevertheless, paediatric centres kept on using ECMO, encouraged by successes in paediatric populations.⁶

^a There are several criticisms of this trial: patients were mechanically ventilated for a long time before being enrolled; inclusion of highly critical patients; the

Progressively, technological improvements led to the development of more efficient and less invasive devices (informally called 'ECMO generation v2.0').

In 2009, two events contributed to the expansion of ECMO use:

- The Influenza H1N1 pandemic, in the course of which VV-ECMO was largely used for patients with respiratory failure.^{6, 8}
- The publication of the CESAR trial (Conventional ventilatory Support versus Extracorporeal membrane Oxygenation for Severe Adult Respiratory Failure), a study conducted in the UK which showed that transferring patients with ARDS to a single reference centre performing ECMO led to better outcomes.⁹

Gradually, the use of ECMO has spread in many centres and its indications have extended to include new ones such as cardiac arrest, collapse due to pulmonary embolism, intoxications, drowning, etc,...

Belgium has experienced a similar increase of ECMO utilisation over the past decade, which came associated to an increase in expenditure.¹⁰

1.3 ECMO techniques

1.3.1 Configurations of ECMO

An exhaustive description of ECMO configurations and devices (membrane, centrifugal pumps, heat exchangers, biocompatibility, ...) is beyond the scope of this report (an illustration of the device is given in Appendix 1.1). Briefly, the configuration of the ECMO circuit and cannulation strategy depends on the organ needed to be supported.

There are two basically different ECMO techniques, i.e. veno-venous (VV) and veno-arterial (VA) ECMO^b. VA-ECMO is used for cardiac, with or

use of multiple centres in which ECMO had not been performed prior to the trial; use of VA ECMO for all patients, while some only required VV-ECMO

^b VAV and VVA cannulation are not covered in this report.



without respiratory failure, while VV-ECMO is used for respiratory failure. The blood is drained from the venous system through a drainage cannula and is returned to the venous (VV-ECMO) or the arterial (VA-ECMO) system after gas exchange occurred in the gas-membrane exchanger. VV-ECMO ensures only blood oxygenation and decarboxylation (carbone dioxide removal) in case of respiratory failure (with preserved cardiac function), whereas VA-ECMO provides gas exchange and circulatory support.¹¹ For a schematic overview see Figure 1.

- In VV-ECMO configuration, blood is classically drained from the right atrium or the inferior vena cava via the placement of the cannula from the femoral vessels, and re-infused via the cannula inserted in right internal jugular vein and reaching the right atrium (See Figure 1). However, depending on specific circumstances, exact placement and type of cannulae may vary anatomically^a. A double cannulation can be avoided by the use of single double-lumen cannulae rather than two single-lumen cannulae. It allows the drainage and reinfusion through the same catheter and is also inserted in the jugular vein. This configuration allows a better mobility for the patient and preserves the other vascular accesses^b. The costs of this type of cannula are higher.^{11, 12}
- In the VA configuration, the draining cannula is usually placed in the femoral vein, and an arterial cannula is most often placed into the femoral artery for infusion (See Figure 1). Depending on clinical circumstances, the exact placement and type of the cannula may also vary anatomically.

The cannulation is usually performed peripherally (through a percutaneous puncture with ultrasound-guiding) by using femoral internal jugular or subclavian/axillary vessels (See Appendix 1.2) but can also be performed centrally (See Appendix 1.3). The latter, requires chest opening by sternotomy, and is performed during surgery. The main advantages of this approach are good drainage and reliable return to the proximal aorta. It is nevertheless, associated with higher risk of bleeding, infection and thrombosis within the pulmonary circulation (in VA configuration).¹¹

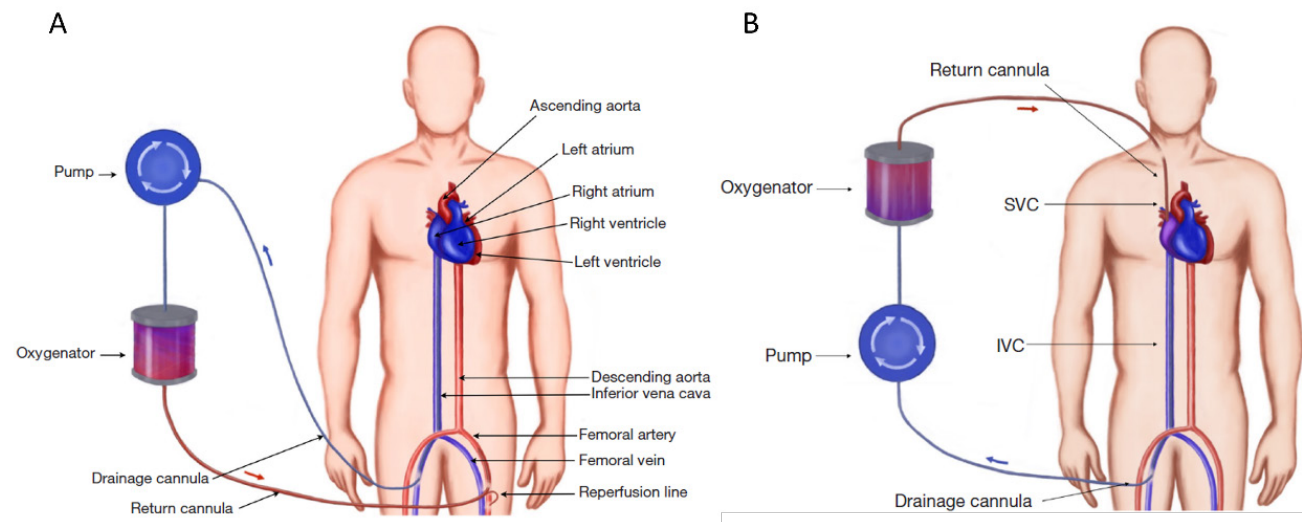
^a In different configurations, blood can be drained from the jugular vessels and re-infused in the femoral vein, or drained from the femoral vein and re-infused in the contra-lateral femoral vein. This configuration is associated with a major drawback called recirculation and corresponding to the withdrawing of re-

infused oxygenated blood by the drainage cannula without passing through the systemic circulation, which decreases the efficiency of ECMO.^{12,13}

^b In such a configuration, the cannula size constraint may limit ECMO flow and subsequently oxygenation capacity.



Figure 1 – Schematic representation of VA (A) and VV-ECMO (B)¹¹



Legend: IVC: inferior vena cava; SVC: superior vena cava



1.3.2 Indications of ECMO

Guidelines that describe the indications and practice of ECMO have been published by the Extracorporeal Life Support Organisation (ELSO)^{a,5}. Criteria for the initiation of ECMO include overall severe cardiac or pulmonary failure that is unresponsive to conventional treatment.^{b,c} This definition can be applied to several cardiopulmonary critical conditions. Cardiac arrest refractory to conventional cardiopulmonary resuscitation (CPR) is also included in these indications.

The list of potential indications is growing but the appropriateness of such growth is much debated in the literature, given the lack of high quality trials supporting ECMO's benefits on extended outcomes (See Chapter 4). The international organization ELSO has suggested patient care practice guidelines for several indications, which are publicly accessible.¹³⁻¹⁵ Therefore, the development of clinical guidelines on the use of ECMO was excluded from the scope of our research. Table 1, offers a full list of indications proposed by ELSO at the time of writing this report.

It is important to highlight that ECMO is not a therapeutic technique aiming to heal the underlying pathological condition. It is a supportive modality providing time for recovery or for the team to stabilize the patient and consider a long-term solution such as the placement of a durable heart ventricular assist device, or heart or lung transplantation (if the patient fulfils the eligibility criteria to be transplanted).³ As such, ECMO is considered as

a temporary supportive technique used as a bridge to recovery, or bridge to transplant^d.

Since the onset of COVID-19, VV-ECMO is also used to support COVID-19 patients with associated refractory ARDS when mechanical ventilation is not sufficient to sustain blood oxygenation levels.¹⁶ ELSO created a register for COVID-19 patients who required ECMO.^e

Table 1 – Indications of ECMO^{5, 13-15}

Type of support	Indications
Respiratory VV-ECMO	• Acute respiratory distress syndrome (e.g., viral/bacterial pneumonia and aspiration) • Acute eosinophilic pneumonia • Diffuse alveolar hemorrhage or pulmonary hemorrhage • Severe asthma • Thoracic trauma (e.g., traumatic lung injury and severe pulmonary contusion) • Severe inhalational injury • Large bronchopleural fistula • Peri-lung transplant (e.g., primary lung graft dysfunction and bridge to transplant)
Cardiac VA-ECMO	Several causes of cardiogenic shock: • Acute myocardial infarction

^a <https://www.elso.org>

^b For VV-ECMO, conventional therapy is standard mechanical ventilation. Criteria required for ECMO are hypoxemic respiratory failure (defined as the ratio between arterial partial pressure in oxygen (PaO₂)/ inspired fraction of oxygen (FiO₂) < 80 mm Hg), after optimal medical management, including, in the absence of contraindications, a trial of prone positioning; hypercapnic respiratory failure (arterial pH < 7.25), despite optimal conventional mechanical ventilation (respiratory rate 35/minute pm and plateau pressure ≤ 30 cm H₂O).¹⁶

^c Regarding VA-ECMO, conventional therapy for cardiac arrest is cardiopulmonary resuscitation (CPR). Conventional management of cardiogenic shock (circulatory failure) include pharmacological (inotropic agents), fluid therapy and potentially intra-aortic balloon pump.¹⁵

^d Bridge to bridge: when ECMO allows to stabilize the patient until a durable mechanical heart support is performed.

^e <https://www.elso.org/Registry/FullCOVID-19RegistryDashboard.aspx>



	• Myocarditis • Post-heart transplant • Post cardiectomy • Hypothermia with cardiac instability • Arrhythmic storm • Back-up support for cardiological interventional procedures • Sepsis • Drug intoxication • Post-partum acute cardiomyopathy • Trauma • Massive pulmonary embolism
VA-ECMO for cardiac arrest (extracorporeal cardiopulmonary resuscitation)	Cardiac arrest refractory to conventional CPR (strict inclusion criteria for eligibility of ECMO ¹⁴)

1.3.3 Complications of ECMO

The use of ECMO is associated with a wide range of inherent complications, some of which can be damaging or life-threatening. Complications can be associated with the invasiveness of the technique or related to the anticoagulation therapy that is needed during the use of ECMO.² Cannulation can give rise to several problems such as bleeding, limb ischaemia^a, thrombosis, vessel perforations, infection or air embolism. Vascular complications occur frequently. A recent meta-analysis (MA) (6 583 patients; 47 studies) estimated that vascular complications occurred in approximately one third of patients (pooled estimate: 29.5%; 95%CI: 23.6%-35.9%) with both types of ECMO.¹⁷ Patients who underwent VA- ECMO had a higher incidence rate of vascular complications compared with those on VV-ECMO (OR: 2.39; 95%CI: 1.87-2.96). Among them, significant bleeding occurred in 15.4% (95%CI: 8.6%-23.7%). Haemorrhages (cerebral,

^a Since the cannula is inserted in the vessels of the leg, blood flow for leg vascularization may be compromised

digestive, and pulmonary), stroke, arrhythmia, haemolysis, renal failure and infections were also reported complications in patients on ECMO.¹⁻³

A registry of ECMO-related complications is held by ELSO (See below).^b

1.4 Reported outcomes and registries

1.4.1 Background

Most clinical studies report on survival. Other studies also report on specific outcomes, such as complications. A few studies also focus on patient's Quality of Life (QoL) after the intervention.

Apart from specific studies there are also patient registries. National registries have been set up in countries that structurally organised the ECMO services according to the approach of centralisation, such as The UK or Italy, (See Chapter 5). These registries are not publicly available.

Besides, the registry from the Extracorporeal Life Support Organization (ELSO)^c is an international voluntary registry that exists since 1989. Data from the ELSO registry are publicly available (upon request) for research purposes.

1.4.2 The ELSO registry

1.4.2.1 Brief history of the ELSO registry

In the 1980s, an alliance between centres performing ECMO in the US was created and led to the establishment of ELSO, in 1989, under the guidance of a steering committee led by Robert Bartlett.⁶

The purpose of ELSO was to gather clinicians, scientists and healthcare administrators to pool data on the use of ECMO, compare outcomes and

^b https://www.elseo.org/Portals/0/Files/Reports/2020_January/Complication%20Trend%20Report%20January%202020.pdf

^c www.elseo.org



discuss its optimal use and implementation.¹⁸ In the 1990s, the initiative extended to Europe and the European Extracorporeal Life Support Organization was funded^a. Later, centres from Asia, Latin-America and Africa joined the organization^b.

As stated in their mission statement^c, the purpose of ELSO is to provide support to centres developing ECMO through knowledge development (guidelines), continuing education, and data collection through a large standardized international registry.¹⁸ Five committees cover the different aspects of the activities of ELSO including: registry^d, publication, quality, education, technology & innovation.^e

Other initiatives of ELSO include the publication of textbooks such as the 'Red Book', that summarizes the current knowledge on several topics related to ECMO.^f

1.4.2.2 ELSO data

The ELSO registry captures data on several clinical aspects for all age groups (neonates, children and adults). Data have been collected from the beginning of the ELSO registry, up to date. They include measurements before ECMO support, such as blood gases, ventilator settings or

haemodynamic variables, and after the initiation of ECMO. Complications of ECMO are collected using predefined categorized lists.⁶ Outcome data are also registered. Data acquisition is performed through a secured online web application.^g

The registry has now more than 160 000 patients^h throughout all continents. It is now available through a live dashboard with the possibility to select data for specific patient populations (location, period, type of ECMO)ⁱ.¹⁹

Short annual summaries of these data are published on their website (i.e. 'International Summary' reports). These short reports offer an overview on outcomes (i.e. survival) and the number of centres and ECMO runs (See Figure 2). A centre-specific report including the data of the centre is also distributed to each respective participating centre.⁶ A list of publications that used the ELSO registry is also available on their website.^j

The main weakness of this registry is that it is based on a voluntary approach and it therefore, does not appraise extensively the use of ECMO at an international level. Furthermore, outcome data are rather limited including only basic outcome data including for instance reason for discontinuation, organ failures and discharge information.⁶

^a EURO-ELSO is now the European branch of ELSO.

^b ELSO Latin-America; APELSO: Asia-Pacific ELSO; SWAAC ELSO: South and West Asia and South Africa ELSO

^c <https://www.else.org/AboutUs/Charter.aspx>

^d The Registry Committee is made up 3 sub-committees: Registry Development Committee (improvement of the efficiency and validity of data collection); Scientific Oversight Committee (promotion of scientific research); Registry Quality Committee (tool development and refining for data collection).

^e <https://www.else.org/AboutUs/Committees.aspx>

^f <https://www.else.org/Publications.aspx>

^g <https://registry.else.org/#/login>

^h Registry dashboard consulted on 21th February 2022

ⁱ <https://www.else.org/Registry/ELSQLiveRegistryDashboard.aspx>

^j <https://www.else.org/Registry/RegistryPublications.aspx>

**Figure 2 – Extracorporeal support registry report for the year 2021⁵****ECLS Registry Report**

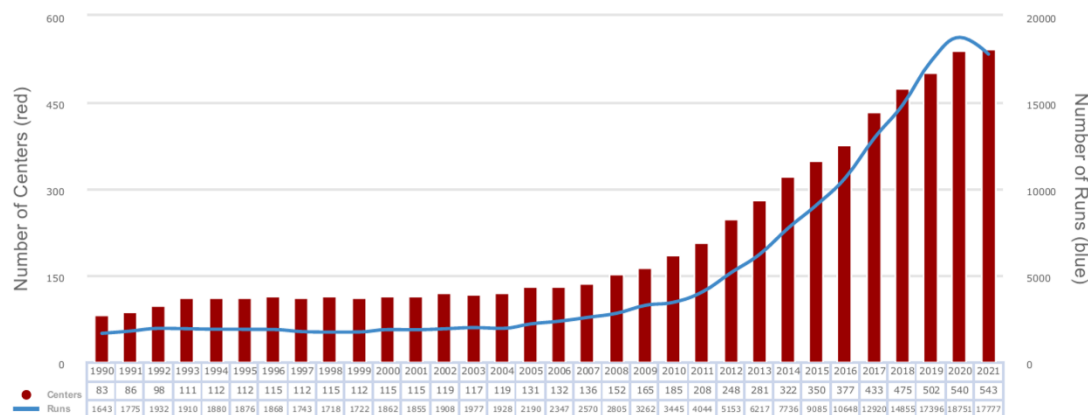
International Summary

April, 2022

Report data through 2021

Extracorporeal Life Support Organization
3001 Miller Rd
Ann Arbor, MI 48103 USA**Overall Outcomes**

	Total Runs	Survived ECLS	Survived to DC or Transfer
Adult			
Pulmonary	42,702	28,419	66%
Cardiac	38,610	23,086	59%
ECPR	11,761	4,934	41%
Pediatric			
Pulmonary	11,850	8,621	72%
Cardiac	15,083	10,949	72%
ECPR	6,131	3,614	58%
Neonatal			
Pulmonary	34,151	29,899	87%
Cardiac	10,127	7,000	69%
ECPR	2,420	1,685	69%
Total	172,835	118,207	68%

Centers by year

1.5 Scope of this report

ECMO is a complex lifesaving procedure administered to critically-ill patients at high risk of dying. This is a high risk technique per se which can give rise to severe potential complications.

As previously mentioned, in recent years, there has been a sharp increase in the use of ECMO in Belgium and internationally (even more so under the current COVID-19 pandemic).

The equipment and necessary disposables linked to its use are expensive, and patients on ECMO require close monitoring, which make it a resource-intensive life-support approach. All of these factors, highlight the importance

of securing a good training, organisation and use of ECMO in Belgium, which could facilitate patient access, while ensuring quality of care.

The key aspects of our research were:

- To offer a comprehensive review of the effectiveness (survival rates) and safety (complications) of ECMO, based on the existing literature, and determine the factors that may have an impact on outcomes, such as the centralisation of ECMO services.
- To provide an overview on availability and use of ECMO in Belgium, and compare existing reimbursement rates to real costs.



- To discuss alternative organisation and funding in other European countries by means of an international comparison.

To restrict the scope of this report, the analysis was limited to the adult population. The age threshold for the “adult” population in this report will be specified in each chapter depending on the sources consulted and the analysis performed (eg. 15+ for the analysis of Belgian data and 18+ for the review of the literature).

Based on the results obtained via this research, draft recommendations to the Belgian authorities on how to optimise the use of ECMO in the country would be drafted.

It is worth noting that the ethical considerations that ECMO entails, along with patients and family members perspectives will be touched upon in a specific section of this report, but that the involvement of patients in this research or the performance of a detailed critical analysis on these aspect were considered to be beyond the scope of this report. Such aspects are thought to deserve a wider debate that should not be limited to the use of ECMO, but to the use of any potentially lifesaving therapies or procedures, for severely ill ICU patients, who are unable to grant their consent.

2 USE OF ECMO IN BELGIUM: PERIOD 2016-2019

2.1 Data source

All general hospitals are required to submit twice a year a large set of data on all inpatient and day-care hospital stays and emergency room contacts: the Minimal Hospital Data (MZG – RHM defined in the [Royal Decree of 27-04-2007](#)) which are transferred to the Federal Public Service for Health, Food Chain Safety and Environment. Available variables pertain, a. o. to demographics, clinical information as diagnoses, comorbidities, treatments and complications, length of stay and discharge status.

The **Hospital Billing Data** contains all reimbursements by the RIZIV – INAMI related to hospitals stays: fees charged by physicians and other healthcare providers, pharmaceuticals and implants, per admission and per diem lump sum payments, etc. In practice, hospitals bill the patient's sickness fund for the provided services for the part covered by the health insurance on the basis of the RIZIV – INAMI nomenclature. A subset of the data available on these transactions is passed yearly from the sickness funds to the RIZIV – INAMI: Anonymous Hospital Stays (AZV – SHA) for inpatient stays and Anonymous Day-care Stays (ADH – HJA) for day-care stays.

The “[Technical Cell – Cellule Technique](#)” (TCT) created in [Law of 29 April 1996 on social provisions](#), is a common service of the [RIZIV–INAMI](#) and [FPS Public Health, Safety of the Food Chain and Environment](#). Its mission is to collect, link, validate, anonymize data relating to hospitals. Each year, the TCT links the Minimal Hospital to the Hospital Billing data for the analysis of links between the expenditures of the health care insurance and the treated condition and for the elaboration of financing rules, accreditation standards and quality conditions in the context of an effective health policy. Access of the KCE to the Technical Cell data is regulated in the same law as the Technical Cell. The data originating from the TCT will be referred to as TCT data.



2.2 Methods

All hospitalizations during which ECMO was used were selected from the TCT data 2016-2019 when at least one of the codes listed in Table 2 was registered.

Table 2 – List of selection codes

Code	Short label	NL – FR label
RIZIV – INAMI billing code/fee (day care – inpatient)		
229670 – 229681	ECMO, patient < 2 years	Plaatsen, functioneel opstarten en wegnamen van een extra corporele membraan oxygenatie (ECMO) systeem, inclusief de eventuele heringrepen, voor langdurige ventilatie en circulatie assistentie, ongeacht de toegangsweg tijdens de eerste twee levensjaren – Placement, démarrage fonctionnel et retrait d'un système d'oxygénation extracorporelle sur membrane (ECMO), en ce compris les réinterventions éventuelles, en vue d'une ventilation et d'une assistance circulatoire de longue durée quelle que soit la voie d'accès au cours des deux premières années de vie
229692 – 229703	ECMO, Veno-Arterial (VA)	Plaatsen, functioneel opstarten en wegnamen van een extra corporele membraan oxygenatie (ECMO) systeem, inclusief de eventuele heringrepen, voor langdurige ventilatie- en circulatieassistentie, met gecombineerde arterio-veneuze toegangsweg – Placement, démarrage fonctionnel et retrait d'un système d'oxygénation extracorporelle sur membrane (ECMO), en ce compris les réinterventions éventuelles, en vue d'une assistance ventilatoire et circulatoire de longue durée, avec voie d'accès artério-veineuse combinée
229714 – 229725	ECMO, Veno-Venous (VV)	Plaatsen, functioneel opstarten en wegnamen van een extra corporele membraan oxygenatie (ECMO) systeem, inclusief de eventuele heringrepen, voor langdurige ventilatieassistentie, met uitsluitend veneuze toegangsweg – Placement, démarrage fonctionnel et retrait d'un système d'oxygénation extracorporelle sur membrane (ECMO), en ce compris les réinterventions éventuelles, en vue d'une assistance ventilatoire de longue durée, avec voie d'accès veineuse exclusivement
211363 – 211783	ECMO surveillance day1	Toezicht op de extracorporele membraanoxygenatie (ECMO) buiten de heekundige bewerkingen : De eerste dag – Surveillance de l'oxygénation membraneuse extracorporelle (ECMO) en dehors des interventions chirurgicales : Le premier jour
211385 –	ECMO surveillance days 2-5	Toezicht op de extracorporele membraanoxygenatie (ECMO) buiten de heekundige bewerkingen : De tweede, derde, vierde en vijfde dag, per dag –



211805		Surveillance de l'oxygénation membraneuse extracorporelle (ECMO) en dehors des interventions chirurgicales : Les deuxième, troisième, quatrième et cinquième jours, par jour
159913 – 159924	ECMO placement material, patient <2 years	Geheel van het gebruiksmateriaal en implanteerbaar materiaal voor het plaatsen van een extra corporele membraan oxygenatie (ECMO) systeem met een diffusie membraan voor langdurige ventilatie en circulatie assistentie ongeacht de toegangsweg, tot de tweede verjaardag – Ensemble du matériel de consommation et du matériel implantable pour le placement d'un système d'oxygénateur extracorporel à membrane (ECMO) avec une membrane de diffusion, pour ventilation de longue durée et assistance circulatoire quel que soit la voie d'accès, jusqu'au deuxième anniversaire
159935 – 159946	ECMO placement material	Geheel van het gebruiksmateriaal en implanteerbaar materiaal voor het plaatsen van een extra corporele membraan oxygenatie (ECMO) systeem met een diffusie membraan voor langdurige ventilatie en circulatie assistentie ongeacht de toegangsweg, vanaf de tweede verjaardag – Ensemble du matériel de consommation et du matériel implantable pour le placement d'un système d'oxygénateur extracorporel à membrane (ECMO) avec une membrane de diffusion, pour ventilation de longue durée et assistance circulatoire quel que soit la voie d'accès, à partir du deuxième anniversaire

ICD-10-PCS* code

5A15223 Extracorporeal Membrane Oxygenation, Continuous

* *International Classification of Diseases, Tenth Revision, Procedure Coding System.*

A global description of the exhaustive use of ECMO in Belgium included all hospitalizations, independently of patients' age. As the present study focusses on the adult population, analyses were further run on patients aged 15 years or older.

Generally, only coupled stays (with information both recorded in the MZG – RHM and in the Hospital Billing Data) controlled and validated by the Technical Cell control process were retained except for the global ECMO utilization description and the clinical profile of the patients. In these cases, hospitalizations with only the ICD-10-PCS code but no ECMO fee registered were included, to take into account patients not covered by the national health insurance. These were excluded from the survival analysis, and also from the cost analysis, as the fee codes were used to classify the stays by type of ECMO. A type "VA" was attributed as soon as a VA-ECMO

placement was performed. Hence a patient with both a VV and a VA placement was classified as "VA".

Table 3 summarizes the filters applied by type of analysis.

**Table 3 – Selection applied per analysis type**

Analysis	Selection criteria
Global description of ECMO use	Valid coupled stays(*) with ECMO ICD-10-PCS code OR ECMO fee
Adult clinical information	Valid coupled stays(*) with ECMO ICD-10-PCS code, > 15 years
Adult clinical information by type of ECMO	Valid coupled stays with ECMO ICD-10-PCS code, AND ECMO fee, > 15 years
Adult demographics, qualification provider and survival analysis by type of ECMO	Valid coupled stays with ECMO fee, > 15 years
Adult costs	Valid coupled stays with ECMO ICD-10-PCS code AND ECMO fee AND ECMO surveillance fee AND ECMO material fee, > 15 years

(*) Including stays with ICD-10-PCS code ECMO with no claim not covered by the national health insurance.

The 7, 30 and 90 days mortality rates were estimated using the Kaplan-Meier method, taking into account the numerous right-censored data as patient health status information is lost after discharge. A Cox proportional hazards (PH) regression was used to verify if there was any difference in risk of mortality between patients undergoing VA or VV-ECMO, correcting for age and gender.

Analyses were performed using SAS software™ (SAS/BASE, SAS/STAT and SAS/GRAPH), version 9.4 M5 for Microsoft Windows.

2.3 Results

The final extraction was done using three lists of codes (Table 4), for a total of 2311 stays and 2901 ECMO (billing code or ICD) over the 2016-2019 period. Details are presented in Appendix 2.1.



Table 4 – Extraction results

	Number of Stays				
	2016	2017	2018	2019	TOTAL
Billing codes					
ECMO intervention or surveillance (PREST)	567	548	596	600	2311
INTERVENTION	465	469	507	524	1965
229670 – 229681 ECMO in patients < 2 years	25	21	30	26	102
229692 – 229703 ECMO, Veno-Arterial (VA)	409	356	345	357	1467
229714 – 229725 ECMO, Veno-Veinous (VV)	32	94	134	145	405
SURVEILLANCE	500	489	520	537	2046
211363– 211783 ECMO surveillance day1	486	486	514	531	2017
211385 – 211805 ECMO surveillance days 2-5	442	422	463	470	1797
ECMO material (IMPLANT)	486	508	571	576	2141
159913 – 159924 ECMO placement material <2 years	25	24	37	29	115
159935 – 159946 ECMO placement material	461	484	534	547	2026
ICD-10-PCS code					
5A15223 Extracorporeal Membrane Oxygenation, Continuous	486	530	609	625	2250
Billing codes or ICD	681	677	775	768	2901



2.3.1 Distribution of overall patient population (n=2543)

Table 5 shows the distribution of patient stays with an ECMO per region and number and type of hospitals performing ECMO. As is commonly observed

for procedures, Brussels is draining patients from the two other regions, due to the high number of academic hospitals.

Table 5 – Distribution of patient population (total)

	2016		2017		2018		2019		TOTAL	
Number of stays, Belgium	589	(100%)	602	(100%)	669	(100%)	683	(100%)	2543	(100%)
Brussels	255	(43.3%)	216	(35.9%)	208	(31.1%)	211	(30.9%)	890	(35.0%)
Flanders	228	(38.7%)	217	(36.0%)	301	(45.0%)	298	(43.6%)	1044	(41.1%)
Wallonia	106	(18.0%)	169	(28.1%)	160	(23.9%)	174	(25.5%)	609	(23.9%)
Academic hospitals	310	(52.6%)	290	(48.2%)	335	(50.1%)	307	(44.9%)	1242	(48.8%)
General hospitals with academic beds	138	(23.4%)	172	(28.6%)	186	(27.8%)	204	(29.9%)	700	(27.5%)
General hospitals	141	(23.9%)	140	(23.3%)	148	(22.1%)	172	(25.2%)	601	(23.6%)
Number of hospitals, Belgium	42		40		44		47		61 (/100 acute hospitals)*	
Brussels	9		10		10		11		12 (11)*	
Flanders	19		16		19		18		27 (54)*	
Wallonia	14		14		15		18		22 (35)*	
Academic hospitals	7		7		7		7		7 (7)*	
General hospitals with academic beds	11		10		12		13		13 (17)*	
General hospitals	24		23		25		27		41 (76)*	

* Number of acute hospitals constant over the 4 years. Acute hospital is defined as having C, D, CD, E and/or M beds.



Every year, ECMO is used in about 40-45% of the Belgian hospitals which means every academic hospital, about 65% of general hospitals with an academic component and about a third of other general hospitals. On average, almost every hospital used it at least once in Brussels while a third of Flemish hospitals and about 40% of Walloon hospitals have recourse to ECMO yearly.

Table 6 – ECMO stays characteristics per hospital and per year

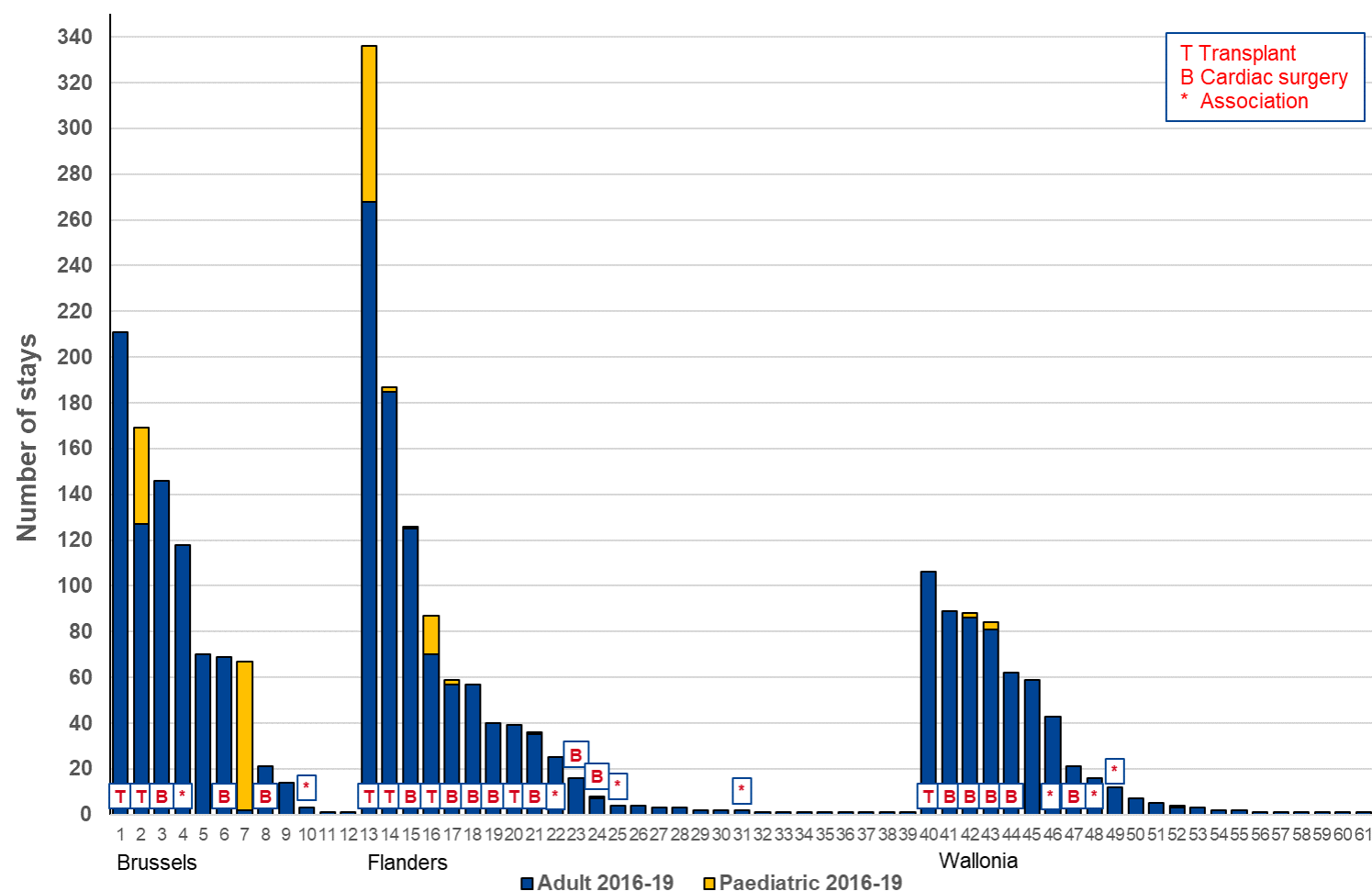
Year / Nb of stays	N hosp	Mean	Std	Min	P25	Median	P75	Max
2016	42	14.0	17.6	1	2	6.5	17	74
2017	40	15.1	16.2	1	2	8.5	23	70
2018	44	15.2	19.9	1	2	8	21	109
2019	47	14.5	18.1	1	1	7	22	83
2016-2019	61	41.7	63.9	1	1	8	62	336

There are between 42 and 47 hospitals practising ECMO each year over the analysed period, and the mean number of stays per hospitals is between 14.0 and 15.2 (Table 6).

Figure 3 shows the number of stays with ECMO per type of hospital per region over the period, with a distinction between adult and paediatric patients: few hospitals have paediatric ECMO stays (12 of them for 2016-2019, with only 4 hospitals having more than 3 paediatric cases). As the scope of this report is on adult, paediatric stays will be further excluded in this chapter.



Figure 3 – Number of stays per hospital by type of hospital



T: site performing heart transplant; B: site with cardiac surgery programme (B3); *: site either with cardiac surgery programme or associated with another hospital with a cardiac surgery programme (see RD 15 July 2004 [\[FR/NL\]](#) and RD 25 April 1997 [\[FR/NL\]](#)).



2.3.2 Geographic distribution of adult population according to ECMO type (n=1801)

In this section, the focus has been put at the hospital site level (=campus) since some hospitals offer ECMO on several sites. Figures from ECMO billing for TCT data match the data from INAMI – RIZIV N documents (there are a few more ECMOs billed in the N documents due to the exclusion of paediatric stays in the TCT data analysis, some stays could not be coupled and thus were not included and the fact that regularisations occur in N documents and not for TCT data).

2.3.2.1 Number of ECMOs per site

To be able to locate the exact site where the ECMO was placed in a hospital, it is necessary to use the placement date registered for the ECMO fee (sometimes in 2015). Overall, the 1801 stays counted 1854 ECMO placements (counting 1 ECMO per placement day, or 2 if both types were billed on the same day (which happened only in two occasions)).

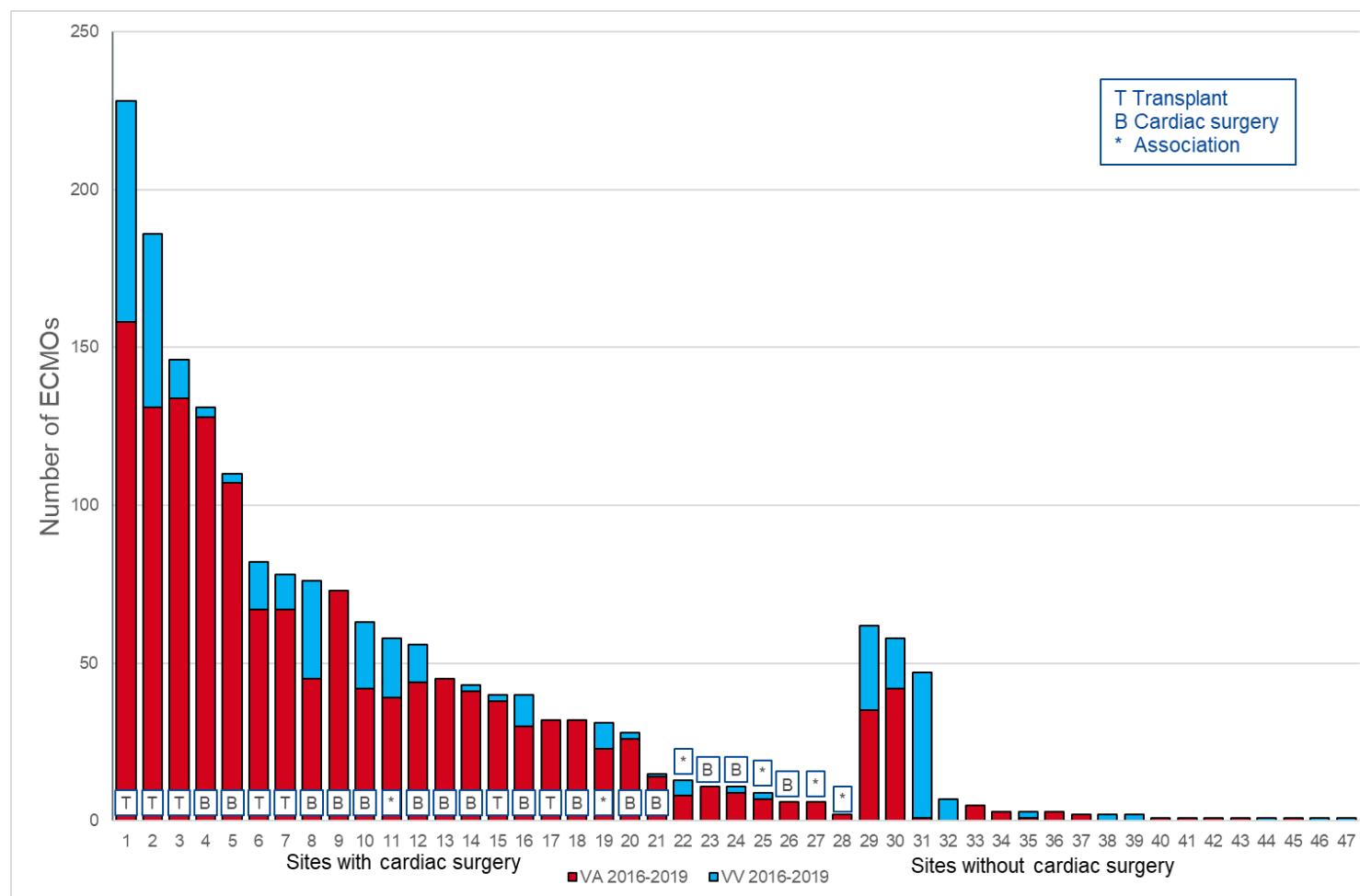
In 1706 or 94.7% of the stays, the hospitalisation took place at the same site. Two sites were visited for 89 stays (4.9%) and 3 for 6 stays (0.3%). The most extreme case showed 25 site changes, between the 3 sites of a same hospital, during a 123 days hospitalisation.

After identification of the site where each placement took place, 16 placements were done on the day the patient was transferred from one site to another. No information is available about any mobile ECMO team. The site with a cardiac care programme was defined as the placement site.

The calculation per site shows that there are more ECMOs placed outside any cardiac care programmes than when sites are aggregated into hospitals.



Figure 4 – Number of ECMOs per hospital sites



The legend VA & VV 2016-2019 still refers to TCT data registration years, although a few ECMOs were placed at the end of 2015. Sites 1-28 offer cardiac surgery (on site or through association with another hospital or site); sites 29-47 do not. T: site performing heart transplant; B: site with cardiac surgery programme (B3); *: site either with cardiac surgery programme or associated with another hospital with a cardiac surgery programme (see RD 15 July 2004 [\[FR/NL\]](#) and RD 25 April 1997 [\[FR/NL\]](#)).

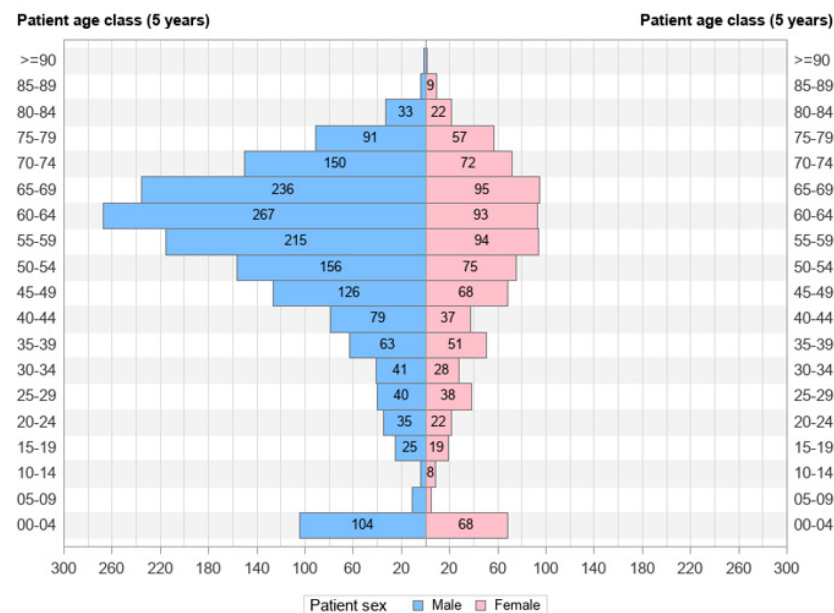

Table 7 – Number of ECMO per type of cardiac care programme hospitals (2016-2019)

Cardiac Care Programme	VA			VV			ALL		
	N site	N ECMO	%Stays	N ECMO	N ECMO	%Stays	N site	N ECMO	%Stays
Heart (& lung) transplantation (T)	7	627	42.9%	6	165	42.2%	7	792	42.7%
Cardiac surgery (B3)	15	653	44.7%	10	87	22.3%	15	740	39.9%
Hospital associations	6	85	5.8%	4	34	8.7%	6	119	6.4%
Others	13	97	6.6%	10	105	26.9%	19	202	10.9%
Total	41	1462	100%	30	391	100%	47	1853	100%

2.3.3 Demographics

2.3.3.1 Whole population (n=2543)

About two thirds of the ECMO adult patients are men, the most common age group is 55-69 years old for both genders (Figure 5). Population pyramids by year and complementary tables are presented in Appendix 2.2.

**Figure 5 – ECMO patient population pyramid (2016-2019)**

2.3.3.2 Adult population with ECMO fee^a (n=1801)

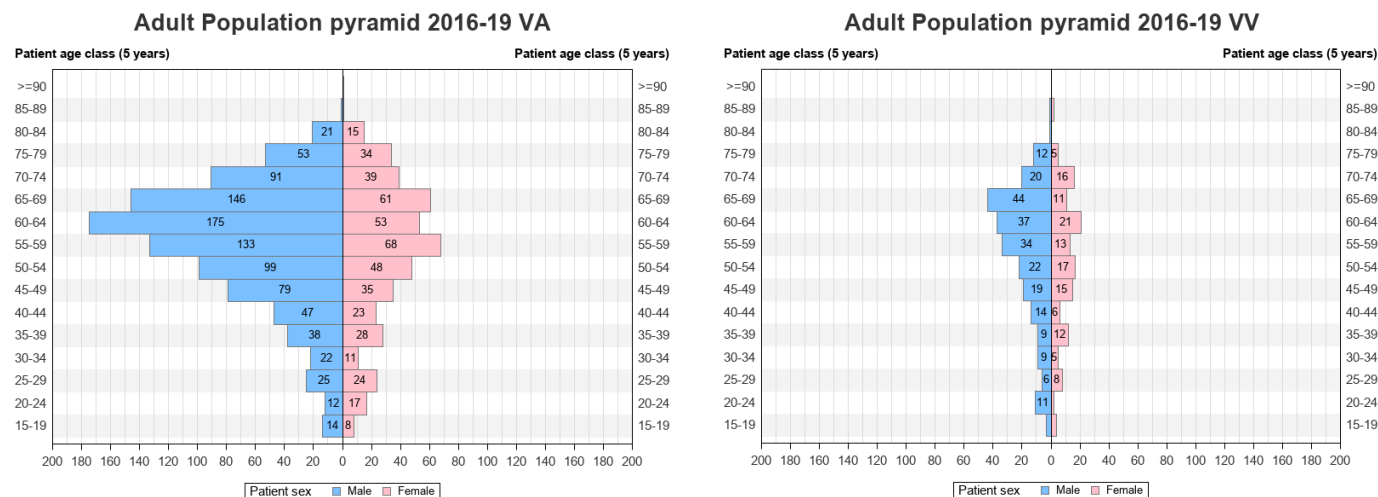
The decreasing share of female patients can be observed in Veno-arterial (VA) approach of ECMO (except for 2019), the same trend is generally observed for the Veno-venous (VV) approach of ECMO (except in 2018).

^a In the following pages, ECMO fee refers to the ECMO intervention: placing, launching and possibly re-intervention of ECMO by a physician, excluding the surveillance or material billing codes.


Table 8 – Number of ECMO fees by type

Frequency Col Pct	Veno-arterial					Veno-venous				
	2016	2017	2018	2019	Total	2016	2017	2018	2019	Total
Male	255 65.4%	235 67.5%	237 70.5%	229 65.8%	956 67.2%	16 57.1%	58 63.7%	76 60.3%	92 68.7%	242 63.8%
Female	135 34.6%	113 32.5%	99 29.5%	119 34.2%	466 32.8%	12 42.9%	33 36.3%	50 39.7%	42 31.3%	137 36.2%
Total	390	348	336	348	1422	28	91	126	134	379

The difference by gender is illustrated by age group for both types of ECMO in Figure 6.

Figure 6 – Patient population pyramid for VA and VV-ECMO




2.3.4 Clinical information

2.3.4.1 Adult population with ICD-10-PCS ECMO procedure (n=1996)

When looking at Major Diagnostic Categories (MDCs), 93% of the stays concerns MDC 004 (tracheostomy with mechanical ventilation 96+ hours with extensive procedure or ECMO), the other 7% are transplants. These data are managed by the FPS Public Health and are the only data offering a global view of all Belgian hospitals and patients, which explains our choice of data over hospitals registries (which are also not centralised).

The most frequent principal diagnoses are presented in Table 9, grouped by 3-digit categories.

Table 9 – Top 20 Principal diagnosis (first 3 digits from ICD-10 codes): veno-arterial (VA) and): veno-venous (VV) approach

Rank	3-digits	Principal diagnosis VA	N-stays	%
1	I21	ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction	235	20.4
2	I25	Chronic ischemic heart disease	75	6.5
3	I50	Heart failure	61	5.3
4	I35	Nonrheumatic aortic valve disorders	36	3.1
5	A41	Other sepsis	34	3.0
6	J44	Other chronic obstructive pulmonary disease	33	2.9
7	I26	Pulmonary embolism	33	2.9
8	I34	Nonrheumatic mitral valve disorders	32	2.8
9	I49	Other cardiac arrhythmias	29	2.5
10	I71	Aortic aneurysm and dissection	28	2.4
11	T82	Complications of cardiac and vascular prosthetic devices, implants and grafts	27	2.3
12	I46	Cardiac arrest	21	1.8



13	I42	Cardiomyopathy	18	1.6
14	J84	Other interstitial pulmonary diseases	18	1.6
15	J15	Bacterial pneumonia, not elsewhere classified	17	1.5
16	I47	Paroxysmal tachycardia	16	1.4
17	I27	Other pulmonary heart diseases	13	1.1
18	J80	Acute respiratory distress syndrome	13	1.1
19	J09	Influenza due to certain identified influenza viruses	12	1.0
20	J10	Influenza due to other identified influenza virus	12	1.0
154 other 3 digits ICD10-CM diagnosis codes			389	33.8
Total VA stays			1152	100%
Rank	3-digits Principal diagnosis VV		N stays	%
1	A41	Other sepsis	25	8.1
2	J44	Other chronic obstructive pulmonary disease	23	7.5
3	J18	Pneumonia, unspecified organism	13	4.2
4	A40	Streptococcal sepsis	10	3.3
5	I21	ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction	10	3.3
6	J09	Influenza due to certain identified influenza viruses	10	3.3
7	J80	Acute respiratory distress syndrome	10	3.3
8	J96	Respiratory failure, not elsewhere classified	10	3.3
9	C34	Malignant neoplasm of bronchus and lung	9	2.9
10	J84	Other interstitial pulmonary diseases	9	2.9
11	A48	Other bacterial diseases, not elsewhere classified	8	2.6
12	T86	Complications of transplanted organs and tissue	8	2.6
13	J10	Influenza due to other identified influenza virus	6	2.0
14	J15	Bacterial pneumonia, not elsewhere classified	6	2.0
15	I34	Nonrheumatic mitral valve disorders	5	1.6



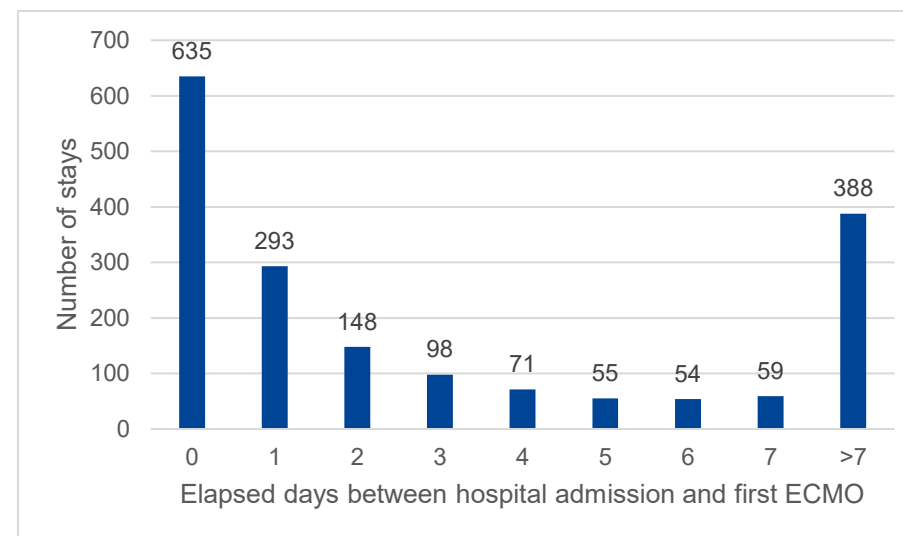
16	J13	Pneumonia due to <i>Streptococcus pneumoniae</i>	5	1.6
17	S06	Intracranial injury	5	1.6
18	B44	Aspergillosis	4	1.3
19	I35	Nonrheumatic aortic valve disorders	4	1.3
20	I50	Heart failure	4	1.3
88 other 3 digits ICD10-CM diagnosis codes			123	40.1
Total VV stays			307	100%

2.3.5 Intervention billing: timing (n=1801)

The timing is defined as the difference of days between the first ECMO date and the admission day.

Figure 7 illustrates the delay between hospital admission^a and first ECMO date. One third of the patients were put on ECMO on the day of admission. The median time before patients were put on ECMO was 1 day. Among patients with a VA ECMO initiated on day 1, 17.7% of them underwent a cardiac surgery on the same day, suggesting that the VA ECMO was placed in the operating theatre. It is worth noting that the administrative nature of these data did not allow to appraise the clinical course of patients who required to be supported by ECMO. For instance, for the use of VV-ECMO, the length of mechanical ventilation before ECMO could not be determined. The interpretation of the timing of ECMO placement is then limited without more clinical data available. .

Figure 7 – Elapsed days between hospital admission and first ECMO



^a N.B.: this is not the admission day in intensive care unit.



2.3.6 Blood products consumption (n=1801)

Respectively 85.5% and 88.7% of the patients having a VA and VV-ECMO received some blood products (cf. extraction criteria) during their stay (details by billing code are presented in Appendix 2.3).

2.3.7 Survival analysis (n=1319)

2.3.7.1 Length of stay, discharge status and transfers between hospitals

For adult patients, the proportion of patients who have been transferred from another hospital before getting the ECMO is 21.2% (Table 10).

The length of hospital stay was shorter in case of VA-ECMO (n=1422, mean=29.8 days, median=15 days) compared to VV-ECMO (n=379, mean=39.3 days, median=25 days) due to an higher in-hospital mortality: the percentage of patients discharged alive from the hospital was 37.6% for VA-ECMO patients and 41.7% for VV-ECMO patients. When discharged alive, 27.6% of the VA-ECMO patients were transferred to another hospital vs 24.1% VV-ECMO patients.

Table 10 – Origin of adult patients getting ECMO by type of hospital (2016-2019)

Arrival → Origin ↓	ECMO hospital			TOTAL
	University	General with academic character	Other General	
University Hospital	14	7	13	34 1.5%
General Hospital (no split avail.)	350	74	38	462 19.8%
Other (community*)	749	610	483	1842 78.8%
Total	1113 47.6%	691 29.6%	534 22.8%	2338 100%

2.3.7.2 Estimated survival probability

The 7, 30 and 90 days in-hospital mortality rate can be estimated using the Kaplan-Meier method, taking into account the numerous right-censored data as patient health status information is lost after discharge (see Table 11). Stays were reasonably assumed to belong to different patients; the survival being theoretically underestimated in case of readmissions of the same patients. The mortality of VA-ECMO patients reaches 29.4% at 7 days (95% CI: 27.1%, 31.9%), 55.2% at 30 days (95%CI: 52.3%, 57.9%) and 70.8% at 90 days (95%CI: 67.8%, 73.7%). The rates are lower in VV-ECMO patients, reaching 16.9% at 7 days (95%CI: 13.5%, 21.1%), 45.6% at 30 days (95%CI: 40.5%, 50.9%) and 67.5% at 90 days (95%CI: 61.5%, 73.4%). The difference at 90 days is not statistically significant considering the numbers of patients still hospitalized.

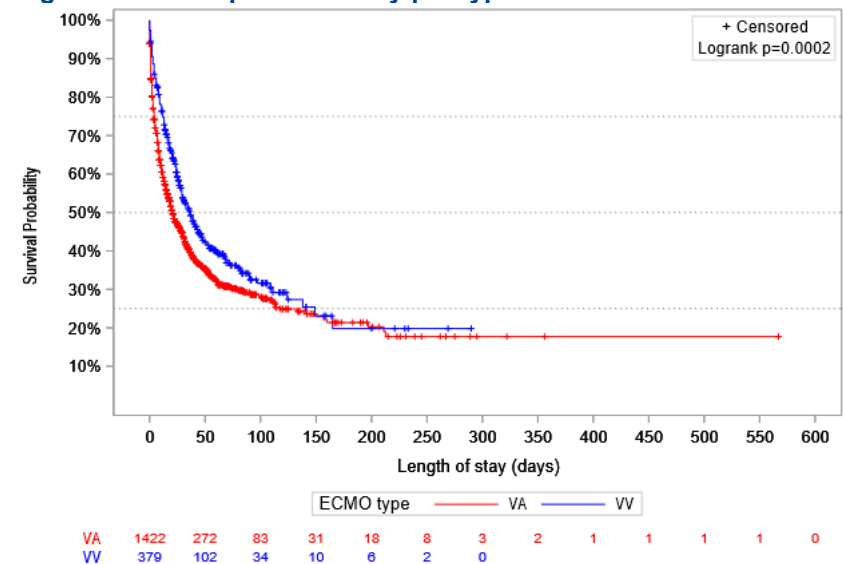


Table 11 – In-hospital mortality per type of ECMO

Type of ECMO	Nb stays	Events	Censored (discharged alive)	Percent Censored	Survival rate		
					7 days (95% CI)	30 days (95% CI)	90 days (95% CI)
VA	1422	888	534	37.6	0.706 (0.681-0.729)	0.448 (0.421-0.475)	0.292 (0.263-0.322)
VV	379	221	158	41.7	0.831 (0.789-0.865)	0.544 (0.491-0.595)	0.325 (0.266-0.385)
TOTAL	1801	1109	692				

A quart of the VA patients died in the 4 days after admission (95%CI: 3, 5) versus 12 days for VV-ECMO patients (95%CI: 9, 16). The median survival time of the VA-ECMO patients was 21 days after admission (95% CI: 19, 25) compared to 37 days for VV-ECMO patients (95%CI: 29, 45).

Figure 8 – In-hospital mortality per type of ECMO



Legend: Kaplan-Meier plot with number of subjects at risk and log-rank test comparing survival trends.



Survival probability curves are pictured per type of ECMO in Figure 8. Both curves of the survival functions show a steep slope in the first days (weeks) of admission which are the most critical for the patients. The chart shows also that the assumption of proportional hazards is not strictly respected as the VA survival probability curve crosses the VV curve. Between days 149 and 150 and between days 165 and 211 the instant survival probability is worse for VV patients than VA patients hospitalized that long. Nevertheless the numbers of stays with such long lengths of stay are small and events are scarce.

Unfortunately, studying the global survival (in- and outside hospital) would have required to link the TCT database with other sources. This was not possible in the time frame of the present project. Similarly, no calculation was made to estimate the survival after ECMO initiation. Instead, the time to event is the length of stay, calculated from the day of admission until hospital discharge. This covers the treatment and management by the hospital staff including the decision to put the patient under ECMO at a certain moment in time.

2.3.7.3 Adjusted hazard ratios

A Cox proportional hazards (PH) regression was used to verify if there were differences in risks of mortality between the patients receiving one of the two types of device, taking sex and age into account. Type of ECMO and sex were introduced in the model as dichotomous variables (type="VA" and sex=0 for male as reference) and age introduced in 3 classes (1: below 50 years, 2: 50-65 years, 3: above 65 years)^a. VA patients are expected to have a higher risk of mortality while age obviously influences mortality and is not equally distributed between VA and VV patients.

Both covariates Severity of illness (SOI) and Risk of mortality (ROM) appearing intuitively as regressors of choice were estimated to be biased and could not be used to adjust the hazard ratios. The numbers of stays in the two first levels were very small but mostly the clinical information on

patients dying very shortly after admission was probably biased towards a minimal encoding (less diagnostic examinations, less complications during the hospitalization). Whatever the ECMO type, patients with a minor severity of illness (=1) deceased earlier (day of admission or 2 days later) than those with a moderate risk (=2).

Table 12 – Hazard ratio adjusted and unadjusted

Variable	Regressions with 1 covariate		Full model	
	p-value	Unadjusted Hazard ratio (95% CI)	p-value	Adjusted Hazard ratio (95% CI)
VA-ECMO vs VV-ECMO	0.0002	1.319 (1.138 – 1.528)	0.0004	1.308 (1.128 – 1.517)
Male vs Female	0.0009	1.243 (1.094 – 1.413)	0.0024	1.220 (1.073 – 1.387)
Age class 1 (<50) vs 3	<.0001	0.649 (0.555 – 0.760)	<.0001	0.668 (0.571 – 0.783)
Age class 2 (50-65) vs 3	<.0001	0.754 (0.658 – 0.864)	<.0001	0.747 (0.652 – 0.855)

Results can be found in Table 12. The hazard ratio for ECMO type adjusted by age and sex shows that VA-ECMO patients have a 30.8% higher risk of mortality than VV patients (95%CI: 12.8% - 51.7%). This risk would have been slightly overestimated if we did not take sex and age into account: 31.9% (95%CI: 13.8% - 52.8%) as these characteristics also predict mortality. Male patients present a 22% higher risk than female patients and the oldest age class (>65 years) has a 33.2% (95%CI: 21.7%, 42.9%) and a 25.3% (95%CI: 14.5%, 34.8%) higher risk of mortality than the younger one and the middle-aged one respectively. Obviously, we cannot say that VA-ECMO leads to more mortality than VV-ECMO as they are not

^a 50 and 65 were chosen as inner bounds, more easily readable than the tertiles 52 and 64 years, that lead to similar conclusions.

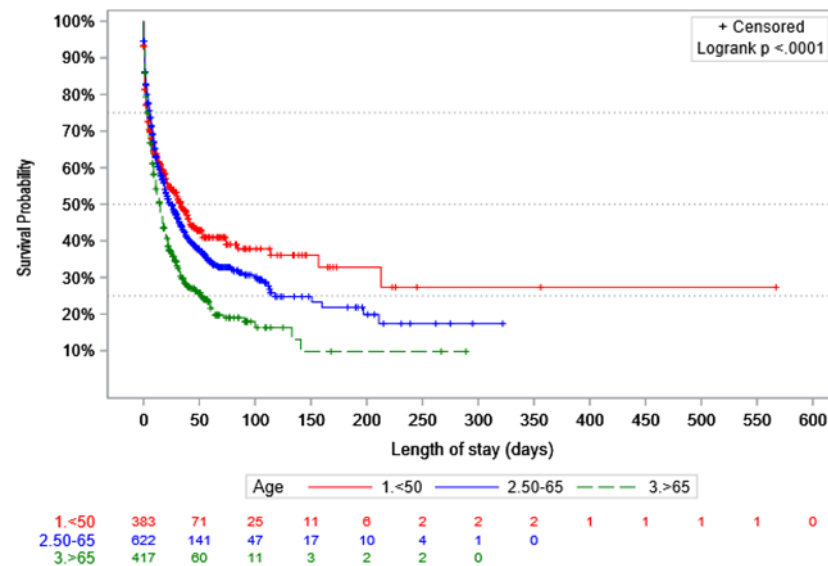


competing techniques administered to a randomized population. Here patient groups were different, they had indications that required one ECMO type in particular.

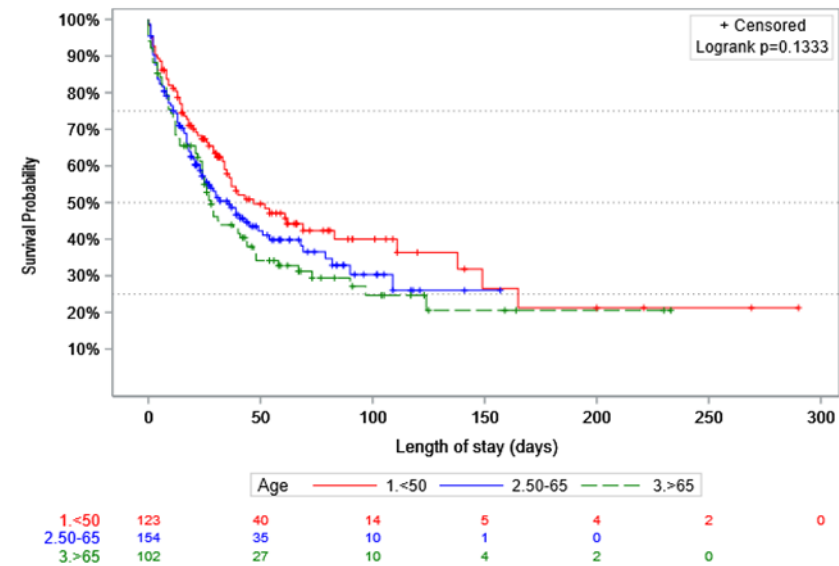
Figure 9a & b show that age seems to have a stronger association in patients with VA-ECMO than in those with VV-ECMO.

Figure 9 – In-hospital mortality according to age

a. Patients with VA-ECMO



b. Patients with VV-ECMO



Kaplan-Meier plots with number of subjects at risk and log-rank test comparing survival trends

2.4 Limitations

The current analysis has a number of limitations. The data source is exhaustive in terms of ECMO patients treated in Belgian hospitals, but the last available year is 2019 which is somewhat older and does not take into account possible changes effected by treating COVID-19 patients. The data

are collected for general and administrative purposes and not specifically for research on the use of ECMO, which brings a limitation to the extent of the information available. An example of this is that due to reimbursement rules, the length of monitoring of ECMO is unknown if beyond five days. Another example is the unavailability of confounding clinical factors to conduct a robust analysis of other factors than sex and age on the survival, or to study the relationship between hospital volume or hospital type on the outcome.



3 USE OF ECMO IN BELGIUM DURING SARS-COV-2 PANDEMIC: PERIOD 2020-2022

3.1 Data source

3.1.1 Clinical Hospital Surveillance (CHS)

Commissioned by the Risk Management Group and launched by Sciensano on the 14th of March 2020, the COVID-19 Clinical Hospital Survey (CHS) is a voluntary online registration^a of patients hospitalized with a confirmed COVID-19 infection in Belgian hospitals. Considering the scarcity of data at the beginning of the outbreak, this survey aims to study risk factors and outcomes of COVID-19 patients to identify severe risk groups and support health policy measures. The participation to the CHS is voluntary, but strongly recommended, for all general hospitals admitting confirmed COVID-19 inpatients. Since April 2020, beside public reporting on their website Sciensano transmitted regular reports based on the CHS to hospitals on patient characteristics and hospital evolution of COVID-19 patients to support their management.²⁰

Originally, individual inpatient characteristics were only registered by means of two forms, one at the time of admission and one at the time of discharge. Variables include age, sex, residence postcode, symptoms, comorbidities, diagnostic information, treatments received, complications, length of stay and discharge status. The variables collected at admission are based on the WHO case report form for COVID-19 supplemented by the input from hospital clinicians.²⁰ A form for patient data on possible stay in Intensive Care Units (ICU) was later introduced on the 14th of September 2020. The latter form collects information on ECMO/ECCO2R, ventilation, ICU treatments, ICU death, etc. Variables pertaining on ECMO/ECCO2R are ECMO duration and ECMO weaning.

Considering that the registration is not mandatory, the coverage of the patients with a confirmed COVID-19 infection reaches approximatively 60%. Details on ECMO/ECCO2R utilization are covered only from the introduction of the ICU form in September 2020, but some retrospective reporting was done.

3.2 Methods

The questions posed in CHS have changed over time. Up until the 18th of November 2021, a more extensive list of clinical information was collected. To increase response rate and reduce missing data, a number of questions was dropped. The sample available for analysis thus runs over two time periods:

1. Patients admitted between 11 March 2020 and 17 November 2021 for which the initially and extended list of questions are available. We'll refer to this period as the "2020–2021 period".
2. Patients admitted between 18 November 2021 and 20 February 2022 for which the reduced list of questions are available. We'll refer to this period as the "2022 period". If both the reduced period and this period are considered together, we'll refer to it as the "full period".

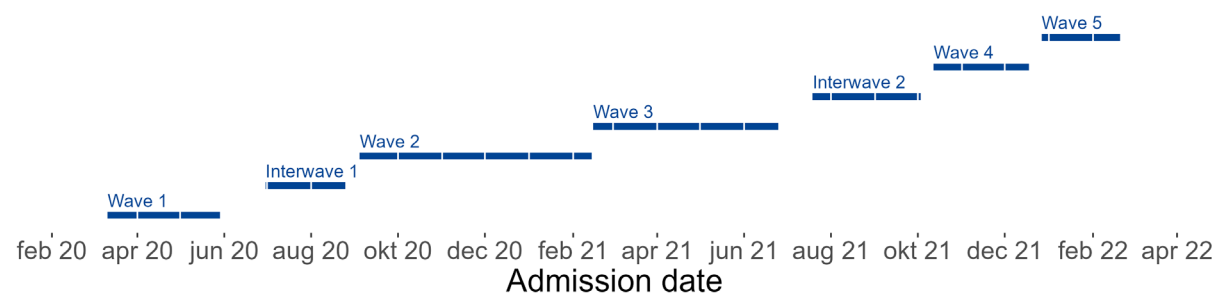
We choose to retain as much information as possible in the sample. As such, the total number of patients on ECMO can differ between descriptive analyses of different questions in the CHS. We choose this approach because of the reduced availability in time of some questions, but also because the response rate per question can vary substantially. We'll clearly indicate in each descriptive analysis the number of ECMO patients concerned and the time period, if it deviates from the default. For some questions in CHS, "unknown" is a possible answer aside from "yes" or "no". We consider not responding to the question also as "unknown" and have chosen not to distinguish between missing answer and "unknown" for the analysis, as the status of the patient on that particular question is not "yes" or "no" but unknown.

^a <https://covid19hosp.healthdata.be>



Sciensano uses waves to subdivide the time since the beginning of the COVID-19 pandemic based on the evolution of the incidence of cases, hospital admissions and decrease. Where possible, descriptive analysis are also presented by wave (see Figure 10).

Figure 10 – COVID-19 waves by hospital admission dates.



All analyses are descriptive in nature and are conducted with R^a version 4.1.2, with, aside from standard R packages, tidyverse, rio, lemon, geomtextpath, and RColorBrewer packages.

^a R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>.

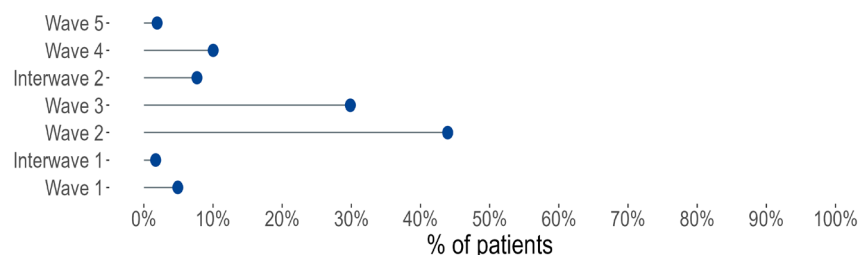


3.3 Results

3.3.1 Number of patients receiving ECMO

The CHS sample contains 469 patients receiving ECMO in the full period with 434 of them (92.5%) in the 2020–2021 period. Almost three-quarter of the patients receiving ECMO were admitted in the second or third wave (see Figure 11).

Figure 11 – Percentage of ECMO patients per COVID-19 wave.

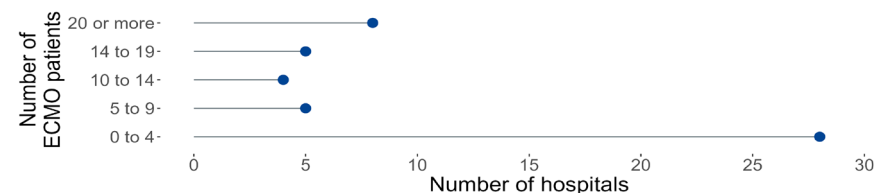


3.3.2 Patient and admission characteristics

3.3.2.1 Admission characteristics

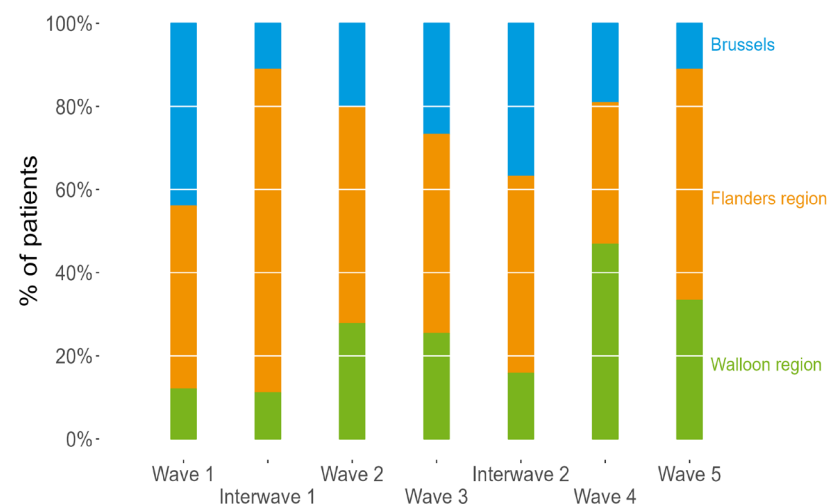
The CHS sample ECMO patients are admitted in 50 different hospitals over the full period. About half of the hospitals in the sample have less than five patients on ECMO during the full period, while eight hospitals have each over 20 ECMO patients (see Figure 12).

Figure 12 – Number of hospitals by category of number of ECMO patients.



Over the full available time period, 48.9% of patients received ECMO in a hospital in the Flanders region, 24.3% in a Brussels hospital and 26.8% in a hospital in the Walloon region. The proportion varies somewhat between waves (see Figure 13).

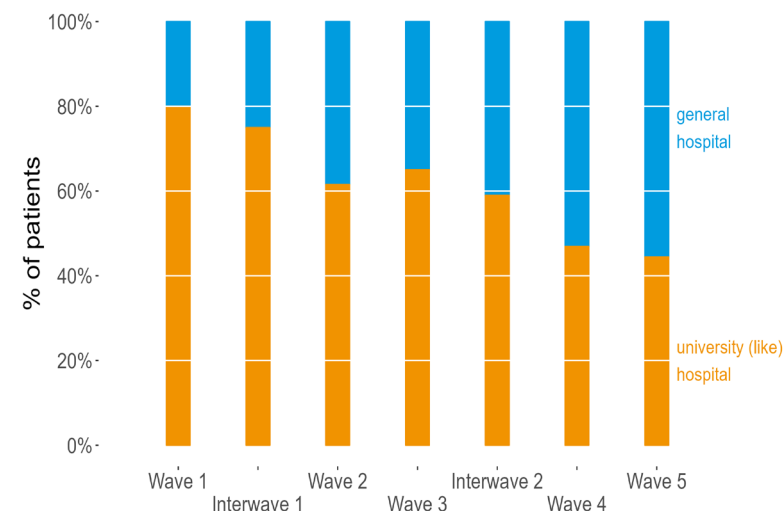
Figure 13 – Number of ECMO patients by hospital region and wave.



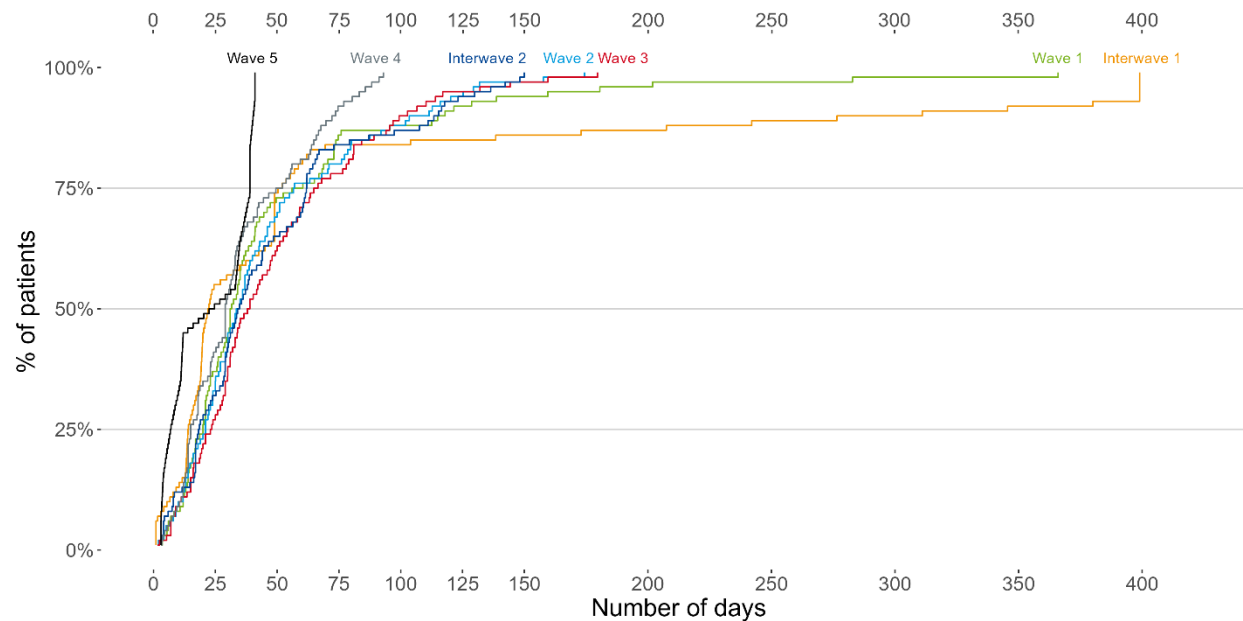


40% of patients receiving ECMO are transferred from another hospital, although not necessarily because of the need for ECMO. A majority of ECMO patients received ECMO in a university (32%) or university like hospital (30%), while the remaining patients received ECMO in a general hospital (38%). Over the course of the pandemic, general hospitals have proportionally started to treat more patients with ECMO (see Figure 14)

Figure 14 – Number of ECMO patients by hospital type and wave.



Half of the ECMO patients stay 33 days or less in the hospital with 10% staying longer than 97 days (median 33 days with IQR 40 days). The length of the hospital stay is fairly comparable between waves for the 75% of ECMO patients with the shortest lengths of stay (see Figure 15), except for the most recent Wave 5. Due to the recency of Waves 4 and 5, the 25% longest stays are relatively shorter than for the other waves.

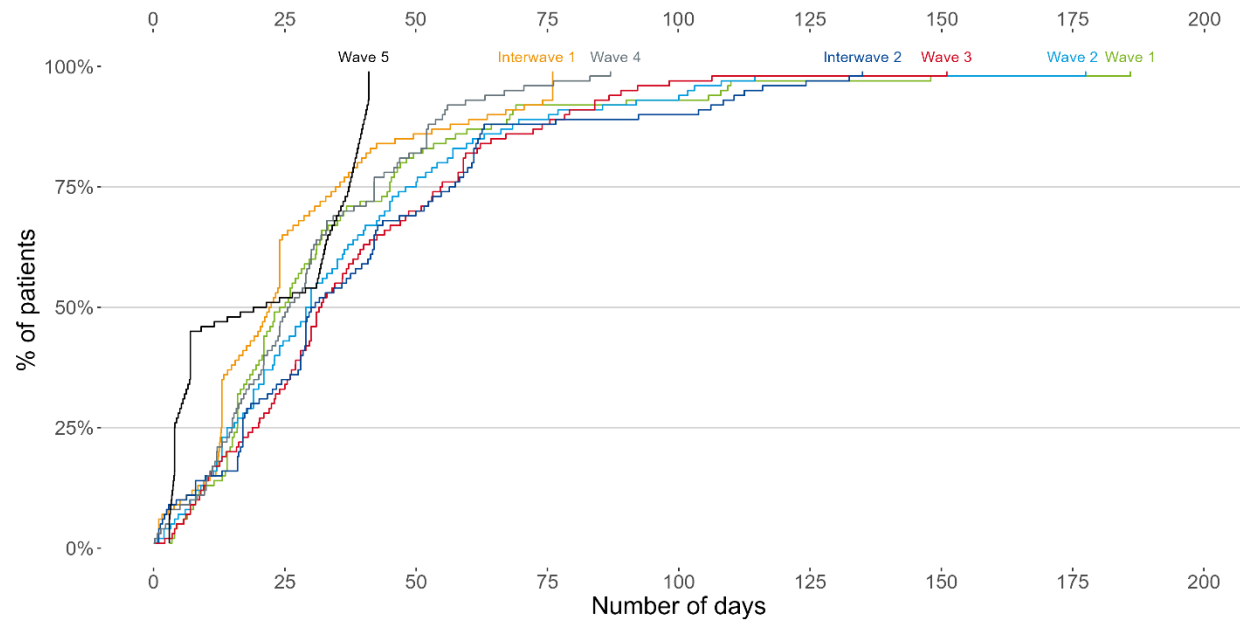
**Figure 15 – Cumulative percentage of ECMO patients by length of stay and wave.**

For 97.4% of ECMO patients in the full period, the length of stay in the intensive care unit (ICU) is available. Half of the ECMO patients stay 29 days or less in the ICU with 10% staying longer than 71 days (median 29 days with IQR 32 days). The length of the stay in the ICU is fairly comparable between waves for the 25% of ECMO patients with the shortest lengths of stay (see Figure 16), except for the most recent Wave 5. For the longer stays, more diversity exists between waves. For 93.7% of ECMO patients in the full period, the time between hospital admission and admission to the

ICU is available. 60% of ECMO patients admitted to the ICU do so on the same day of being admitted to the hospital, while for 10% of the ECMO patients, it takes 6 days or longer to be admitted to the ICU. For 98.7%, the remaining time in hospital after discharge from the ICU was available too. 67% of ECMO patients were discharged from the hospital on the same day as being discharged from the ICU. Most likely either because they died (see also the section on vital status below) or were transferred to another hospital.



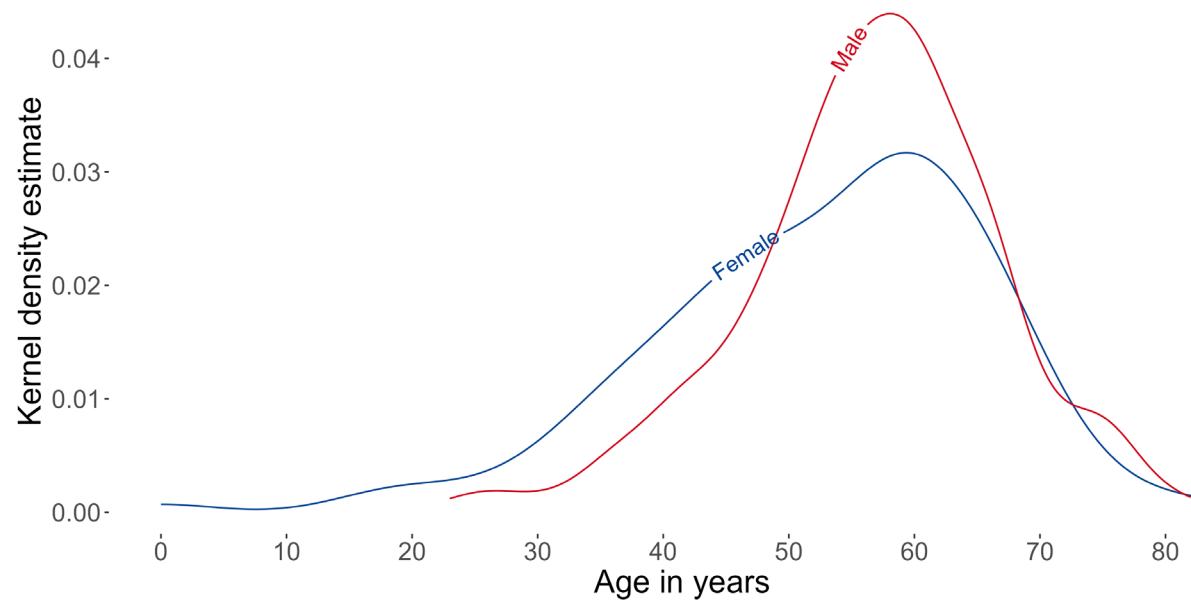
Figure 16 – Cumulative percentage of ECMO patients by length of stay in ICU and wave.



3.3.2.2 Age and sex

For 465 patients receiving ECMO (99.1%), age and sex information is available. Female patients account for 28% and are on average 52.6 years old (sd 13.4), while 72% of ECMO patients are male of on average 56.6 years old (sd 10.1). Median age is respectively 55 (IQR 17) and 57 (IQR 12). The age and sex distribution (see Figure 17) shows that there are overall younger female ECMO patients while male ECMO patients tend to be older.

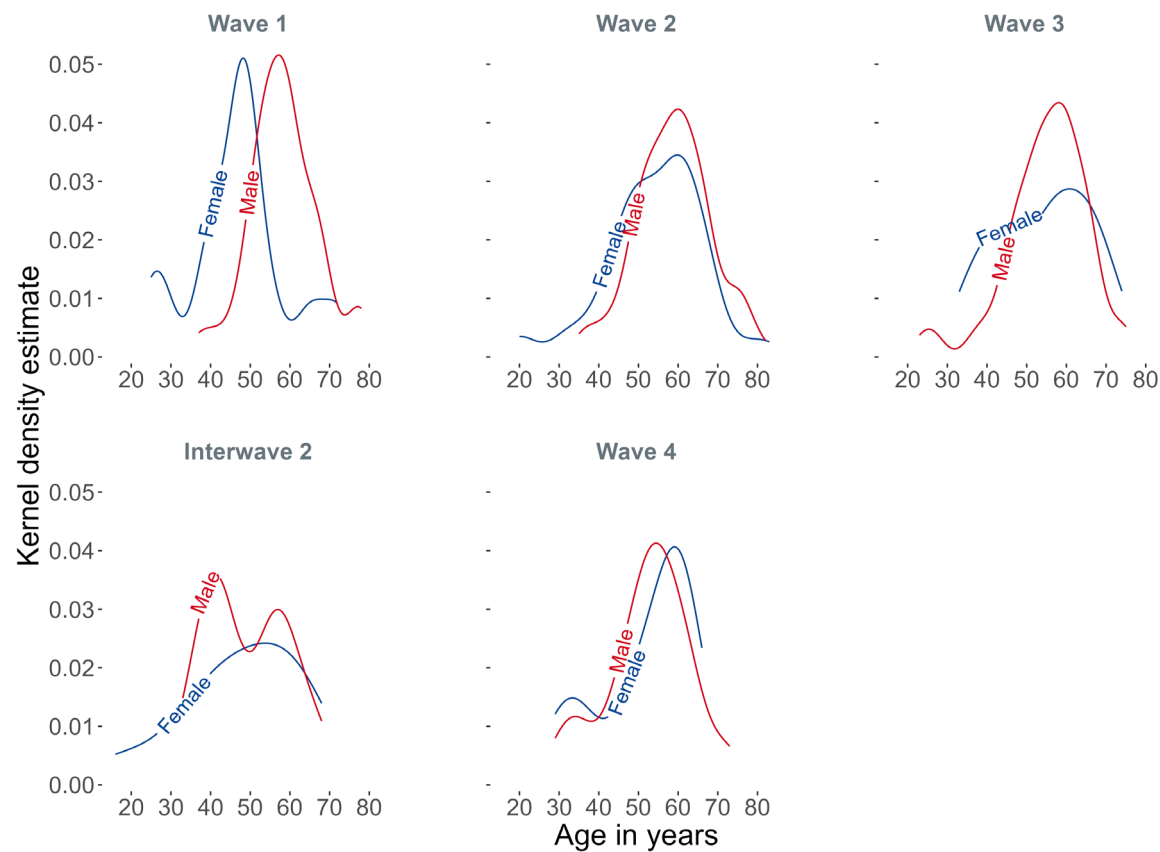
Figure 17 – Age distribution of ECMO patients by sex.



Age and sex patterns vary slightly over waves (see Figure 18). Female ECMO patients tend to be in general younger than male patients across wave up until the fourth wave, where the pattern is reversed. The age range for female patients widens for the second wave up until the fourth wave where the ranges become more similar again. Interwave 2 shows a somewhat atypical peak in number of male ECMO patients between 30 and 40 years old. Unfortunately, no other information is available to further explore this pattern.



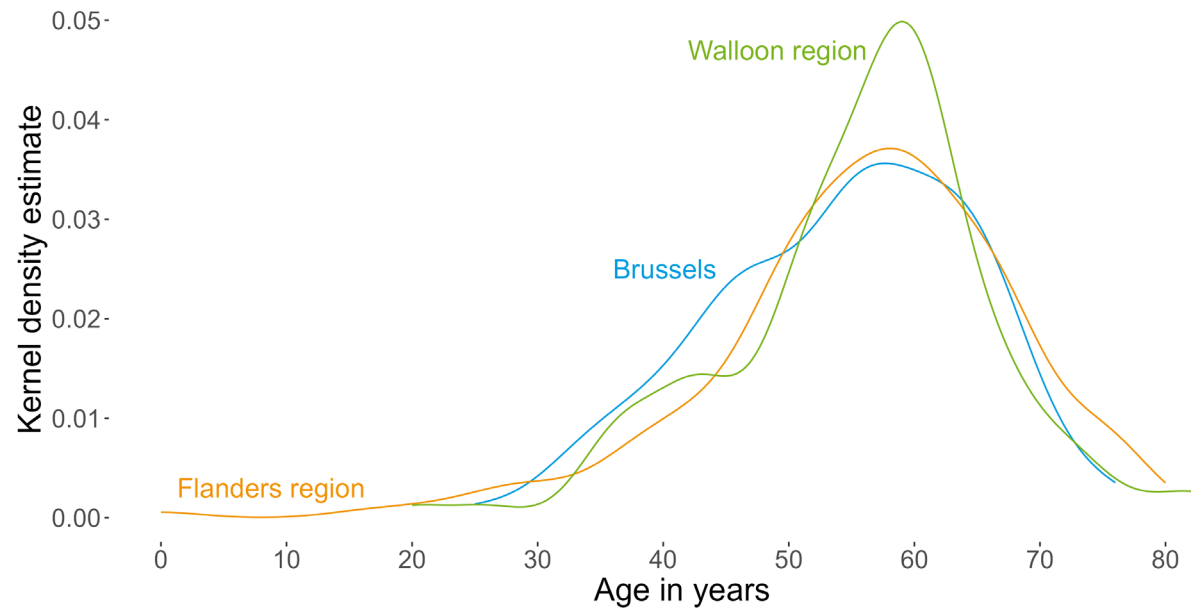
Figure 18 – Age distribution of ECMO patients by sex and wave (Interwave 1 and Wave 5 not shown due to less than five patients in at least one stratum).



ECMO patients treated in hospitals in the Walloon region have a higher concentration of 50 to 65 year old patients compared to the other regions (see Figure 19). Brussels has a larger group of younger patients between

30 and 50 while in the Flanders region, a larger group of patients over 70 is treated with ECMO.

Figure 19 – Age distribution of ECMO patients by hospital region.



ECMO patients that are transferred from other hospitals have a similar age distribution than patients not transferred (see Figure 20). University hospitals treat a larger proportion of younger patients with ECMO than university like or general hospitals, while general hospitals treat a larger proportion of older patients (see Figure 21).



Figure 20 – Age distribution of ECMO patients transferred from another hospital or not.

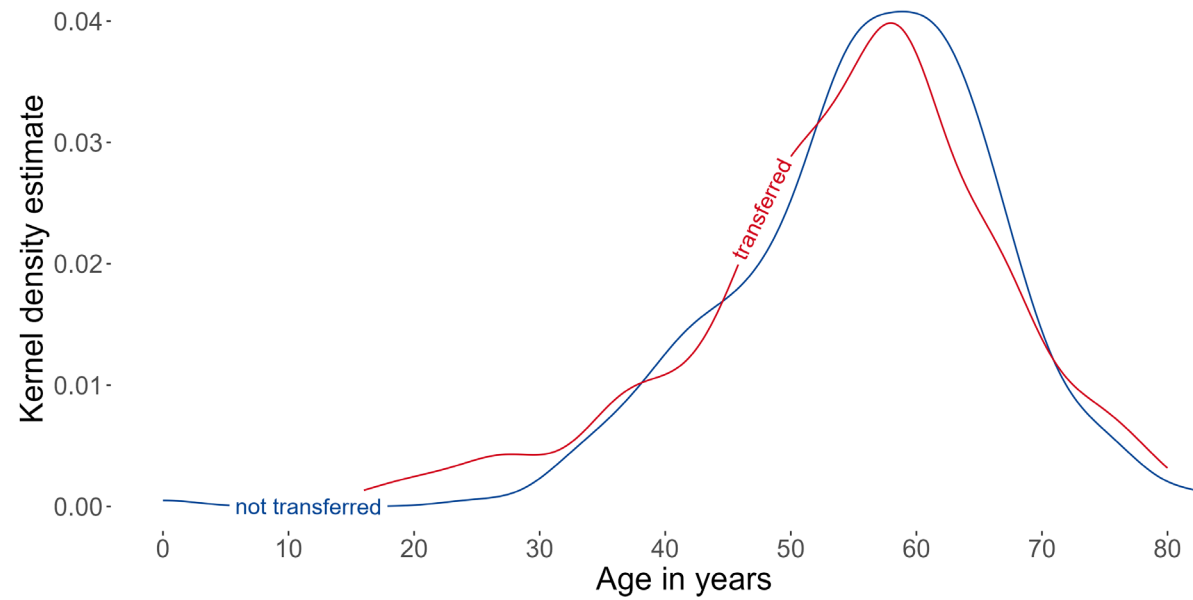
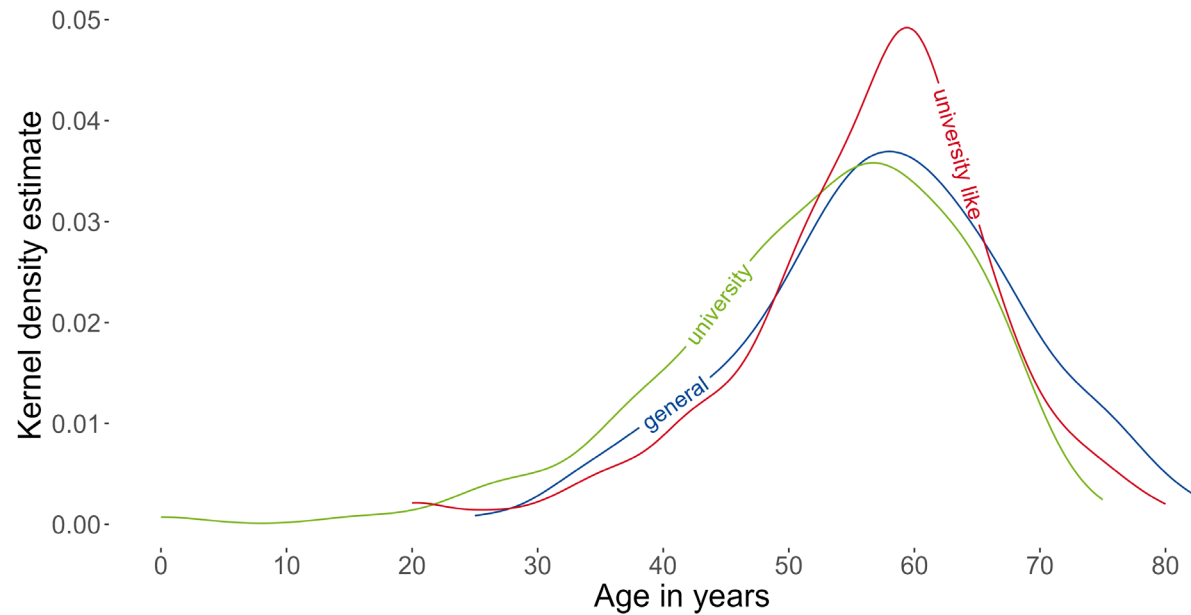


Figure 21 – Age distribution of ECMO patients by hospital type.

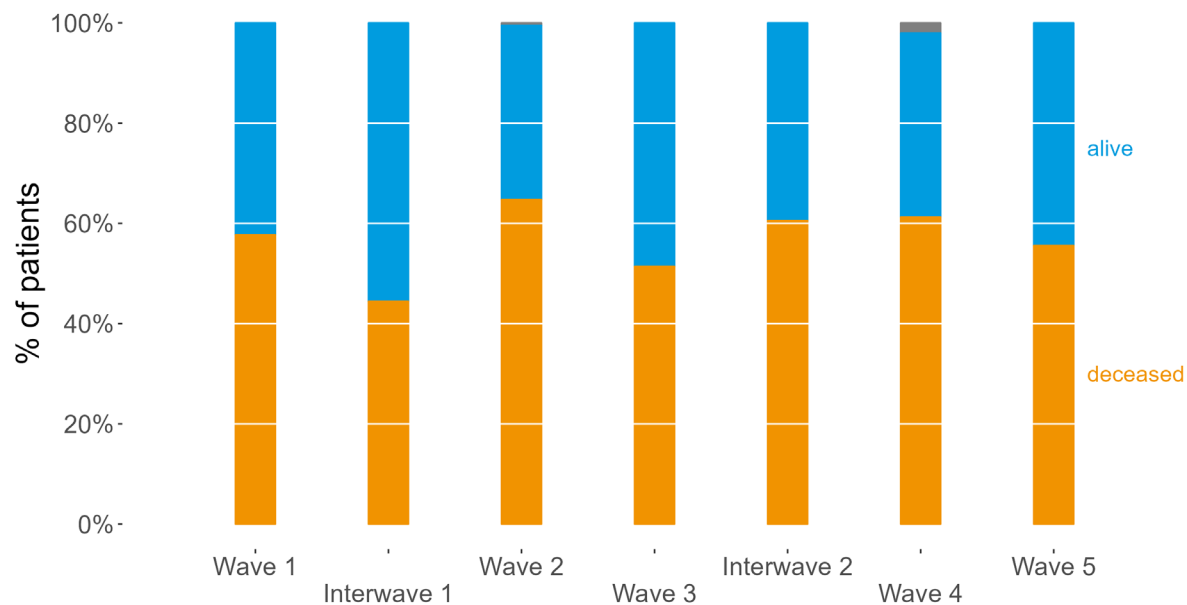


3.3.2.3 Vital status

ECMO patients left the hospital alive in 40.2% of the cases, while for 59.4% the vital state at discharge is deceased (with 0.4% unknown) of which the majority (89%) of the deceases are related to COVID-19. The proportions of vital state have remained fairly stable across waves, taking into account the relatively small number of ECMO patients in certain waves (see Figure 22).



Figure 22 – Number of ECMO patients alive or deceased at discharge (grey represents unknown).



Deceased patients are on average older as can be seen on Figure 23. This pattern remains essentially the case for hospitals with a limited number of ECMO patients as well as for hospitals treating relatively higher numbers of ECMO patients (see Figure 24). We refrained from performing a more detailed analysis per hospital due to too many hospitals with relatively few patients.



Figure 23 – Age distribution of ECMO patients alive or deceased at discharge.

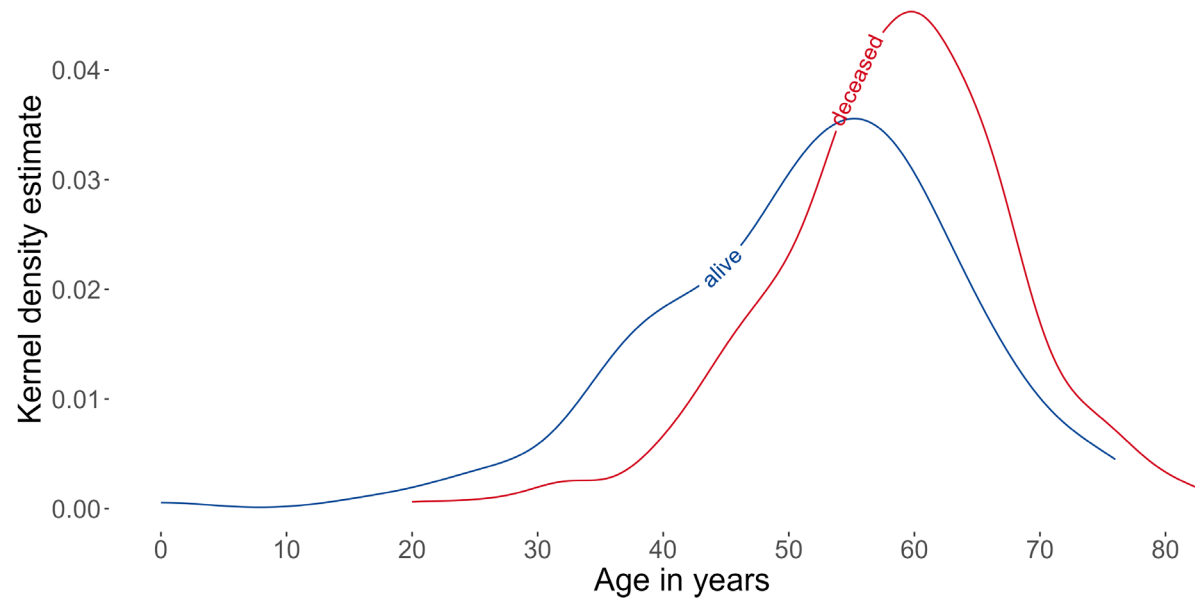
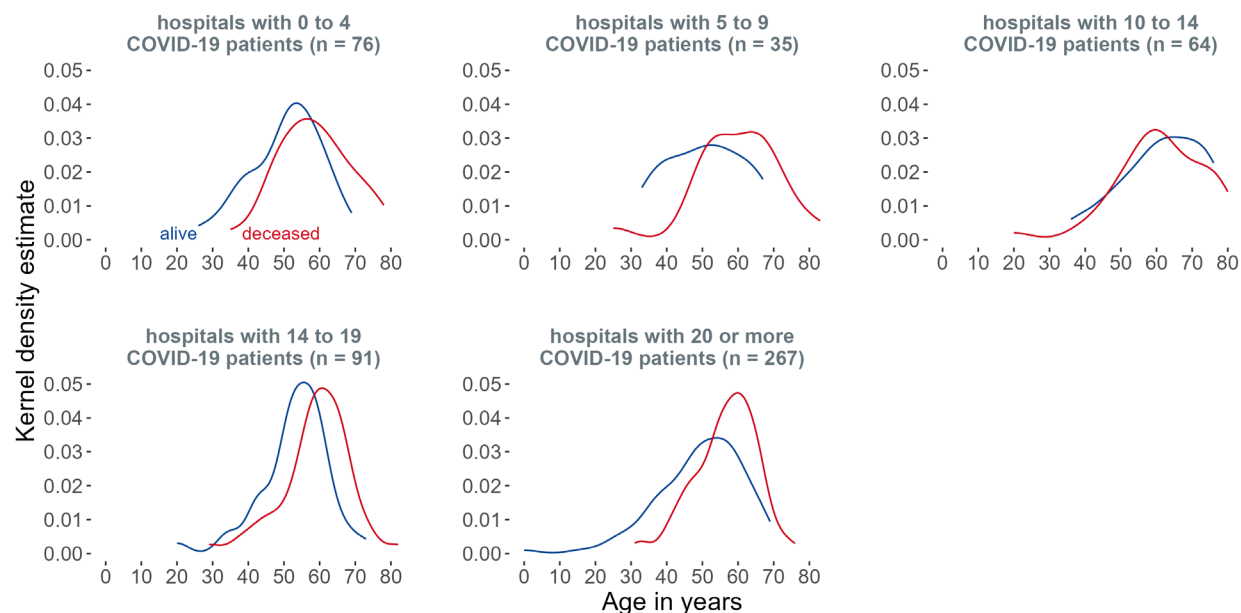




Figure 24 – Age distribution of ECMO patients alive or deceased at discharge by ECMO hospital volume.



Between brackets is the total number of patients in the hospital category. Some patients received ECMO in multiple hospitals e.g. after transfer and are represented in more than one hospital category.

3.3.3 Clinical parameters

3.3.3.1 Pneumonia

The reason for ICU admission was respiratory insufficiency in most cases (92.7%), with shock (vasopressor + lactate > 2 mmol/L), acute kidney injury (KDIGO definition), acute brain dysfunction or post-operative monitoring as other reasons.

Of the 434 patients in the 2020–2021 time period, 90% have a pneumonia confirmed by medical imaging (X-ray or CT-scan), while for 2%, no

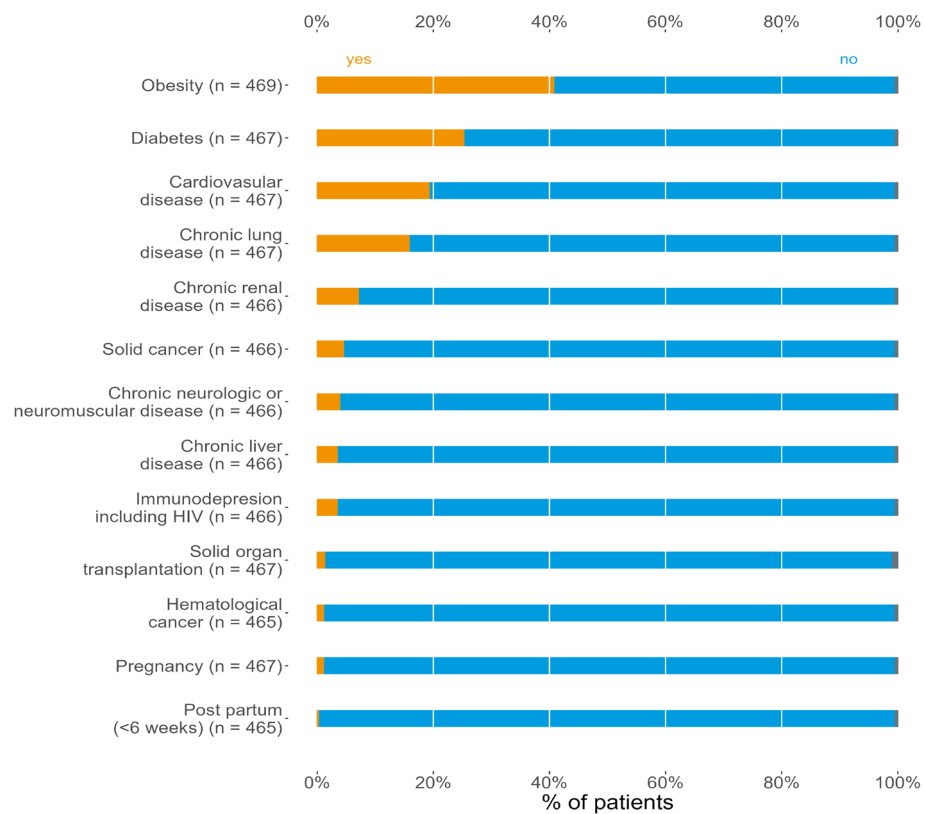
pneumonia is confirmed by medical imaging. For the remaining 6%, no information is available.

3.3.3.2 Pre-existing conditions

CHS contains a series of binary questions on pre-existing conditions and illnesses. The proportion of ECMO patients with these pre-existing conditions is shown in Figure 25. For each of the pre-existing conditions, the number of ECMO patients for which the information was available varies slightly and is provided between brackets in the figure.

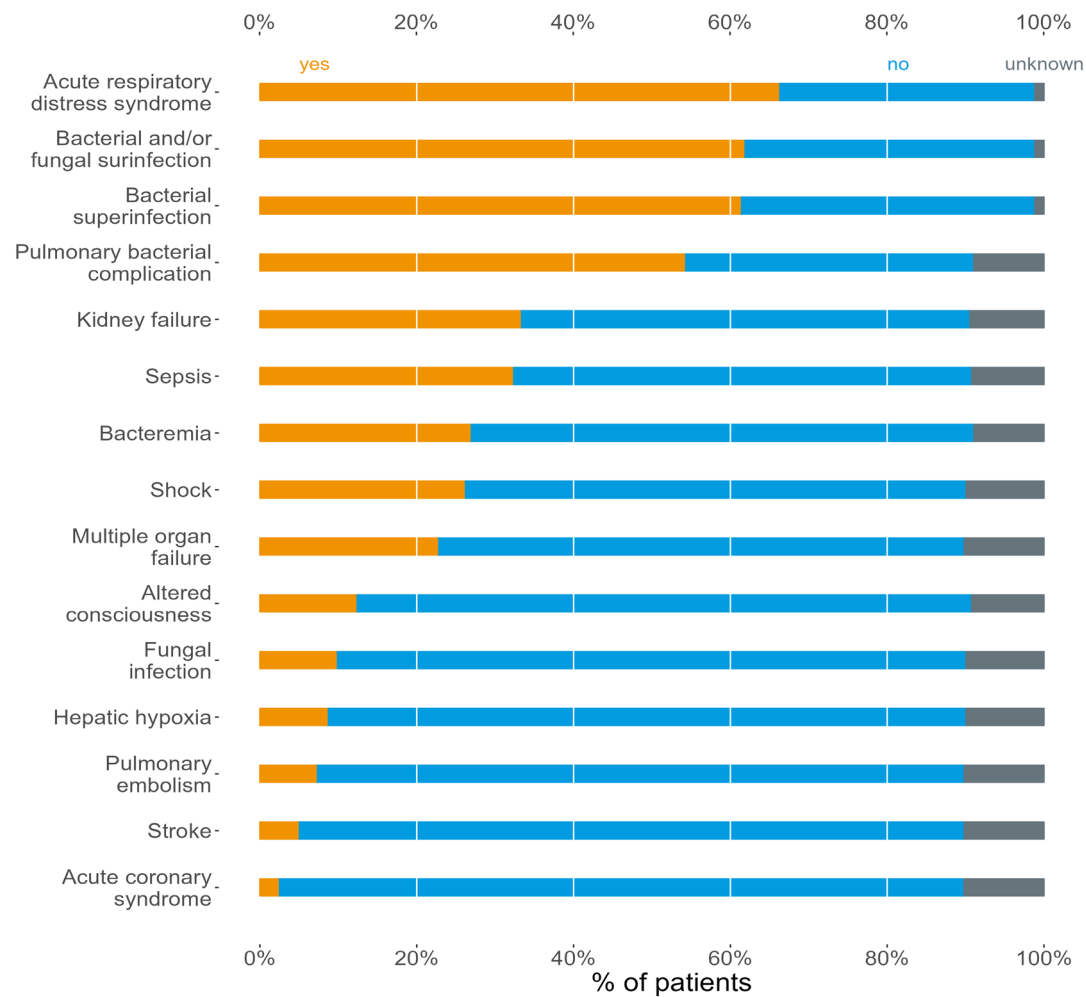


Figure 25 – Proportion of ECMO patients by pre-existing condition (full period available questions; grey bar represents unknown status).



3.3.3.3 Complications

CHS contains a number of binary questions on complications that arise during the hospital stay. The complications possibly relevant for ECMO are available only for the 2020–2021 period and are shown in Figure 26.

**Figure 26 – Proportion of ECMO patients by COVID-19 complication (2020–2021 period).**



3.3.3.4 Sequential Organ Failure Assessment (SOFA)

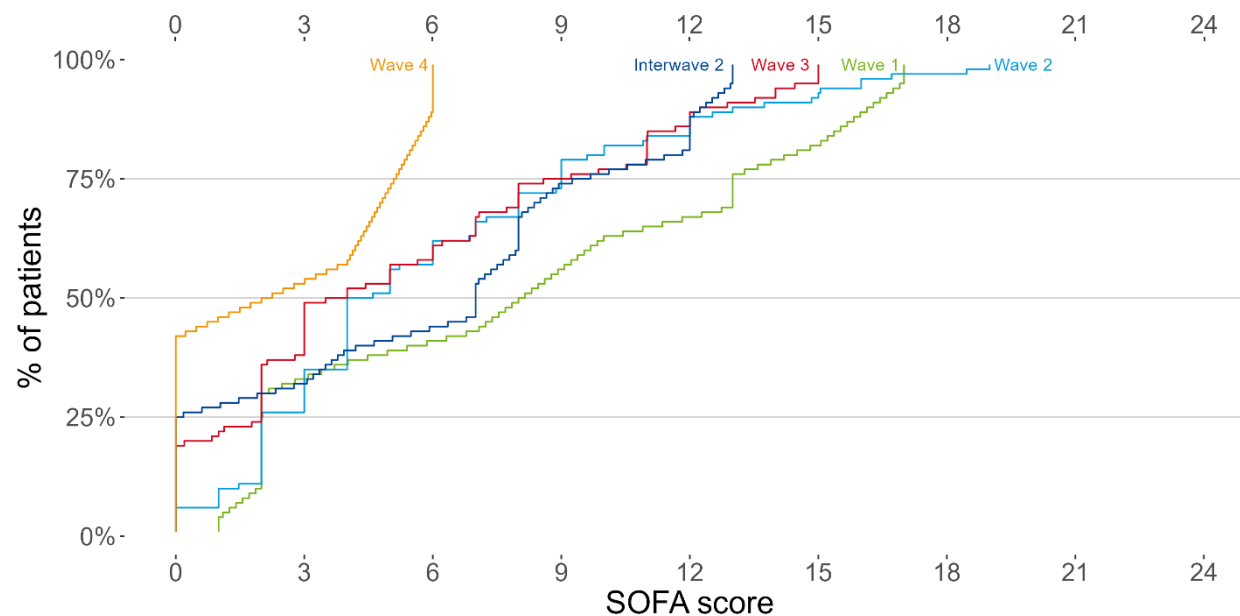
For ECMO patients on ICU, CHS records the Sequential Organ Failure Assessment (SOFA) score for the 2020–2021 period. The SOFA score concerns a scoring of six organ systems^a from 0 to 4 according to the degree of dysfunction or failure. These scores are summed to a total SOFA score and range from 0 (best) to 24 (worst).

The majority of ECMO patients in the sample have no SOFA score (Wave 1: 58.%, Wave 2: 52.1%, Wave 3: 54.9%, Interwave 2: 61.1%, 72.7%). For ECMO patients with SOFA scores, these differ between waves but with large variation within wave (see Figure 27). Depending on wave, between 6% (Wave 2) and 42% (Wave 4) receive a SOFA score of 0 resembling the best score. Wave 4 seems to differ the most from ECMO patients in other waves, with in general lower SOFA scores, but it's also the smallest group of patients for which a SOFA score is available. Wave 1 seems to have in general ECMO patients with the worst SOFA scores.

^a Respiration, coagulation, liver, cardiovascular, central nervous system and renal.



Figure 27 – Cumulative percentage of ECMO patients by SOFA score and wave (2020–2021 period; Interwave 1 and Wave 5 not shown due to less than five patients in at least one stratum).



3.3.4 Ventilation

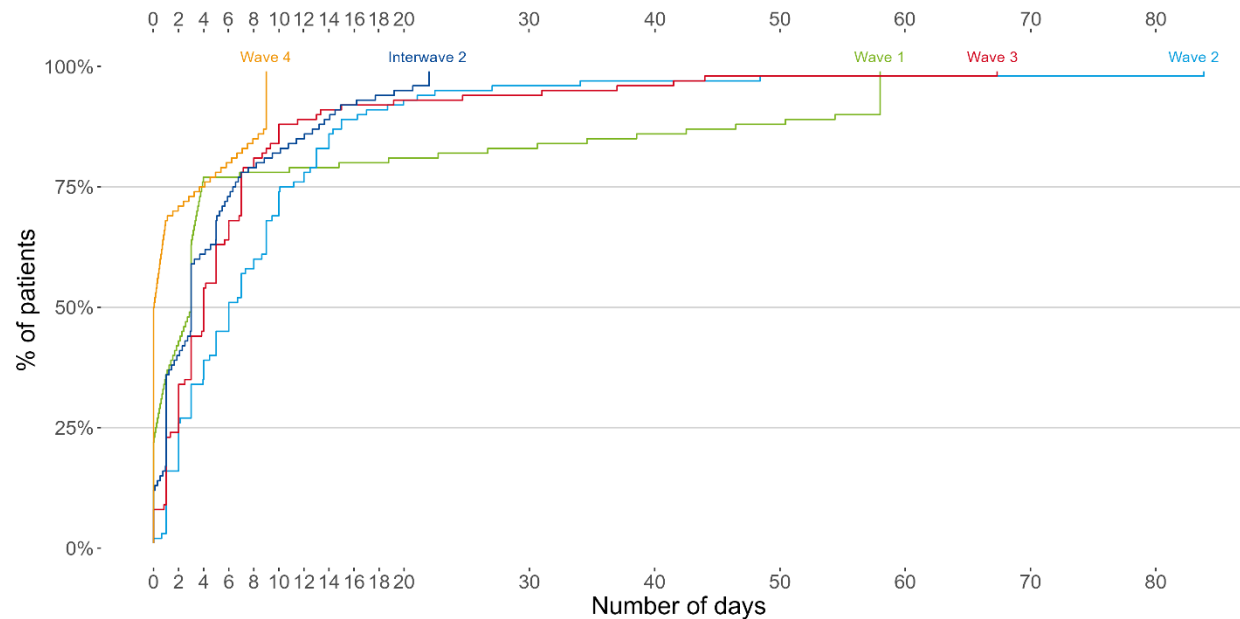
For patients eventually on ECMO, the CHS ICU questions also cover the use of non-invasive and invasive ventilation for respiratory support. This section describes these as well as the use of ECMO itself in the sample of ECMO patients.

3.3.4.1 Non-invasive ventilation

Almost half of the ECMO patients (48.2%) also received non-invasive respiratory support (modality not specify in the survey), during the ICU stay for the 2020–2021 period. Half of the ECMO patients spend 5 days or less on non-invasive ventilation, with 10% spending 15 days or longer on non-invasive ventilation (median 5 days with IQR 7 days). The distribution of length of non-invasive differs between waves in particular for the 25% of patients with the longest support (see Figure 28).



Figure 28 – Cumulative percentage of ECMO patients by length of non-invasive ventilation and wave (2020–2021 period; Interwave 1 and Wave 5 not shown due to less than five patients).

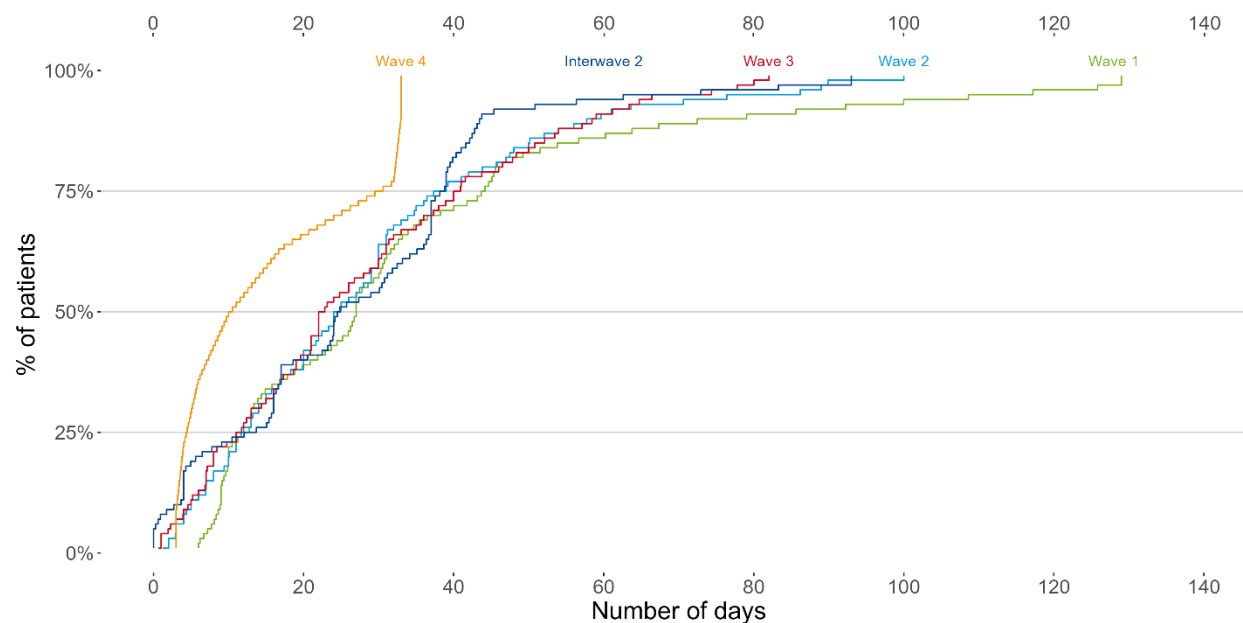


3.3.4.2 Invasive ventilation

The majority of ECMO patients (84%) also received invasive respiratory support during the ICU stay for the 2020–2021 period. Half of the ECMO patients spend 24 days or less on invasive ventilation, with 10% spending 57 days or longer on invasive ventilation (median 24 days with IQR 46.4 days). Invasive ventilation length is quite similar between waves, with the exception of Wave 4 and the 25% of ECMO patients with the longest support (see Figure 29).



Figure 29 – Cumulative percentage of ECMO patients by length of invasive ventilation and wave (2020–2021 period; Interwave 1 and Wave 5 not shown due to less than five patients).



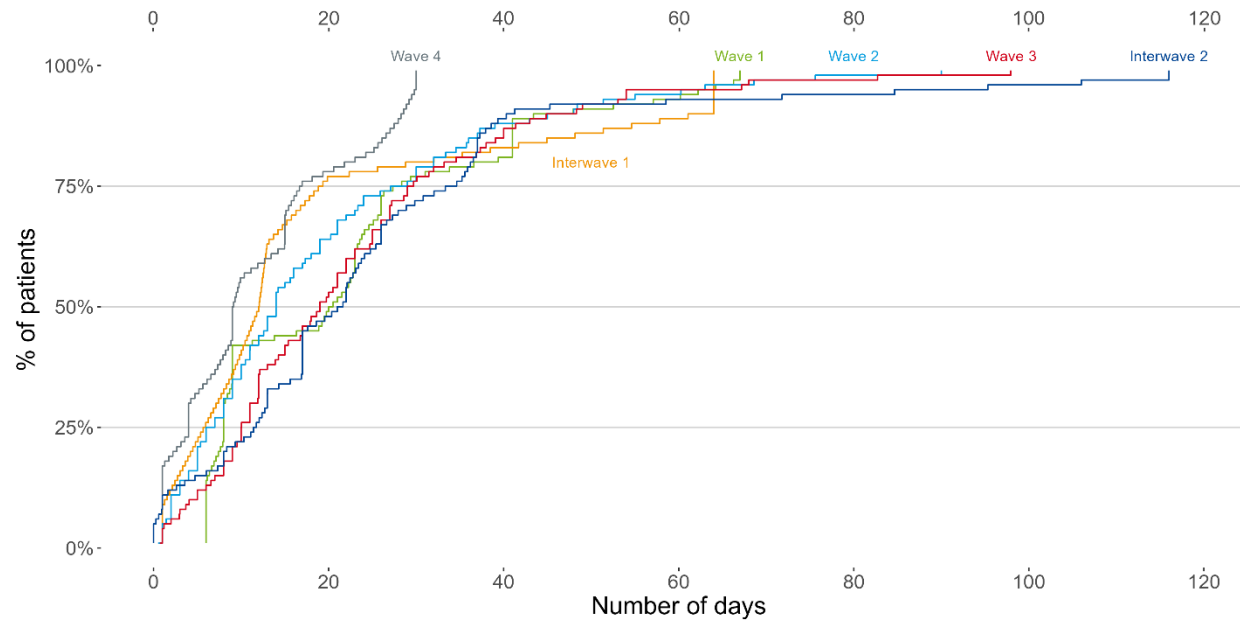
Of the ECMO patients that also received invasive ventilation, almost half died before the respiratory support could be weaned (46.3%). For 28.8%, weaning is successful while for 24.9% no information was available.

3.3.4.3 ECMO

For 86.5% of ECMO patients, the length they spend on ECMO is available for the full period. Half of the ECMO patients spend 15 days or less on ECMO, with 10% spending 43 days or longer on ECMO (median 15 days with IQR 20 days). The distribution of length of ECMO differs between waves, in particular for Interwave 1 and Wave 4 that tend to have patients less long on ECMO (see Figure 30).



Figure 30 – Cumulative percentage of ECMO patients by length of ECMO and wave (Wave 5 not shown due to less than five patients).

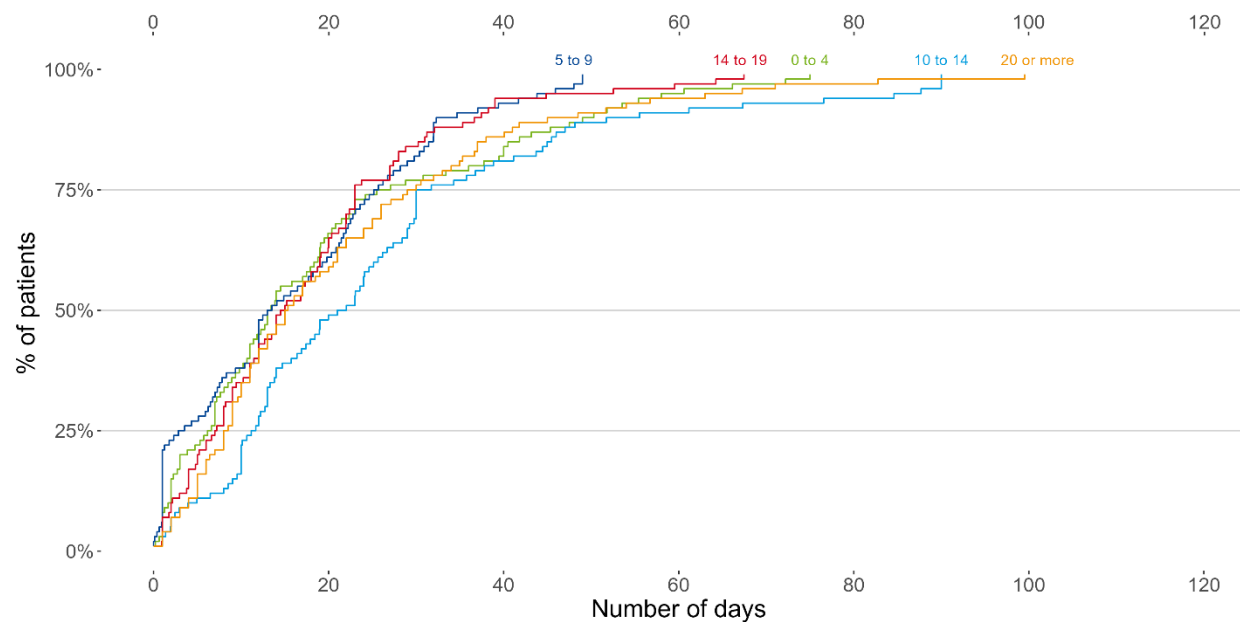


Of the ECMO patients in the period 2020–2021, 43.6% died before the respiratory support could be weaned successfully. For 37.7%, weaning is successful while for 18.7% no information was available.

The number of ECMO patients a hospital has in the full period seems to make little difference in the length distribution of ECMO, with exception of hospitals that had between 10 to 14 patients where the 75% of patients with the shortest ECMO lengths stay on average longer on ECMO than the other hospital categories (see Figure 31).

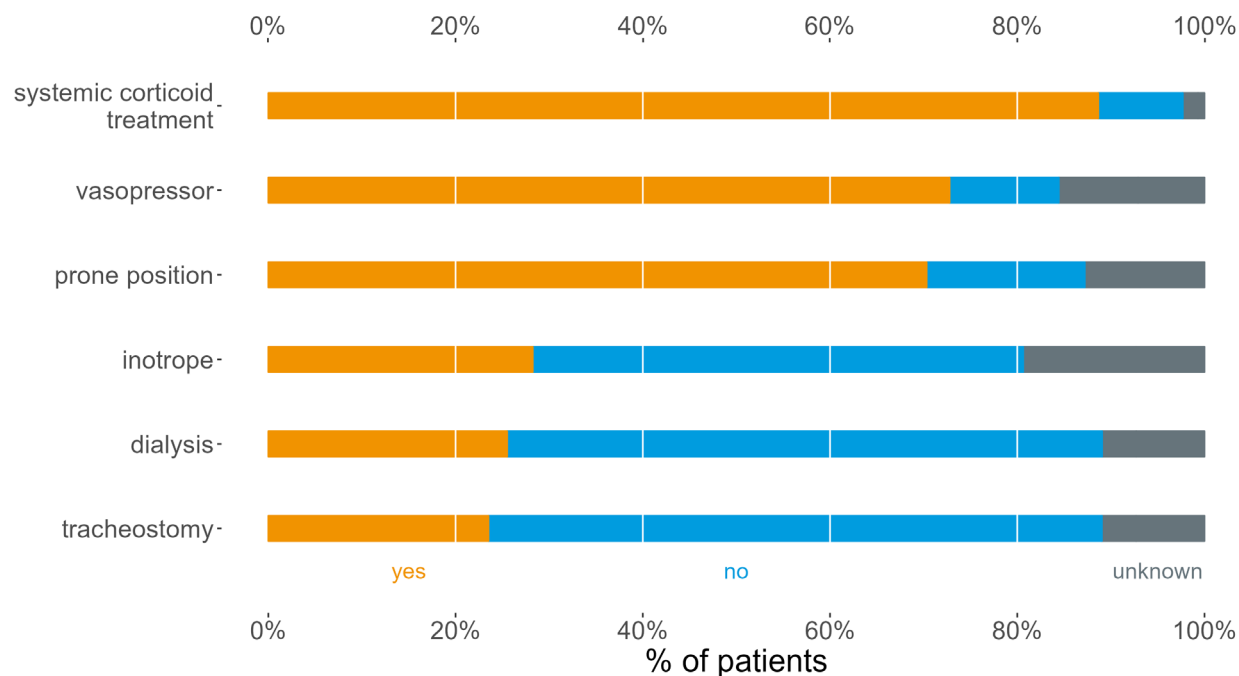


Figure 31 – Cumulative percentage of ECMO patients by hospital category of number of ECMO patients.



3.3.5 Treatment

Almost all ECMO patients receive systemic corticoid treatment (88.7%; 2.3% unknown) in the 2020–2021 period (see Figure 32). Almost three quarters of ECMO patients receive a vasopressor or are put in the prone position (respectively 72.8% and 70.3%). About a quarter of ECMO patients received an inotrope, a tracheostomy or dialysis (respectively 28.2%, 23.5% and 25.5%).

**Figure 32 – Proportion of ECMO patients receiving treatments (2020–2021 period).**

3.4 Limitations

Although the CHS is voluntary and has a fairly high response rate covering about 60% of COVID-19 patients, for certain variables, data is missing on the patients in the CHS.²⁰ Specifically for our study, the ECMO question in CHS does not make the distinction between ECMO and ECCO2R (See Chapter 4 for an explanation of this technique). The adaptation in November 2021 to increase response rate and reduce missing data by reducing and simplifying the survey, has had little impact in the current analysis as it

concerned relatively few patients, but could potentially hinder future research. Other more general limitations are discussed in Van Goethem et al.²⁰ These limitations warrant caution if one would want to extrapolate the results beyond the descriptive analysis of the sample provided in this section.



4 REVIEW OF LITERATURE: EFFECTIVENESS AND SAFETY OF ECMO

4.1 Introduction

ECMO is a lifesaving support technique that can be used for severe respiratory and cardiac failure or cardiac arrest. ECMO is regarded as a rescue therapy when conventional management fails to improve patients' conditions. Despite the fact that its use has widely grown over the years, the evidence on the benefit of ECMO in comparison to conventional therapies remains relatively controverted.²¹⁻²³

This chapter aims at providing an overview of the literature on the efficacy and safety of VA and VV-ECMO for adults.

4.2 Methods

An overview of the literature was deemed sufficient as this report is not a Health Technology Assessment but a Health and Service Research (HSR), with a focus more on the organizational aspects and the use of ECMO.

With this in mind, a step-wise approach was applied:

- First, good quality Health Technology Assessments (HTAs) in the topic of interest, with a scope similar to our research project, were searched for in the INAHTA database^a and the EunetHTA POP Database.^b If any published reports were identified, these were used as the starting point of our review. Broad search terms were used: "ECMO OR (Extracorporeal Membrane Oxygenation)" in the EunetHTA POP database, and "ECMO" as a MESH term in the INAHTA database.

- Second, a search for systematic reviews (SRs) in Medline, EMBASE and the Cochrane library was completed by two researchers^c to look for recent, high-to-moderate quality SRs, which could either serve the same purpose (be used as a starting point of our review) in the absence of relevant HTAs, or be used to update the research base assessed in any relevant HTA found. To this end, a search strategy was developed and adapted to each database. All databases were searched from 2006 to February 2021, with no language restriction. For Embase, conference papers and duplicates from Medline were excluded. Each strategy used a combination of appropriate MeSH terms and free text words. More details on this search can be found in Appendix 4.1 of this report. The quality of SRs was assessed based on the AMSTAR-2 tool^{d,24}

Our clinical research question was formulated using the PICOS (Participants-Interventions-Comparator-Outcomes-Study Design) framework (See Table 13). In order to limit our search to the most common indications for ECMO, the use of programmed ECMO (for high-risk cardiac procedures or surgery) and infrequent indications for ECMO (such as intoxications, hypothermia, post-partum/pregnancy, pheochromocytoma, stress cardiomyopathy, heart/lung transplant dysfunction) were excluded. Studies on Extracorporeal CO₂ removal (ECCO₂R) were also excluded. No other exclusion criteria was applied.

^a <https://database.inahta.org/>

^b <https://www.eunetha.eu/pop-database/> Covering HTAs that are ongoing, planned, or published in the last 3 months.

^c Discrepancies were verified by a third researcher and discussed until a consensus was reached

^d https://amstar.ca/Amstar_Checklist.php


Table 13 – PICO strategy- inclusion criteria

	Inclusion	Exclusion
Participants	Adults (≥ 18 years) with cardiac or respiratory failure, refractory to conventional management	• Children • Neonatal
Intervention	• VV-ECMO (respiratory failure) • VA-ECMO (cardiac arrest, cardiogenic shock)	• Programmed ECMO (high risk cardiac procedure/surgery) • Specific rare conditions (intoxications, hypothermia, post-partum/pregnancy, phaeochromocytoma, stress cardiomyopathy, graft dysfunction) • Extracorporeal CO₂ removal (ECCO₂R)
Comparator(s)	• For VV-ECMO : Conventional mechanical ventilation • For VA-ECMO: usual care with specific therapies (such as temporary mechanical support)	/
Outcome(s)	Efficacy (survival) and safety (adverse events)	Non patient-related outcomes (e.g.: better preservation of donor organs, ventricular unloading, anticoagulation strategies)

^a It was verified that no relevant studies were missing in the more recent HTA/SR.

Design	Systematic review (with or without meta-analysis - MA)	Other designs
Languages	English, French, Dutch, Spanish	

- Third, once a good quality HTA (or in its absence, a SR) was identified, its content was described in detail. If more than one high or moderate quality HTA/SR was found covering the same scope (i.e. same population, indications, type of ECMO, etc), the most recent was in principle preferred. However, the retrieved evidence (number of included studies^a, overall quality, general conclusion) was first confronted between the identified HTA/SR, to ensure that the conclusion was similar. If any inconsistencies were found, the HTA/SR being more inclusive (more relevant studies identified via their search), was included in our analysis.

If more than one good or moderate quality HTA/SR covering different aspects of our PICOs were found (e.g. different sub-populations, different indications, etc), these were all included and described in our analysis.

Only the content of the SR was summarised, and no re-analyses of the original studies included in the SR were performed.

- Finally, in order to offer an update on the content of the HTAs or SRs selected in the previous steps, without engaging into a full SR of primary studies, two steps were followed:
 - First, the list of any ongoing clinical studies mentioned in any HTAs or SRs included in our research were searched for and any completed and published studies from that list were considered in our review.



- Second, an expert consultation was performed to request references or copies of any more recent studies that, in their view, could be interesting/informative and add value to our review. Any studies identified by this means being publicly available, were assessed for relevance and considered for inclusion in our overview.

With regards to the need to update existing meta-analyses (MA), the Ottawa method for rapid reviews²⁵ was followed, i.e. an update was considered only if new evidence appeared to contradict or had the potential for changing the overall conclusions of the HTA/SR. In all other cases, the results of the more recent studies would still be described in detail and their quality assessed via the RoB tool of the Cochrane group^a, in order to offer a more complete view of the available evidence, but no update of MAs would be performed.

All limitations linked to our rapid approach are listed in a specific section of this report (See Limitations of available evidence).

4.3 Results

4.3.1 Veno-venous ECMO

4.3.1.1 Existing evidence and quality assessment

HTA reports

- **Description of the HTA report from the National Institute of Excellence in Health and Social Services (Quebec)**

As the starting point of our review, we retrieved only a Health Technology assessment (HTA) from the National Institute of Excellence in Health and Social Services from Quebec (Institut National d'Excellence en Santé et en Service Sociaux- INESSS).²⁶ It was published in 2019 and included articles published until June 2018. It focused on several aspects of both VV and VA-ECMO, such as efficacy, safety and organisational aspects of the

implementation of ECMO. A structural and economical assessment in the province of Quebec was also performed. For the present review, we only focused on the efficacy and safety aspects. The PICO strategy and the main characteristics are presented in Table 14.

Table 14 – Inclusion and exclusion criteria of the report from the National Institute of Excellence in Health and Social Services (INESSS)²⁶

	Inclusion	Exclusion
Participants	Adults (aged ≥ 18 years) with: • Acute respiratory distress syndrome (ARDS) • Cardiac arrest • Cardiogenic shock	ECMO used in the setting of: • Postcardiotomy • Lung transplant
Intervention	VV-ECMO (ARDS) VA-ECMO (cardiac arrest, cardiogenic shock)	• Programmed ECMO (high risk coronary artery bypass grafting) • Extracorporeal CO2 removal (ECCO2R)
Comparator(s)	• Conventional invasive and non-invasive ventilation (for VV-ECMO) • Conventional cardiopulmonary resuscitation (for cardiac arrest) • Temporary mechanical support (for cardiogenic shock)	
Outcome(s)	Efficacy (survival) and safety (complications)	

^a <https://www.riskofbias.info/welcome>



Design	SR, narrative review, guidelines, HTA report, RCT, observational studies	Case report, case series (n<30), editorials, abstracts
Time frame	Search ^a in October 2016 and update in June 2018	
Languages	English, French	

Nine studies on the use of ECMO for respiratory failure were included: one randomized controlled trial (RCT)²⁷, 4 systematic reviews (SR) (one was an HTA report)²⁸⁻³¹ and 4 cohorts studies.³²⁻³⁵ One study was from France, 4 from Asia, 1 from Australia and 3 from North America.

The population and the studies included differed greatly between the 4 SRs, despite the fact that they were published over a relatively short time period (2016-2018), with two of these SRs^{28,30} including more studies than the other two. However, despite the high number of studies included in the SR from Tilmann et al.³⁰ (27 studies; n=1674), only 5 of those studies allowed a comparison between patients treated with ECMO versus conventional ventilation. The SR from Xia et al.²⁸ was more inclusive because it included older studies.

Although the main cause of respiratory failure was attributed to ARDS two SRs and one cohort study also included other causes (eg. chronic obstructive pulmonary disease (COPD)/asthma, intoxication...).^{29, 30, 33} Moreover, the SR by Travers et al.³⁰ included studies using Extracorporeal CO₂ removal (ECCO₂R) and Pumpless Extracorporeal Lung Assist (PECLA) instead of VV-ECMO.

The main outcome was hospital mortality except for one study that assessed the QoL at one year.³⁵ The quality of studies was heterogeneous. Characteristics and quality of the studies, according to the authors of the report are presented in Table 15.

Temporary respiratory supports different from VV-ECMO^{36, 37}:

- Extracorporeal carbon dioxide removal (ECCO₂R) is a respiratory supportive technique designed to remove carbon dioxide (CO₂) from the blood, through an extracorporeal gas exchanger. It does not provide significant blood oxygenation. In contrast to ECMO that entails high blood flow rates, ECCO₂R requires lower blood flow rates (0.4-1L/minute). The device includes a drainage cannula inserted in a central vein (or artery), and a return cannula into the venous system.
- The technique was originally developed through a pumpless approach, with an arterio-venous configuration. The driving force for gas exchange consisted in the arteriovenous pressure gradient. Such devices are called arteriovenous pumpless extracorporeal lung assist (PECLA) or interventional lung assist (iLA).
- More effective veno-venous ECCO₂R devices have replaced the arterio-venous approach and require now only a single double lumen venous catheter.

^a Searched databases were Medline (Ovid), Embase, Cochrane Database of Systematic Reviews (CDSR), Cochrane technology Assessment Database (HTA), National Health Service Economic Evaluation Database (NHS EED)

**Table 15 – Studies included in the report from the National Institute of Excellence in Health Care and Social Services (INESSS)**

Author (year)	Design	Country	Number of studies and/or patients	Indication of VV-ECMO	Comparator	Outcome	Quality ^o
Xia ²⁸ (2018)	SR	China	13 studies (1 423 patients)	ARDS	Conventional ventilation	Hospital & 3,6 month mortality	Moderate
Travers ³⁰ (2016)	SR	US	8 studies (793 patients)	ARDS* #	Conventional ventilation	Hospital mortality	Low
Tillmann ²⁹ (2017)	SR	Canada	27 studies (1 674 patients)	ARDS #	Conventional ventilation	Hospital mortality	Moderate
Wilcox ³¹ (2017)	SR	Australia, Canada	6 studies (457 patients)	ARDS	Conventional ventilation	Hospital mortality	High
Combes ²⁷ (2018)	RCT	France	249 patients	ARDS	Conventional ventilation	2 month mortality	High
Alshahrani ³² (2018)	Retrospective cohort	Arabia	35 patients	ARDS	Conventional ventilation	Hospital mortality	Low
Takauji ³⁴ (2017)	Retrospective cohort	Japan	180 patients	ARDS	Conventional ventilation	Hospital mortality	Moderate
Kanji ³³ (2016)	Retrospective cohort	Canada	2 440 patients	Respiratory failure #	Conventional ventilation	Hospital mortality	Low
Wang ³⁵ (2017)	Prospective cohort	China	72 patients	ARDS	Conventional ventilation	Quality of life	Moderate

*Legend: ^o the quality was assessed with AMSTAR (A MeaSurement Tool to Assess systematic Reviews), ROBINS-I (Risk of Bias in Non-randomized Studies or Intervention), or Effective Public health practice project. * Two studies used Extracorporeal CO2 removal (ECCO2R) and Pumpless Extracorporeal Lung Assist (PECLA) that are different from VV-ECMO; # Other etiologies of respiratory failure different from Acute Respiratory Distress Syndrome (ARDS) were included (intoxications, chronic obstructive disease, asthma)*

**Acute Respiratory Distress Syndrome (ARDS):**

- ARDS is a life-threatening condition recognized as an acute respiratory failure that occurs in the setting of critical illness. It is characterized by the acute onset of bilateral lung infiltrates corresponding pulmonary oedema unrelated to heart failure. A decrease of oxygen level (hypoxaemia) in the blood stream ensues.
- Underlying causes of ARDS are numerous and include sepsis from pulmonary or extra-pulmonary origin, chest injury, inhalation of harmful substances, aspiration of gastric content and inflammatory diseases.
- Supportive therapies mainly focus on the improvement of the oxygen level in the blood through mechanical ventilation strategies and prone positioning of patients. VV-ECMO is considered in the most severe cases.

Quality assessment

According to the AMSTAR-2 criteria, the HTA by INESSS was of good quality^a. The design of included studies largely varied (cohort studies, RCTs and several SRs) and no MA was conducted. (See Appendix 4.2).

Systematic reviews

We identified 3 recently published SRs fulfilling our inclusion.³⁸⁻⁴⁰ Two of them were published in 2021^{39, 40} and one in 2020³⁸ (See Table 16).

- The SR from Zhu et al.⁴⁰ assessed the 90-day survival in patients with ARDS (See Table 4). Two RCTs^{9, 27} and 5 observational cohort studies (4 retrospective^{32, 41-43}, 1 prospective⁴⁴), accounting for 867 patients, were included. The survival at 90 days was available in 4 studies^{9, 27, 41,}

⁴² and was meta-analysed separately for RCTs and observational studies. Secondary outcomes included survival at other different time-points and hospital survival. According to the AMSTAR 2 criteria, the SR is of high quality (See Appendix 4.3).

- The SR from Wang et al. included 18 studies (2 399 patients: 898 on ECMO; 1501 with conventional ventilation) and focused on a heterogeneous set of outcomes including mortality at different time-points and the occurrence of complications (bleeding, haemorrhagic stroke and the need for renal epuration).³⁹ The majority of the studies included in the previous SR from Zhu et al.⁴⁰ were included in this one. However, this SR from Wang et al. was more inclusive and retrieved many studies that were excluded by Zhu et al. for several reasons (combined treatment with ECCO2R, wrong comparator, no measure of survival or great bias of participants baseline characteristics). It should also be noted that old studies (before 2000)^b were included. According to the AMSTAR 2 criteria, the quality is very low (See Appendix 4.4).
- The third SR from Combes et al.³⁸ only included the two RCTs available on this topic (429 patients) and meta-analyzed 90-day survival. According to the AMSTAR 2 criteria, the quality is high (See Appendix 4.5).

^a It should be noted that authors did not provide a list of excluded studies in their report. When the included studies are compared with the content of others SRs, there is no indication that they inappropriately excluded studies.

^b We noticed an error in one reference (Mi MY et al. actually refers to the trial from Combes A et al published in 2018)

**Table 16 – Most recent systematic reviews on VV-ECMO**

Author (year)	Number of studies	Number of patients	Outcome(s)	Quality
Zhu Y ⁴⁰ (2021)	7 (2 RCTs)	867	90-day survival	High
Wang J ³⁹ (2021)	18 (4 RCTs)	2 399	Several outcomes: mortality at different time-points, pneumonia, haemorrhagic stroke, bleeding, need for renal replacement therapy	Very low
Combes A ³⁸ (2020)	2 RCTs	429	90-day survival	High

Selection of the reference source and quality of retrieved evidence

The most recent SR with the higher quality was the SR from Zhu et al.⁴⁰ No major inconsistencies were identified between this SR, and the SR from Combes et al.³⁸ that had a similar level of quality. Moreover, the SR from Zhu et al. included the two studies from the SR from Combes et al.³⁸ We choose the SR from Zhu et al.⁴⁰ as the best source to report the current evidence.

Seven studies (2 RCTs^{9, 38} and 5 observational studies^{32, 41-44}), accounting for 867 patients, were included in this SR (See Table 17) and a MA was performed. All the primary studies included in the INESSS HTA²⁶ were also included in this SR.⁴³ The results are presented in the next section. The cause of respiratory failure was ARDS^a.

^a In the EOLIA trial²⁷. EOLIA, ECMO was considered if PaO₂/FiO₂ < 50 mmHg for > 3 hours or < 80 mmHg for 6 hours acidosis (pH < 7.25) with a partial pressure of arterial carbon dioxide of at least 60 mm Hg for more than 6 hours. In the CESAR trial⁹., ECMO was considered if the Murray

The level of quality was assessed by the authors of the review by means of the Jadad tool for RCTs, or by the Newcastle-Ottawa Scale (NOS) for nonrandomized studies. Overall, the level of quality of the included studies was good (See Table 17).

Table 17 – Primary studies from the SR by Zhu F et al.

Author (year)	Design	Country	Number of patients	Quality ^o
Peek ⁹ (2009)	RCT	UK	ECMO:90 CMV: 90	High
Combes ²⁷ (2018)	RCT	France	ECMO:124 CMV: 125	High
Noah ⁴¹ (2011)	Retrospective cohort	UK	ECMO:75 CMV: 75	Good
Pham ⁴⁴ (2013)	Prospective cohort	France	ECMO:52 CMV: 52	Good
Tsai ⁴² (2015)	Retrospective cohort	Taiwan	ECMO:45 CMV: 45	Good
Alshahrani ³² (2018)	Retrospective cohort	Saudi Arabia	ECMO:17 CMV: 18	Good
Yang ⁴³ (2020)	Retrospective cohort	China	ECMO:21 CMV: 38	Good

Legend: ^o the quality was assessed with the modified Jadad score (RCT) or the Newcastle-Ottawa Scale; CMV: conventional mechanical ventilation; ECMO: extracorporeal membrane oxygenation; RCT: Randomised controlled trial

score⁴⁵. 3. (from all four variables: PaO₂/FiO₂ ratio, positive end-expiratory pressure, lung compliance, and chest radiograph appearance-and FiO₂=1) of 3.0 or higher, or uncompensated hypercapnoea with a pH of less than 7.20 despite optimum conventional treatment.



4.3.1.2 Outcomes: results

Analysis of outcomes

The SR from Zhu et al. (7 studies^{9, 27, 32, 41-44}, 867 patients), randomized and observational studies were meta-analysed separately. Mortality at 90 days was available in 4 studies (2 RCTs^{9, 27} and 2 observational studies^{41, 42}). Both MAs on RCTs and cohort studies were rather consistent and showed that VV-ECMO was significantly associated with a better 90-day survival in comparison with patients who did not received VV-ECMO. In addition, similar results were found at different time-points (See Table 18 and Table 19):

- When the 90-day mortality data of the two RCTs^{9, 27} (429 patients) were pooled together, the ECMO group exhibited, at different time points, a significantly lower mortality rate compared with the group of patients who were treated only with conventional mechanical ventilation (See Forest plots in Appendix 4.6). Authors assessed the quality of the evidence for each outcome, using GRADE. The quality of the evidence was in all cases rated as moderate^a (See Table 18).

Table 18 – Pooled analysis of the mortality in RCTs included in the SR by Zhu F et al.⁴⁰

Outcomes	Pooled Ratio (95%CI)	Risk	I ²	p-value	Quality evidence (GRADE)	of
Mortality 90 days	0.74 (0.59-0.93)		0%	0.01	moderate	
Mortality 30 days	0.57 (0.36-0.89)		58%	0.01	moderate	
Mortality 60 days	0.73 (0.58-0.93)		0%	0.01	moderate	
Mortality longest follow-up (180 days)	0.77 (0.61-0.96)		0%	0.02	moderate	

^a Study limitations: different management between ECMO group and control group in the study from Peek et al. and high crossover rate between study arms in the study from Combes et al.

- Two of the observational cohort studies reported on 90-days mortality.^{41, 42} VV-ECMO was significantly associated with a better survival. No significant heterogeneity was found between studies and the quality of evidence was rated as low according to GRADE (See Table 19).

Similar results were observed for 30 and 60-days mortality (GRADE: very low^b). Hospital mortality (3 studies^{32, 43, 44}) and survival at longest follow-up^c (5 studies^{32, 41-44}) was not significantly associated with a better survival. (Forest plots are presented in Appendix 4.7).

Table 19 – Pooled analysis of the mortality in observational studies included in the SR by Zhu F et al.⁴⁰

Outcomes	Pooled Ratio (95%CI)	Risk	I ²	p-value	Quality evidence (GRADE)	of
Mortality 90 days	0.61 (0.46-0.81)		0%	<0.01	low	
Mortality 30 days	0.47 (0.30-0.75)		38%	0.01	very low	
Mortality 60 days	0.55 (0.40-0.75)		0%	<0.01	very low	
Mortality longest follow-up ^a	0.74 (0.55-1.00)		64%	0.05	very low	
Hospital mortality	0.89 (0.60-1.32)		65%	0.57	very low	

Interpretation

- From this SR, it can be concluded that good quality evidence is somewhat limited and stems from two multicenter RCTs (n= 429)^{9, 27} indicating that VV-ECMO improves 90-day survival. The quality of the evidence, assessed with GRADE, is moderate. Although the quality of evidence arising from observational studies is low to very low, there is no inconsistency between results from RCTs and observational studies. We noticed that the pooled effects on hospital mortality and mortality at

^b Risk of bias due to the observational design of studies, low level of precision.

^c Longest follow-up ranged from 60 to 270 days in observational studies



longest follow-up meta-analysed from the cohort studies, were not statistically significant. This may be due to the high heterogeneity between studies. It should be noted that the mortality at longest follow-up has a trend (p value: 0.05) favoring ECMO.

- The same interpretation has been made by the authors from the SR-MA published one year before by Combes et al.³⁸ and that combined both available RCTs (relative effect for 90-day mortality: 0.75; 95CI: 0.60-0.94). Authors used GRADE and rated, the level of evidence as high.
- Another MA published in 2019²¹ focused on 60-day survival and included nearly the same studies collected in the SR of Zhu et al., except for 2 observational studies^{32, 43}. The same RCTs were included and meta-analyzed separately from observational studies. The results were also in line with the SR from Zhu et al. (RR 0.73; 95CI: 0.58-0.92). The level of evidence was rated as moderate, using GRADE score. When data from RCTs were pooled with the data of 3 observational studies from Noah et al.⁴¹, Pham et al.⁴⁴ and Tsai et al.⁴², the 30-day mortality was significantly lower in patients who received VV-ECMO (RR 0.69; 95CI: 0.50-0.95).

Conclusion

Based on the current evidence, our review indicates that the use of VV-ECMO is associated with a reduced mortality when compared with conventional mechanical ventilation, in patients with severe ARDS. The level of evidence is mainly based on two RCTs and the quality of evidence is moderate.

4.3.2 *Veno-arterial ECMO for cardiac arrest (extracorporeal cardiopulmonary resuscitation) and cardiogenic shock*

4.3.2.1 *Existing evidence and quality assessment*

HTA reports

- **Description of the HTA report from Ontario Health and Technology Agency**

As the starting point of our review regarding the use of ECMO for cardiac arrest, the HTA from the Ontario Health and Technology Agency, was identified. This HTA was the most recent that covered the use of VA-ECMO in the setting of cardiac arrest (and also cardiogenic shock).⁴⁶ It has been published in March 2020 and comprised articles published between 2010 and September 2018. It assessed how effective, how safe and cost-effective VA-ECMO is for treating cardiac arrest and cardiogenic shock. For the present chapter, the focus was only on the efficacy and safety aspects. The PICO strategy is presented in Table 20.



Table 20 – Inclusion and exclusion criteria of the report from the Ontario HTA

	Inclusion	Exclusion
Participants	- Adults (≥ 18 years) with cardiac arrest refractory to conventional cardiopulmonary resuscitation - Adults (≥ 18 years) with cardiogenic shock refractory to conventional medical management: drugs, mechanical support (e.g., intra-aortic balloon pump, percutaneously inserted temporary ventricular support device [e.g., Impella], surgically implanted temporary ventricular support devices)	/
Intervention	- Cardiac arrest: Extracorporeal cardiopulmonary resuscitation (VA-ECMO) - Cardiogenic shock: VA-ECMO used as a bridge to recovery, heart transplantation, or implantation of longer-term surgically implanted devices	VV-ECMO
Comparator(s)	- For refractory cardiac arrest: standard care, e.g. conventional CPR - For refractory cardiogenic shock: standard care, i.e. drugs, temporary mechanical support (e.g. intra-aortic balloon pump, percutaneously inserted temporary ventricular support devices, surgically implanted ventricular assist devices)	/
Outcome(s)	Survival, 30-day and long-term	/

^a The HTA assessment from Almeida et al. (2017) was rated at high risk of bias in all domains while the report from the Washington State Health Care

	- Favorable neurological outcome 30-day and long-term - Successfully weaned or bridged to permanent ventricular assist device (VAD) or heart transplant - Length of stay (in ICU) - Quality of life - Complications	
Design	SR, RCT, observational studies	Editorials, commentaries, case report, conference abstracts, letters
Time frame	Search on September 2018 (articles published between 2010 and 2018)	
Languages	English	

Five SRs met the inclusion criteria^{30, 47-50} but two were discarded by the authors for low quality according to the ROBIS criteria (Risk of Bias Among Systematic reviews)^{a, 30, 47} Three SRs were included.⁴⁷⁻⁴⁹ One of them⁴⁹ included all the studies incorporated on the two other SRs.^{47, 48} Therefore, only this SR from Ouweneel et al.⁴⁹ was kept (9 studies on cardiac arrest-3127 patients; 4 studies on cardiogenic shock-235 patients).

The 13 primary studies from this SR⁴⁹ were included⁵¹⁻⁶³ in the Ontario HTA, along with 2 other studies retrieved from the search strategy (one on cardiac arrest and one on cardiogenic shock)^{53, 64}, and their outcomes extracted to perform MAs. Study characteristics are presented in Table 21 and Table 22).

Authority (2016) was rated at high risk of bias in the domains 'Identification and selection of studies' and 'Risk of bias in the review'.



Studies on cardiac arrest included in the assessment from Ontario HTA

Ten studies on cardiac arrest were included: nine observational cohort studies derived from the SR from Ouweneel et al.⁵¹⁻⁵⁹ and one study which was retrieved from the search strategy.⁵³

The majority of studies were conducted in Asia except one in Germany. Four studies included in-hospital cardiac arrest^{51, 52, 58, 65} while 4 others focused on out-of-hospital cardiac arrest.^{53, 54, 56, 57} Two studies included in and out-of-hospital cardiac arrest.^{55, 59} Four were prospective cohort studies^{52, 54, 56, 57} and 6 retrospective cohort studies.^{51, 53, 55, 58, 59, 65} Follow-up times for outcome assessment varied from the hospital stay period to 24 months. One study reported on a long-term follow-up with a median time of 37 months.⁵¹ Samples size ranged from 48 to 955 patients.

For most studies, the use of ECMO was based on the clinical-based decision of the treating physician. Six studies used a propensity score matching.^{51-54, 56, 58} Propensity scores were mainly based on age, gender, comorbidities and the characteristics of CPR such as duration of CPR or initial cardiac rhythm. The details of matching variables are presented in Appendix 4.8.

According to the Newcastle Ottawa scale (applied on studies extracted from Ouweneel et al.) or ROBINS-I criteria (applied on the study from Choi et al.⁵³), the quality of studies was overall, judged low by the authors of the HTA (See Table 21).

Table 21 – Studies on cardiac arrest included in the report from Ontario HTA

Author (year)	Design	Country	Total number of patients (number of matched patients)	Indication of ECMO	VA-	Comparator	Longest follow-up (months)	Quality
Blumenstein ⁵¹ (2016)	Retrospective cohort (propensity score matched)	Germany	353 (104)	IHCA		CPR	Long-term [#]	Low ^o
Chen ⁵² (2008)	Prospective cohort (propensity score matched)	Taiwan	172 (92)	IHCA		CPR	12	Fair ^o
Choi ⁵³ (2016)	Retrospective cohort (propensity score matched)	Korea	36 547 (640)	OHCA		CPR	In-hospital [*]	Low ^{oo}
Chou ⁶⁵ (2014)	Retrospective cohort	Taiwan	66	IHCA		CPR	12	Low ^o
Kim ⁵⁴ (2014)	Prospective cohort (propensity score matched)	Korea	499 (104)	OHCA		CPR	3	Fair ^o
Lee ⁵⁵ (2015)	Retrospective cohort	Korea	955	IHCA/OHCA		CPR	In-hospital [*]	Low ^o
Maekawa ⁵⁶ (2013)	Prospective cohort (propensity score matched)	Japan	162 (48)	OHCA		CPR	3	Low ^o



Sakamoto ⁵⁷ (2014)	Prospective cohort	Japan	454	OHCA	CPR	6	Low [°]
Shin ⁵⁸ (2013)	Retrospective cohort (propensity score matched)	Korea	406 (120)	IHCA	CPR	24	Fair [°]
Siao ⁵⁹ (2014)	Retrospective cohort	Taiwan	60	IHCA/OHCA	CPR	12	Low [°]

Legend: CPR: cardiopulmonary resuscitation; IHCA: In-hospital cardiac arrest; OHCA: out-of-hospital cardiac arrest; * In hospital mortality refers as mortality during hospital stay; #median long-term follow-up was 1136 days; ; ° The quality was assessed with Newcastle-Ottawa Quality Assessment Scale for Cohort studies; °° The quality was assessed with ROBINS-I tool

Studies on cardiogenic shock included in the assessment from Ontario HTA

Five studies on cardiogenic shock were included: four studies⁶⁰⁻⁶³ derived from the SR from Ouwenel et al.⁴⁹ and one study published later.⁶⁴

The majority of studies were conducted in Asia, Europe and US (See Table 22). Four studies were retrospective cohorts and one was prospective. The sample sizes were fairly limited (all less than 100 participants). Ischaemic cardiomyopathy (myocardial infarction) was the most common cause of cardiogenic shock. Two studies included post cardiectomy cardiogenic shock^{61, 64} and one study included rarer causes of cardiogenic shock (such as postpartum cardiomyopathy for instance).⁶¹ Follow-up times for outcome assessment were 30 days^{61, 63} or the hospital stay duration.⁶⁰ One study⁶⁴ reported a longer follow-up (See Table 22).

In 3 studies, the comparator group consisted of Ventricular Assis device (VAD),^{60, 61, 64} whereas Intra-aortic balloon pump (IABP) was used as comparator in 2 other studies.^{62, 63} None of the studies used a propensity score matched analysis.

According to the Newcastle Ottawa scale or ROBINS-I criteria, the quality of all included studies was low (See Table 22).

Temporary mechanical circulatory supports different from VA-ECMO^{66, 67}:

- The Intra-aortic balloon pump (IABP) is a percutaneous device consisting of a catheter on which is connected a balloon. It is inserted in the aorta, through the femoral arteria. The balloon is inflated when the heart relaxes (diastole), and deflated when the heart contracts (systole). The inflation increases the perfusion of the heart while the deflation modestly enhances the cardiac output (approximately 0.5L/minute).
- A ventricular assist device (VAD) is a mechanical circulatory device used to support the heart function. It pumps the blood from the heart and send it into the blood flow in the body. Several types of VAD are available and include:
 - Impella© (Abiomed, MA, USA) is an axial pump percutaneously inserted in the heart ventricle (most frequently left ventricle) and crossing the aortic valve. It provides a haemodynamic support to the left (or right) ventricle, and increases the cardiac output.
 - The Tandemheart© (Tandemlife, PA, USA) device is a extracorporeal centrifugal pump with an inflow cannula placed in the femoral vein and reaching the left atrium through a puncture across the intra-atrial septum. The pump draws out the oxygenated blood and sends it to the outflow cannula placed in



the femoral artery. It requires an experienced interventional team to perform the transseptal puncture.

- Some VADs are called non-percutaneous VADs because they require a surgical placement (sternotomy). For instance, the centrifugal pump Centrimag® (Thoratec Corporation, CA, USA) uses an inflow cannula generally placed into the left ventricle and an outflow cannula in the aorta (or in a peripheral branche).

Table 22 – Studies on cardiogenic shock included in the report from Ontario HTA

Author (year)	Design	Country	Number patients	of	Cause of cardiogenic shock	Comparator	Longest follow-up (months)	Quality [°]
Chamogeorgakis ⁶⁰ (2013)	Retrospective cohort	US	79		• Ischaemic cardiomyopathy • Decompensated cardiomyopathy	VAD ¹	In-hospital	Low [°]
Lamarche ⁶¹ (2011)	Retrospective cohort	Canada	61		• Myocardial infarction • Idiopathic dilated cardiopathy • Post cardiectomy • Myocarditis • Other*	VAD ²	30 days	Low [°]
Mohite ⁶⁴ (2018)	Retrospective cohort	UK	56		• Post-cardiectomy	VAD ³	Long-term [#]	Low ^{°°}
Sattler ⁶² (2014)	Retrospective cohort	Germany	24		• Ischaemic cardiomyopathy	IABP	30 days	Low [°]
Sheu ⁶³ (2010)	Prospective cohort	Taiwan	71		• Ischaemic cardiomyopathy	IABP	30 days	Low [°]

Legend: IABP: intra-aortic balloon pump; VAD: ventricular assist device; [#] longest follow-up: 2800 days; ¹ Impella axial flow pump or TandemHeart centrifugal pump; ² Impella 5.0 or Impella RD ³ non percutaneous VAD: Centrimag (Thoratec, CA, USA); * Causes include: failing left ventricular assist device, decompensated hypertrophic cardiomyopathy, peripartum cardiomyopathy, postcardiac transplants with right ventricle failure, myocarditis, refractory ventricular arrhythmia ; [°] The quality was assessed with Newcastle-Ottawa Quality Assessment Scale for Cohort studies; ^{°°} The quality was assessed with ROBINS-I tool



Quality assessment

The quality of the Ontario HTA, using AMSTAR-2 criteria (See Appendix 4.9) was rated as moderate, because study selection and data extraction of studies was not performed in duplicate. The absence of investigation of publication bias by the use of a funnel plot was not considered, since authors checked the ongoing clinical trials potentially relevant for the review, in ClinicalTrials.gov website^a and because there was a high proportion of similar studies included by the SRs (see below). We considered thus that the probability of publication bias was low.

Systematic reviews

Cardiac arrest

Three recently published SRs identified via our search strategy, were in accordance with our PICO strategy.⁶⁸⁻⁷⁰ One of them was published in 2020⁶⁹ and the two others in 2019^{68, 70} (See Table 23). Miraglia et al. performed a MA of propensity-score matched cohort studies on the use of VA-ECMO for in and out-of-hospital cardiac arrest, in comparison to conventional CPR.⁶⁹

- Six studies, accounting for 1108 matched patients, were included. Outcomes were the following: 30-day and long-term^b survival and 30-day and long-term^b favorable neurological outcome^c. All studies included in this SR were included in the report by the Ontario HTA agency.⁴⁶
- According to the AMSTAR 2 criteria, this SR is low quality (See Appendix 4.10).
- Twohig et al. performed in 2019 a SR and MA of the effectiveness of VA-ECMO versus conventional CPR in cardiac arrest.⁷⁰ The primary outcome was survival at hospital discharge or 30-day survival. In

addition, an analysis of the parameters involved in the outcome (no or low-flow, bystander CPR, initial shockable rhythm) was conducted.

- Authors included 17 studies but only 9 studies described ECMO vs CPR and were used in the MA (2 626 patients). All those studies were included in the report from Ontario HTA.⁴⁶ Among them, five^{51, 53, 54, 56, 58, 65} were included in the MA from Miraglia et al.-2020⁶⁹ (See Appendix 4.11 for the list of included articles in each SR).
- According to the AMSTAR 2 criteria, this SR is very low quality (See Appendix 4.12).
- Chen et al. published in 2019 a SR and MA comparing the clinical efficacy of VA-ECMO with conventional CPR in patients undergoing in- and out-of- hospital cardiac arrest.⁶⁸ Primary outcome was 30 days survival and secondary outcomes were neurological outcome and survival at 3-6 months and 1 year.
 - Authors included 13 studies (3 026 patients), all of which were already included in the Ontario HTA report. For comparison with the SRs from Miraglia et al.⁶⁹ and Twohig et al.⁷⁰, (See Appendix 4.11).
 - According to the AMSTAR 2 criteria, this SR is of low quality (See Appendix 4.13).

^a <https://clinicaltrials.gov/>

^b Beyond 30 days

^c Neurological outcome is based on the Cerebral Performance Category (CPC) scale or the Modified Glasgow Outcome Score

^d Two studies reported on the same cohort of patients.

**Table 23 – Most recent systematic reviews on VA-ECMO for cardiac arrest**

Author (year)	Number of studies	Number of patients	Outcome(s)	Quality
Miraglia ⁶⁹ (2020)	6	1 108	• 30-day survival • Long-term survival[#] • Neurological outcome	Low
Twohig ⁷⁰ (2019)	9	2 626	• 30-day survival • Hospital discharge survival	Very low
Chen ⁶⁸ (2019)	13	3 026	• 30-day survival • Long-term survival[*] • Neurological outcome	Low

Legend: [#] defined as > 30 days; ^{*} 3, 6 and 12 months survival

Cardiogenic shock

We did not identify any recently published SRs comparing VA-ECMO to a control group.

Selection of the reference source and quality of retrieved evidence

Cardiac arrest

The two most recent identified documents, published in March and April 2020 were the HTA from Ontario HTA⁴⁶ and the SR from Miraglia et al.⁶⁹ Both studies were consistent (similarities in the included studies and results). The report from Ontario HTA displayed a higher level of quality. The studies included in both documents showed similar results for the different outcomes (survival and neurological outcomes).

Since the report from Ontario HTA had a higher quality, according to AMSTAR-2 criteria, and because it provided more detail on the quality of the studies and additional outcomes (weaning of ECMO and bridge to long-term VAD or heart transplant, complications), it was selected as the main source of evidence.

As indicated above in Table 21, the quality of studies included in the HTA report from Ontario was assessed with the NOS or ROBINS-I tool^a. The quality of studies was low.

Cardiogenic shock

Since no more recent SR comparing the effectiveness of VA-ECMO with other types of support were identified, the HTA from Ontario was chosen as the reference source for our review.

As indicated above in the Table 22, the quality of studies included in the HTA from Ontario HTA was assessed with the NOS or ROBINS-I tool^b. The quality of studies was low.

^a In the HTA report from Ontario Health, the quality of studies was extracted from the SR from Ouweneel et al. who used NOS. The quality of the additional included study was assessed by ROBINS-I.



4.3.2.2 Outcomes: results

Analysis of outcomes

Cardiac arrest

• Survival

Authors from the HTA Ontario performed a first analysis by pooling data for in- and out-of-hospital cardiac arrest and a second by making the distinction between the two types of cardiac arrest. Short-term (30 days) and long-term survival^a were analysed (within studies using propensity score matching):

- Overall, VA-ECMO was associated with a benefit in terms of 30-days survival (6 studies^{51-54, 56, 58}; 1 108 patients). According to GRADE, the quality of evidence was very low (See Table 24). However, when analyzed separately, a statistically significant benefit on 30-days survival was demonstrated only for patients who underwent in-hospital cardiac arrest (3 studies- 316 patients).^{51, 52, 58} Conversely, the pooled risk ratio for patients with out-of-hospital cardiac arrest was not statistically significant (2 studies^{53, 54}; 792 patients)
- VA-ECMO was associated with a benefit on long-term survival (5 studies^{48, 51, 52, 56, 58}; 468 patients). According to GRADE, the quality of evidence was low (See Table 24). When making the distinction, ECMO was associated with a statistically significant improvement of long-term survival both in and out-of- hospital (2 studies^{54, 56}; 152 patients) and in-hospital (3 studies^{51, 52, 58}; 316 patients) cardiac arrest (See Table 12).

• Neurological outcomes

Data for neurological outcomes were identically analysed, by pooling data (or not) between in and out-of-hospital cardiac arrest, at two different time-points (short and long-term), and within studies using propensity score

matching. Favourable neurological outcomes was determined as Cerebral Performance Category (CPC) score of 1 or 2, or a Modified Glasgow Outcome Score (MGOS) ≥ 4 (See Appendix 4.14).

- Overall VA-ECMO was significantly associated with a 30-day favourable neurological outcome when compared with conventional CPR (5 studies^{51-54, 58}; 1 060 patients). According to GRADE, the quality of the evidence was very low (See Table 24). The analysis separating in and out-of-hospital settings showed a benefit on the neurological outcome for patients who experienced in-hospital cardiac arrest (3 studies^{51, 52, 58}; 316 patients), but not for those who had out-of-hospital cardiac arrest (2 studies^{53, 54}; 744 patients).
- VA-ECMO was associated with long-term^a favourable neurological outcome (5 studies^{51, 52, 54, 56, 58}; 468 patients). According to GRADE, the quality of evidence was moderate (See Table 24). This association was shown both for patients who had in-hospital (3 studies^{51, 52, 58}; 316 patients) and out-of-hospital cardiac arrest (2 studies^{54, 56}; 152 patients).
- **ECMO weaning or bridge to long-term ventricular assist device or heart transplant**

Only one cohort study, conducted in 2008 focused on the successful weaning of ECMO, or on the fact that patients could receive a heart transplant or a long-term VAD, after being resuscitated.⁵² In this study, about half of the patients were weaned from ECMO (49.2%). In addition, the number of patients who received a heart transplant, or a long-term VAD, was significantly higher in the ECMO group when compared to patients who were treated by conventional CPR (See Table 24).

^a Defined according the follow-up duration of studies ranging between 3 and 24 months



• Complications

The rate of complications was poorly reported. In one study (353 patients)⁵¹ patients who received VA-ECMO had significantly more complications than those who received conventional CPR. These complications related to reduced vascularization of the legs, and bleeding (or haematoma) requiring blood transfusions.

The rates of sepsis or acute kidney injury were not different between both groups. The quality of the evidence was rated 'low' according to GRADE criteria (See Table 24).

Table 24 – Results from the meta-analysis undertaken in the report from Ontario HTA (use of ECMO for cardiac arrest)

Outcomes	Pooled risk ratio (95%CI)	Number of studies	Number of matched patients ^{\$}	Quality of evidence (GRADE)
30-day survival	- Overall: 1.54 (1.03-2.30) - In-hospital cardiac arrest: 2.03 (1.30-3.18) - Out-of-hospital cardiac arrest: 1.18 (0.71-1.97)	6 3 3	1 108 316 792	Very low
Long-term* survival	- Overall: 2.17 (1.37-3.44) - In-hospital cardiac arrest: 1.99 (1.16-3.41) - Out-of-hospital cardiac arrest: 2.74 (1.13-6.67)	5 3 2	468 316 152	Low
30-day favorable [#] neurological outcome	- Overall: 2.02 (1.29-3.16) - In-hospital cardiac arrest: 2.18 (1.24-3.81) - Out-of-hospital cardiac arrest: 2.61 (0.56-12.20)	5 3 2	1 060 316 744	Very low
Long-term* survival favorable [#] neurological outcome	- Overall: 2.86 (1.64-5.01) - In-hospital cardiac arrest: 2.50 (1.33-4.71) - Out-of-hospital cardiac arrest: 4.64 (1.41-15.25)	5 3 2	468 316 152	Moderate
Successfully weaned or bridged to long term VAD or heart transplant (1 study)	- ECMO weaning 49.2% - Heart transplant 8.5% (ECMO) vs 0% (CPR); p=0.004 - Long-term VAD 5.1% (ECMO) vs 0% (CPR); p=0.04	1	172	Very low
Complications	- Reduced vascularization of the legs 17.3% (ECMO) vs 1.9% (CPR); p=0.02 - Bleeding (or haematoma) requiring blood transfusions 32.7% (ECMO) vs 13.5% (CPR); p=0.03	1	353	Low

Legend: * Defined according the follow-up duration of studies ranging between 3 and 24 months; [#] based on the Cerebral Performance Category (CPC) scale= 1 or 2 or the Modified Glasgow Outcome Score ≥ 4 ; ^{\$} variables used for matching are presented in Appendix 7.



Cardiogenic shock

• Survival

Meta-analysis was undertaken according to the type of comparator group (See Table 25):

- VA-ECMO was associated with a significant improvement on 30-day survival when compared to IABP (2 studies^{62, 63}; 95 patients).
- Conversely, VA-ECMO was not associated with a benefit on 30-day survival when compared with temporary percutaneous VAD (2 studies^{60, 61}; 140 patients)
- One study compared VA-ECMO with temporary non-percutaneous VAD and showed a decrease of 30-day survival in patients treated with VA-ECMO (56 patients).⁶⁴ This study also reported a lower long-term survival at different time points (6, 12 and 48 months) with VA-ECMO.

The quality of the evidence was very low for 30-day and long-term survival, according to GRADE (See Table 25).

• Neurological outcome

No studies reported on neurological outcomes.

• ECMO weaning or bridge to long-term ventricular assist device or heart transplant

Two cohort studies^{60, 61} were focused on the successful weaning of ECMO, or on the fact that patients could receive a heart transplant or a long-term VAD, after cardiogenic shock. When comparing patients who were supported by VA-ECMO and those who were supported by a percutaneous VAD, the studies did not show any significant differences in the proportion of people weaned-off ECMO or who received a permanent VAD, or who were transplanted (See Table 25).

Only study focused on post-cardiotomy cardiogenic shock, compared ECMO, with non-percutaneous VAD implanted during surgery (Centrimag®-Thoratec, CA, USA). This study reported a significantly higher proportion of patients with successful weaning (or upgrade to long-term VAD) in the non-percutaneous VAD.⁶⁴ According to GRADE, the level of quality was very low.

• Complications

Two studies (135 patients) reported on the rate of complications.^{60, 64} Chamogeorgakis et al. did not identify more limb complications in patients under VA-ECMO or VAD.³⁸ Mohite et al. described more septic shock and systemic inflammatory response in patients who received VA-ECMO, in comparison with patients under non-percutaneous VAD. The other complications (haemorrhage, stroke, renal failure or hepatic failure) did not differ between the two groups. The quality of evidence was very low according to GRADE criteria (See Table 25).

**Table 25 – Results from the Ontario HTA on the use of ECMO for cardiogenic shock**

Outcomes	Pooled risk ratio (95%CI)	Number studies	of	Number matched patients	of	Quality of evidence (GRADE)
30-day survival	- ECMO vs IABP: 2.11 (1.23-3.61) - ECMO vs percutaneous VAD: 0.94 (0.67-1.30) - ECMO vs non-percutaneous VAD: 0.38 (0.16-0.86)	2		95		Very low
		2		140		
		1		56		
Long-term* survival	ECMO vs non-percutaneous VAD: lower survival (logrank p= 0.015)	1		56		Very low
30-day and long-term favorable neurological outcome	-	No study		-		-
Successfully weaned or bridged to long term VAD or heart transplant	- No significant difference in the proportions of weaned off bridged to long-term VAD or transplanted between ECMO or VAD groups - Successful weaning or upgrade to long-term VAD: 54% vs 28%;p=0.048	2		140		Very low
		1		56		
Complications	- Limb complications 13% (ECMO) vs 13% (VAD) - Septic shock 28% (ECMO) vs 4% (VAD) (p=0.01) - Systemic inflammatory response 50% (ECMO) vs 4% (VAD); p<0.001	1		79		Very low
		1		56		

Legend: * Defined according the follow-up duration of studies ranging between 3 and 24 months; ECMO: extracorporeal membrane oxygenation; VAD: ventricular assist device

Conclusion

Cardiac arrest

The evidence of the effectiveness of VA-ECMO compared to conventional CPR for cardiac arrest is limited and the quality of the evidence is low.

In comparison with conventional CPR:

- VA-ECMO may be associated with benefits in term of 30-day survival for patients who experienced in-hospital cardiac arrest. The level of uncertainty is nevertheless substantial (GRADE: Very Low)
- VA-ECMO may improve long-term^a survival both for in and out-of-hospital cardiac arrest. The quality of the evidence is nevertheless low (GRADE: low).
- VA-ECMO may be associated with a better 30-day neurological outcome^b as defined by the included studies, for patients who

^a Defined according the follow-up duration of studies ranging between 3 and 24 months

^b Neurological outcome is based on the Cerebral Performance Category (CPC) scale or the Modified Glasgow Outcome Score



experienced in-hospital cardiac arrest. Uncertainty is nevertheless high (GRADE: very low)

- VA-ECMO is associated with a better long-term neurological outcome as defined by the included studies (GRADE: moderate)
- VA-ECMO may be associated with more complications such as bleeding requiring blood transfusions or decreased vascularization of the leg (GRADE: low).

A similar interpretation was made by Miraglia et al.⁶⁹ (published in April 2020) for 30-day and long-term survival.

Cardiogenic shock

From the MA from Ontario HTA⁴⁶, it can be concluded that the evidence of the effectiveness of VA-ECMO compared to other type of management (IABP or VAD) for cardiogenic shock is very limited and the quality of evidence is very low.

- VA-ECMO may improve 30-day survival when compared to IABP but uncertainty is substantial (GRADE: very low).
- VA-ECMO may not be more effective than percutaneous VAD on 30-day survival (GRADE: very low). One study suggests that VA-ECMO may be associated with worsened 30-day and longer term survival, compared with non-percutaneous VAD but uncertainty is substantial (GRADE: very low).
- Only 3 studies reported on the weaning of mechanical supports (ECMO or VAD) or bridging to long-term VAD or heart transplantation.^{60, 61, 64} Results are heterogeneous and inconsistent: two studies did not report any difference between patients with ECMO versus transient VAD^{60, 61}, while one study described more patients who weaned-off from VAD than from ECMO.⁶⁴ The quality of the evidence is very low.
- Regarding the occurrence of complications, it is difficult to formulate sound conclusion since comparisons are heterogeneous. The quality of the evidence is very low. VA-ECMO may not be associated with more limb ischaemia when compared to percutaneous VAD. However, the

occurrence of septic shock and systemic inflammatory response may be more frequent in patients managed with VA-ECMO than those with non-percutaneous VAD.

Table 26 – General conclusions

Settings	Conclusions	Quality of evidence (GRADE)
Respiratory failure	In comparison with conventional mechanical ventilation, VV-ECMO is associated with a reduced mortality in patients with severe ARDS	Moderate [§]
Cardiac arrest	In comparison with conventional CPR, • VA-ECMO may improve: ○ 30-day survival (IHCA) ○ Long-term survival* (IHCA-OHCA) ○ 30-day neurological outcome[#] (IHCA) • VA-ECMO improves long-term neurological outcome • VA-ECMO may lead to more complications (bleeding requiring blood transfusions, decreased vascularization of the leg)	○ Very low ○ Low ○ Very Low Moderate Low
Cardiogenic shock	• In comparison with IABP, VA-ECMO may improve 30 day-survival • In comparison with percutaneous VAD, VA-ECMO may not be more effective	Very low Very low

Legend: ARDS: Acute respiratory distress syndrome; IHCA: in- hospital cardiac arrest; IABP: Intra-aortic balloon pump; OHCA: out-of- hospital cardiac arrest; VAD: ventricular assist device.

** Survival from 3 to 24 months; [#]defined as Cerebral Performance Category (CPC) scale: 1 or 2 or Modified Glasgow Outcome Score $\geq$ 4; [§] quality of evidence based only on randomized controlled trials and not on observational studies*



4.3.3 More recent evidence

As explained in our methods section, a question was posed to Belgian experts in this field regarding more recent studies or evidence not captured via our review of SRs. This was done during a virtual meeting held on the 21 of March 2022. Two additional publications were provided by experts during the expert consultation meeting: one phase- 2 RCT and one observational prospective study:

- An observational prospective cohort study included 63 refractory ventricular fibrillation/ventricular tachycardia out-of-hospital cardiac arrests. Through the implementation of a resuscitation program rapidly providing ECMO, authors showed a neurologically favorable^a survival to hospital discharge by 43%.⁷¹
- Another phase 2 open-label randomized trial (ARREST trial, set up by the same team) assigned 30 OHCA (ventricular fibrillation or pulseless ventricular tachycardia) patients to early ECMO-facilitated resuscitation or standard advanced cardiac life support (ACLS) treatment. Survival to hospital discharge was observed in 43% of patients in the ECMO resuscitation arm, whereas it was reported in 7% in the ACLS group (risk difference 36.2%; credible interval: 3.7-59.2; posterior probability of ECMO superiority: 0.9861). The study was stopped early at the first preplanned interim analysis because the posterior probability of ECMO superiority, exceeded the prespecified monitoring boundary.⁷²
- A single-centre RCT conducted in Czech republic assessed the effect of an early invasive management of 256 adults with refractory out-of-hospital cardiac arrest.⁷³ The early invasive strategy included a transport to a cardiac catheterisation centre for invasive treatment and extracorporeal cardiopulmonary resuscitation was performed (VA-ECMO) if a return of spontaneous circulation was not achieved. The

control group received standard advanced life support on site. The trial was stopped prematurely since the strategy did not improve survival with favourable neurological outcome at 180 days in comparison with the control group (OR: 1.63; 95%CI: 0.93-2.85). However, the authors mentioned that the trial was possibly underpowered to detect a clinically relevant difference.

4.4 Discussion

4.4.1 Main findings

According to our review, the current body of evidence is limited for both VA- and VV-ECMO and the quality of evidence is moderate at best.

- To date, the most robust evidence arises from the two multicenter RCTs^{9, 27} on the use of VV-ECMO, in a total of 429 ARDS patients. In patients suffering from severe ARDS, survival is improved with VV-ECMO. However, the level of quality is moderate, and it is important to mention that the interpretation of both studies is limited due to several drawbacks.^b In the study from Combes et al., the crossover between arms reached 28%.²⁷ The extent to which this cross-over may have reduced the effect size observed, remains unknown. In the trial from Peek et al., only 75% of patients in the intervention group received ECMO and the management regarding lung protective ventilation differed between arms.⁹
- In the setting of refractory cardiac arrest, the use of VA-ECMO is associated with an improvement of survival and neurological outcomes, mostly for in-hospital cardiac arrest. The quality of evidence is very low-to- low regarding 30-day favorable neurological outcomes and short and long-term survival. Patients who survived the early phase following

^a Defined as Cerebral Performance Category (CPC) 1 or 2.

^b A Bayesian approach was used to reanalyse the EOLIA trial: statistical prior distributions reflecting the degree of enthusiasm or scepticism of the effectiveness of ECMO were used to build probability models and a Bayesian

meta-analysis of previous published studies was performed. Authors showed that the posterior probability of any mortality benefit (risk ratio<1) with ECMO was high, ranging between 88 and 99%.⁷⁴.



cardiac arrest, have a better long-term neurological outcomes with VA-ECMO (the quality is rated as moderate).

- In the setting of cardiogenic shock, survival was increased with VA-ECMO only when the comparison was performed with IABP. No benefit is demonstrated when VA-ECMO is compared with other mechanical support percutaneous devices (VAD). One study even described a higher mortality of patients under ECMO in comparison with non-percutaneous VAD.⁶⁴ The level of the evidence is very low.

4.4.2 Limitations of available evidence

Aside from the most rigorously designed studies for VV-ECMO^{9, 27}, the studies on VA-ECMO have notable shortcomings.

- One of the first limitation arises from the study design. Both for cardiac arrest or cardiogenic shock, there is no RCT comparing VA-ECMO with standard therapies. Some studies using propensity scores are available for cardiac arrest patients, but none of the studies on cardiogenic shock used propensity score matched analysis to reduce the bias due to confounding variables. It is also important to mention that studies using propensity score matched only a proportion of included patients rather than the whole cohort. Besides, the samples size in the available studies is limited. As mentioned in the HTA from Ontario⁴⁶, this is a limitation since propensity score analysis works better in studies with a larger sample size.
- Another limitation comes from the heterogeneity of studies. As such, targeted patient populations vary across studies on cardiogenic shock. The most common reported etiology of cardiogenic shock is coronary syndrome. Nevertheless, some studies mixed other causes such as decompensated heart failure, myocarditis or post-surgery cardiogenic shock. This accounts for a substantial limitation since the natural

evolution (and the potential recovery) is different among the pooled diseases. A recent MA⁷⁵ (29 989 patients) showed that 30-day mortality of VA-ECMO varies across cardiogenic shock aetiologies. It was lower for myocarditis (40%), and higher after coronary syndrome (60%), or after surgery (59%).⁷⁵ The definition of cardiogenic shock also differed between studies.

The variety of comparator groups for cardiogenic shock also contributes to the heterogeneity. In our results, analysis were performed in each type of comparator (IABP, percutaneous or non-percutaneous VAD). Medical treatments (mainly inotropic drugs) were never a comparator group.

Moreover, IABP is no more routinely recommended by the guidelines^a and percutaneous VADs are not recommended due to the limited evidence on their benefit (Class IIb) (See Appendix 4.15).⁷⁶

- Studies are prone to selection bias. As mentioned in the HTA from Ontario⁴⁶, both for cardiogenic shock and cardiac arrest, the decision to use VA-ECMO was based on the judgement of the attending physician, in many studies. Even when propensity scores were used (CPR duration, initial rhythm, comorbidities) residual confounding/collider bias might have been present.
- Overall, complications occurring during the period under ECMO were poorly reported.
- Although most of the included studies on cardiac arrest were conducted in Asian countries, quite similar results were also observed in other more recent studies performed in the US.

^a Guidelines from the European Society of Cardiology (ESC): IABP may only be considered in patients with mechanical complications (Class IIa C recommendation)⁷⁴

**Shortcomings of studies on VA-ECMO :**

- Design: no RCT, propensity scores assumption, limited sample size
- Heterogeneity:
 - Comparator groups variations for cardiogenic shock (temporary percutaneous or nonpercutaneous VAD, IABP, medical treatment);
 - Various aetiologies of cardiogenic shock
 - Variations in the definition of cardiogenic shock (heterogeneous criteria to start ECMO)
- Difficulty to generalise findings : IABP no more routinely recommended in cardiogenic shock; VAD not routinely recommended by the guidelines.
- Selection bias: decision to use VA-ECMO in cardiac arrest or cardiogenic shock based on the judgement of the treating physician, in studies

4.4.3 Limitation of this review

- First, we did not conduct a conventional SR of literature. Nevertheless, our approach was inspired by the Ottawa method for rapid reviews,²⁵ during which evidence was extracted from studies with a moderate-high quality according to AMSTAR-2 criteria. In addition to this, a consultation of experts was conducted to ensure that no important references, would be missing from our overview.
- Second, due to our selection criteria, the scope of our research was limited to the most common indications of ECMO. Several rarer conditions that might require ECMO were not considered such as VA-

ECMO for severe pulmonary embolism as a cause of cardiogenic shock and cardiac arrest. Evidence for this indication will have to be further determined.

4.4.4 Perspectives and ongoing studies

There is still considerable uncertainty regarding the benefits of ECMO, notably for cardiogenic shock and cardiac arrest.

- Currently^a, four multicentric RCTs assessing the efficacy of VA-ECMO for cardiogenic shock compared to medical treatment (i.e. pharmacological treatments such as inotropes) are in progress (See Table 27). Those trials will provide an information of utmost importance because up to now, many studies have performed comparisons mainly with other mechanical support devices.
 - The EURO SHOCK trial and the ECLS SHOCK trial are multicenter international studies that randomize patients between VA-ECMO therapy and standard care (medical treatment only; no mechanical support devices) for cardiogenic shock after acute coronary syndrome. Their primary outcome is 30-day survival. A cost-effectiveness is planned in the EURO SHOCK trial. Results are expected by August 2023 (ECLS SHOCK) and February 2024 (EURO SHOCK), respectively. The third trial (the ECMO-CS Trial) is being conducted in the Czech Republic and will include less patients (See Table 27).
 - The multicentric ANCHOR trial is quite similar and will assess the efficiency of VA-ECMO combined with IABP^b versus conventional treatment (excluding any mechanical support device) after coronary syndrome. Their primary outcome is 30-day survival. Results are expected by February 2024.

^a Last search conducted the 06th December 2021 on ClinicalTrials website (www.clinicaltrials.gov)

^b IABP is used with the aim to unload the left ventricle



- With regard to out-of-hospital cardiac arrest, the efficacy of VA-ECMO is being explored in the INCEPTION randomized trial: it aims to determine the effect on survival and neurological outcomes in patients who had ventricular fibrillation. A cost-effectiveness analysis will also be conducted (See Table 27).
- To our best knowledge, after the RCTs from Combes et al. and Peek et al. no further RCTs on the efficacy of VV-ECMO in patients with ARDS have been pursued. Combes et al. mentioned that another large study on the effectiveness of VV-ECMO in ARDS patients is unlikely mainly due to ethical considerations, and that future research should focus on the identification of the patients most likely to benefit from ECMO and on optimization of treatment strategies after ECMO initiation (prone positioning during ECMO, ventilatory strategies, transfusion policy, early physical therapy).³⁸

Table 27 – Ongoing studies of interest^a

NCT number	Title	Status	Estimated completion date
NCT03813134	Testing the Value of Novel Strategy and Its Cost Efficacy in Order to Improve the Poor Outcomes in Cardiogenic Shock (EUROSHOCK)	Ongoing	February 2024
NCT04184635	Assessment of ECMO in Acute Myocardial Infarction Cardiogenic Shock (ANCHOR)	Ongoing	November 2024
NCT03637205	Prospective Randomized Multicenter Study Comparing Extracorporeal Life Support Plus Optimal Medical Care Versus Optimal Medical Care Alone in Patients With Acute Myocardial Infarction Complicated by Cardiogenic Shock Undergoing Revascularization (ECLS-SHOCK)	Ongoing	August 2023
NCT04990349	Normoxemic Versus Hyperoxemic Extracorporeal Oxygenation in Patients Supported by Veno-arterial ECMO for Cardiogenic Shock (ECMOxy)	Not yet recruiting	December 2022
NCT04039594	Outcomes of Patients With Venoarterial Extracorporeal Membrane Oxygenation	Recruiting	July 2025
NCT04728932	LEVOSIMENDAN to Facilitate Weaning From ECMO in Severe Cardiogenic Shock Patients (LEVOECMO)	Completed	November 2023

^a References retrieved from the consulted HTA reports with an update conducted on December 06th 2021 (studies that were referred as 'ongoing' in

the reports from HTA and that are now published were not reported in the table)



NCT03549923	Evaluation of Early CRRT InTerventions in Patients With ECMO (ELITE)	Recruiting	April 2022
NCT04330651	Post-Surgery Extracorporeal Life Support (PC-ECLS)	Recruiting	January 2029
NCT04405817	Outcome of Patients Treated With ECLS	Recruiting	December 2025
NCT02527031	A Comparative Study Between a Pre-hospital and an In-hospital Circulatory Support Strategy (ECMO) in Refractory Cardiac Arrest (APACAR 2)	Not recruiting	Unknown
NCT03528291	Transient Circulatory Support in Cardiogenic Shock (ALLOASSIST)	Recruiting	Unknown
NCT03101787	Early Initiation of Extracorporeal Life Support in Refractory OHCA (INCEPTION)	Unknown	Unknown
NCT03658759	ECPR Treatment Protocol: Rapid Response VA-ECMO in Refractory Out-of-hospital Cardiac Arrest (RESuSCITATe Registry)	Unknown	Unknown
NCT02754193	Effects of Induced Moderate Hypothermia on Mortality in Cardiogenic Shock Patients Rescued by Veno-arterial Extra Corporeal Membrane Oxygenation (Hypo-ECMO)	Completed	Study completed
NCT03592810	Multi-center Observational Study to Assess Optimal ECMO Settings During the First Hours of Extracorporeal Cardiopulmonary Resuscitation	Completed	Unknown
NCT03431467	A Prospective Randomised Trial of Early LV Venting Using Impella CP for Recovery in Patients With Cardiogenic Shock Managed With VA-ECMO (REVERSE)	Recruiting	January 2025
NCT02301819	ExtraCorporeal Membrane Oxygenation in the Therapy of Cardiogenic Shock (ECMO-CS)	Recruiting	December 2022
NCT03021538	Bypass vs. ECMO in Lung Transplantation (BELT)	Terminated (failure to enroll)	/

Legend: DSMB: Data Safety and Monitoring Board



5 REVIEW OF LITERATURE: ORGANIZATION OF ECMO SERVICES

Key-Points

- ECMO is a challenging and high-risk technique. Clustering ECMO cases in high-volume centres has been shown to be associated with better outcomes. A favourable relationship between yearly ECMO volume and outcomes has been reported in various studies (after adjustment for confounding variables).
- Overall, the minimum annual cut-off for ECMO cases to observe an effect on outcomes, ranges from 15 to 20.
- Studies that have not shown a beneficial relationship between ECMO volume and outcomes were generally limited since they were based on administrative registries comprising few clinical data.
- International guidelines and expert recommendations advocate for organising ECMO services in high volume centres in order to gain the sufficient level of expertise.
- ECMO volume threshold is not the only surrogate marker to assess the expertise of centres. Several organisational factors are recommended by guidelines: standardised protocols for the eligibility of patients for ECMO, continuous education of team members, hospital networks connected by ECMO mobile teams, or analyses of outcomes through registries.

5.1 Introduction

In many countries, the utilisation of ECMO grew over the past decade.⁷⁷ This increase followed the publication of two studies showing better outcomes for patients with respiratory failure, transferred to reference centres performing VV-ECMO.^{5, 9, 41}

Since then, the number of centers performing ECMO has grown internationally. However, experts have stated that this rise has mostly come about in the absence of oversight or coordination.⁷⁸ Indeed, as described in our International comparison (See Chapter 7), the organisation of ECMO by healthcare services varies considerably among countries, with few adopting a centralised approach, despite the fact that the international guidelines from ELSO advocate for centralised ECMO services.⁵ The rationale of the concept of centralisation is that increasing the volume of ECMO cases in a limited number of reference centres, promotes efficiency and safety.

This chapter focuses on the centralisation of ECMO services and other organisational aspects required to successfully implement an ECMO program.

5.2 Research question and methods

This chapter looks at the organisational factors that could play a role in the efficiency and safety of ECMO. More specifically, it focuses on the centralisation of ECMO services into reference centres. The research question was formulated as follows: “Does centralisation of ECMO services bring benefits in terms of effectiveness and safety?”.

To this end, the same stepwise approach used in our clinical review chapter, was used to identify any relevant study (See Chapter 4 for details, including search terms):



- First, any Health Technology Assessments (HTAs) identified via our search in the INAHTA database^a and the EunetHTA POP Database.^b studying the impact of centralization on outcomes were considered, and used as the starting point of our review.
- Second, the search for recent systematic reviews previously mentioned (See Chapter 4 for details and appendix 4.1 for full search strategy), was used to also identify any SRs on factors having an impact on ECMO's efficacy and or safety.
- It was followed by a snowballing approach from the references of the articles identified in the previous steps, to retrieve further documents. Moreover, we consulted the ELSO international guidelines and a retrieval of grey literature was performed through Google Advanced. The following words were used: ("ECMO" OR "ECLS") AND ("centralization" OR "organization").
- Finally, we consulted experts to request references of any publication that was not included in our review, and that could be informative from their point of view.

Our research question was formulated using the PICOS (Participants-Interventions-Comparator-Outcomes-Study Design) framework (See Table 28).

^a <https://database.inahta.org/>

Table 28 – PICO strategy- inclusion criteria

	Inclusion	Exclusion
Participants	Adults (≥ 18 years) requiring ECMO for circulatory or respiratory failure	• Children • Neonatal
Intervention	VV-ECMO and or VA-ECMO	/
Comparator(s)	Comparison between high and low ECMO volume centres	/
Outcome(s)	Efficacy (survival) and safety (adverse events)	/
Studies	Observational studies Systematic review Guidelines	/

5.3 Results

5.3.1 Evidence retrieved from HTA agencies

Only one HTA from the National Institute of Excellence in Health Care and Social Services from Quebec (Institut national d'excellence en santé et en service sociaux- INESSS) was retrieved.²⁶ This HTA was used as the starting point of our review. It addressed the organisational aspects of the implementation of ECMO services.

The authors of this report identified only an Italian study that assessed the impact of a centralised and structured ECMO program.⁷⁹ Cotza et al. compared the survival of patients before and after adopting the ELSO guidelines in one centre (i.e. formal team management composed by a clinician ECMO director and a staff coordinator, internal guidelines, teaching and collecting and discussing data). They showed a decrease of hospital

^b <https://www.eunetha.eu/pop-database/> Covering HTAs that are ongoing, planned, or published in the last 3 months.



mortality (62% versus 44%) along with an increase in patients discharged from hospital (12.5% versus 44%). However, this study included a very small number of patients (n=18) and no statistics were performed.

The HTA mentioned that no clear conclusion could be drawn based on this single study, and referred to the ELSO guidelines (See Section 1.1.1).

5.3.2 Evidence retrieved from literature

5.3.2.1 Included studies

We identified 11 studies assessing the impact of centralisation on effectiveness or safety. Results are presented in Table 29. Four studies were from the US⁸⁰⁻⁸³, 3 from Europe (Germany^{84, 85}, France⁸⁶), and 3 from Asia (Korea^{87, 88}, Japan⁸⁹). Nine were retrospective cohort studies based on the analysis of data from national or international registries.^{80-83, 85, 87-90} One of these studies included international data retrieved from the ELSO registry.⁹⁰ Two studies assessed the impact of the implementation of an ECMO program through a design before-after, in one centre.^{79, 84} A study was a retrospective analysis of data prospectively collected during the first hit of the SARS-CoV-2 pandemic in France.⁸⁶ Among studies based on registry analysis, the sample sizes varied from 1 197 to 56 222^a. The number of included patients in studies not based on registries ranged from 18 to 302.

All studies reported on hospital mortality, while one study focused on 90-day survival.⁹¹ Two studies reported on the association of ECMO volume and the occurrence of complications^{80, 85} and a further one on the proportion of patients weaned off from ECMO.⁷⁹ One study focused specifically on interhospital transfers of patients requiring ECMO.⁸⁰

Ten studies provided adjusted odds ratio.^{80-85, 88-91} One study provided crude mortality data according to the type of centre⁸⁷, and the remaining was only descriptive and did not perform a statistical analysis.⁷⁹

Information on the type of ECMO cannulation was available in 6 studies.^{79, 84-86, 89, 90}

Two studies focused exclusively on VV-ECMO,^{86, 89} whereas one study included only VA-ECMO.⁸⁵ Clinical information related to the indications of ECMO was not reported in 2 studies.^{82, 88}

Effects of centralisation

Studies with a favorable effect on outcome

A benefit on survival was reported by the majority of studies: 8 studies described an association between the volume of ECMO cases and the outcome (See Table 2).

- Among them, 6 studies were based on national or international registries:

International: The study from Barbaro et al. was the first to find an association between higher hospital ECMO volume and lower adjusted mortality, for patients supported with ECMO during the time frame 1989-2013.⁹⁰ Authors used the data of 290 hospitals, from the ELSO registry and included 56 222 patients, among which 10 588 were adults. The analysis was adjusted for a number of mortality risk factors (See Table 1). The relationship was observed for high (>30 cases per year), medium (15-30 cases per year), and intermediate ECMO volume centres (6-14 cases per year), when compared to low-volume centres that performed less than 6 ECMO annually (See Table 29 – Description and results of included studies). Interestingly, authors also considered a subgroup of patients included between 2008 and 2013, corresponding to a period during which technology innovation occurred and the use of ECMO went up. The beneficial volume-outcome relationship persisted in this subgroup.

- Europe: The study from Becher et al. analysed data from a German health database and focused on VA-ECMO for cardiogenic

^a It should be noted that the study from Barbaro et al. included 56 222 patients but only 10 588 were adults.



shock^{a,85} They described an association between low volume VA-ECMO and poorer survival, along with the occurrence of several complications (bleeding, stroke, abdominal ischemia, and limb ischemia). The analysis was adjusted for pertinent variables associated with outcome. It should be noted that the thresholds to define the experience of centres were considerably high and that low-category centres corresponded to an annual volume reaching 50 VA-ECMO.

- Asia: Three studies conducted in Korea and Japan analysed data from national registries.⁸⁷⁻⁸⁹ Korean studies included both types of ECMO^{87, 88} while the Japanese one focused on VV-ECMO.⁸⁹ The three studies identified a relationship between higher ECMO volumes and better hospital survival. Two studies⁸⁷⁻⁸⁹ reported odds ratio adjusted for relevant variables while the other described the crude mortality ratio according to the annual ECMO volume.¹³ It should be mentioned that the thresholds were heterogeneous. In the Korean studies, the lowest volume category was defined by thresholds of 10 and 20, respectively.^{87, 88} It is probably related to the different time frame analysed in both studies: the study with the lowest thresholds analysed data from 2004 when ECMO was not so widely used. For patients with respiratory failure, the Japanese study set the lower and upper thresholds at 8 and 17, respectively.
- US: The study from Aguayo et al. specifically targeted patients who required to be transferred to an ECMO-centre.⁸⁰ They showed that low-volume centre status was associated with a higher risk of hospital mortality, when compared with high volume centre status (adjustment was performed based on age, gender and comorbidities). In this study, there was no delineated thresholds since they were defined according to the tertiles of the ECMO volume distribution.

- A German study compared, two periods corresponding to low and high volume ECMO time frames between 2011 and 2016. They observed a relationship of high volume with better hospital survival.⁸⁴
- A recent study, conducted in France during the first wave of the SARS-CoV-2 pandemic, reported on the results of a new ECMO network organisation.⁸⁶ From March 2020, the surge in demand for VV-ECMO led ICUs to reorganise their services by a centralised approach for ECMO services in the region of Ile de France ('Great Paris'). Though a multivariate analysis, authors showed a relationship between high ECMO volume centres (≥ 30 VV-ECMO/year) with a better 90-day survival, when compared to low ECMO volume hospitals (< 30 VV-ECMO/year).

Studies without a favorable effect on outcome

Three studies did not identify a positive impact of the centralization of ECMO services on the outcome of patients (See Table 2).⁸¹⁻⁸³ The three studies analysed national administrative registries: two studies used the same US-national registry (US-National Inpatient Sample)^{81, 83}, while one study retrieved data limited to the state of Pennsylvania, US.⁸² Due to the administrative nature of the database, all studies displayed a lack of detailed clinical data, including the type of cannulation (VA versus VV-ECMO), for instance. For this reason, authors did not have access to specific clinical variables and their analysis was very partially adjusted for confounders.

- Both studies carried out with the data from the US National Inpatient Sample, showed that patients admitted in high and medium ECMO volume centres were less likely to survive after discharge, in comparison with low volume centres.^{81, 83} In these studies, the categorisation of ECMO volume was based on the tertiles of ECMO volume distribution and not on a determined threshold volume. It is worth noting that the indications of ECMO differed between studies. In the most recent study, post-cardiotomy cardiogenic shock was the aetiology accounting for almost half of the patients. Conversely, this aetiology was excluded in

^a Post-cardiotomy shock was excluded



the older study. For both studies, respiratory failure was the second most frequent reason to initiate ECMO.

- In the study conducted on the registry from Pennsylvania⁸², it was found that there was little evidence on a relationship between volume and outcome: once hospitals had as few as 50 cases total cumulative

experience or performed just 10 cases annually, there was no clear improvement in outcomes. In their model, there was no more relationship of annual ECMO volume with risk-adjusted mortality beyond the threshold of 10 cases/year, or a total cumulative experience of 50 cases (curve essentially flat).

Table 29 – Description and results of included studies

Study	Design and Sample Size	Study population	Results
Barbaro et al.⁹⁰ (2015)	Retrospective multicentre study (from ELSO registry) n = 56 222	Data from 290 hospitals between 1989 and 2013: • Neonates (n= 30 909) • Children (n = 14 725) • Adults (n = 10 588) Among adults: • VA-ECMO 51% • VV-ECMO 49% Number of patients per yearly ECMO volume category between 2008-2013: • 621 (1-5/year) • 1 249 (6-14/year) • 2 099 (15-30 /year) • 3 790 (> 30/year)	• Association of high ECMO volume (> 30/year) and medium ECMO volume (15-30/year) with lower hospital mortality, in comparison with low-volumes centres (< 6/year): • High volume (>30/year): ○ aOR* (95CI): 0.61 (0.48-0.79) for the period 1989-2013 ○ aOR* (95CI): 0.61 (0.46-0.80) for the period 2008-2013 • Medium volume (15-30/year): ○ aOR* (95CI): 0.75 (0.59-0.94) for the period 1989-2013 ○ aOR* (95CI): 0.72 (0.55-0.96) for the period 2008-2013 • Intermediate volume (6-14/year): ○ aOR* (95CI): 0.81 (0.66-0.99) for the period 1989-2013 ○ aOR* (95CI): 0.82 (0.64-1.05) for the period 2008-2013 * adjustment was made on: calendar year, age, primary diagnosis, ECMO type, pre-ECMO acute renal failure, comorbidities, pre-ECMO cardiac arrest, pre-ECMO measures including duration of mechanical ventilation, arterial blood pH, PaCO₂, PF ratio
Lebreton et al.⁸⁶ (2021)	Retrospective multicentre study n = 302	Patients with severe ARDS due to COVID-19 and requiring VV-ECMO	• Association of high ECMO volume (≥ 30 VV-ECMO/year) with higher 90-day survival, in comparison with centres with < 30 VV-ECMO/year: ○ aOR* (95CI) 2.98 (1.46-6.04) * adjusted on: pre-ECMO, high-dose corticosteroids, diabetes, hypertension, immunocompromised, mobile ECMO Transfer, neuromuscular blockade, pre-ECMO PaCO₂, Pre-



Study	Design and Sample Size	Study population	Results
			ECMO plateau pressure, pre-ECMO prone positioning, pre-ECMO liver component of the SOFA score, pre-ECMO cardiovascular component of the SOFA score, pre-ECMO PF ratio
Bailey et al.⁸¹ (2018)	Retrospective multicentre study (from national registry in US-National Inpatient Sample) n = 18 684	Adult patients who received ECMO between 2008 and 2014: - Post cardiectomy 42% - Heart transplant 4% - Lung transplant 6% - Cardiogenic shock 5% - Respiratory failure 43% Number of patients per yearly ECMO volume terciles*: 2 548 (low) 5 278 (medium) 10 858 (high)	- Association of high ECMO volume with higher hospital mortality, in comparison with low ECMO volume centres: - aOR* (95CI): 1.61 (1.25-2.07) - Other variables associated with hospital mortality aOR* (95CI): - Cardiogenic shock (reference: postcardiotomy) 2.23 (1.55-3.21) - Respiratory failure (reference: postcardiotomy) 1.81 (1.51-2.17) - Lung transplant (reference: postcardiotomy) 0.51 (0.36-0.71) - Age 1.01 (1.01-1.02) - Female gender 0.85 (0.73-0.98) - Coronary disease 1.28 (1.00-1.63) - Heart failure 0.81 (0.69-0.96) - Hypertension 0.52 (0.42-0.64) - Diabetes 0.79 (0.63-0.99) - Chronic pulmonary disease 0.76 (0.59-0.96) - Peripheral vascular disease 1.61 (1.24-2.09) - Comorbidities (Elixhauser score) 1.16 (1.09-1.22)
			*adjusted on socioeconomic, demographic, and comorbid factors
McCarthy et al.⁸³ (2016)	Retrospective multicentre study (from national registry in US-National Inpatient Sample) n = 1 197	Adult patients who received ECMO between 2002 and 2011: - Cardiogenic shock 53% - Respiratory failure 29% - Heart transplant 5% - Lung transplant 12% - Trauma/drowning 1%	- Association of high ECMO volume with higher mortality in comparison with low ECMO volume centre: aOR* (95CI): 1.89 (1.31-2.70) - Other variables associated with hospital mortality; aOR* (95CI): - Gender (male) 1.85 (1.49-2.30) - Elective admission 0.51 (0.37-0.70) - Respiratory failure (reference: cardiogenic shock or cardiopulmonary failure) 0.68 (0.47-0.98) - Arteria hypertension 0.41 (0.28-0.61) - Congestive heart failure 1.44 (1.00-2.07)



Study	Design and Sample Size	Study population	Results
		Number of patients per annual ECMO volume terciles*: • 467 (low) • 285 (medium) • 445 (high)	○ Lung transplant (reference: cardiogenic shock or cardiopulmonary failure) 0.37 (0.23-0.60) ○ Pulmonary circulation disorder 2.05 (1.34-3.14) ○ Coagulopathy 1.58 (1.11-2.26) ○ Obesity 0.49 (0.31-0.77) ○ Weight loss 0.21 (0.14-0.34) * adjusted on baseline patient-related demographics, patients' comorbidities, ECMO indications, and potential similarities among patients within a single institution
Banjas et al.⁸⁴ (2018)	Retrospective single centre study in Germany (pre-post) n = 131	Adult patients who received ECMO between 2011 and 2016, in one centre (comparison of two periods 2011-2013 and 2014-2016): • Lung failure (41%) • Cardiogenic shock (44%) • Septic shock* (15%) * use of VVA-ECMO	• Higher in-hospital mortality was associated with the period of time with < 20 ECMO/year: ○ aOR* (95CI): 3.19 (1.19-8.51) • Other variables associated with hospital mortality aOR* (95CI): ○ Age 1.08 (1.04-1.12) ○ Lactate (pre-ECMO) 1.01 (1.00-1.02) * adjustment variables not clearly mentioned
Becher et al.⁸⁵ (2020)	Retrospective study on a nationwide registry: German Federal Health Monitoring System n = 10 207	Adult patients who received VA-ECMO* between 2013 and 2016: • Acute coronary syndrome 60.8% • Acute heart failure 37.5% • Post-heart transplantation 1.8% Number of patients per yearly ECMO volume category: • 5 421 (≤ 50/year) • 2 799 (50-100/year)	• Association of high ECMO volume (>100/year) with lower 30-day in-hospital mortality in comparison with low ECMO volume centres (≤ 50/year): aOR* (95CI): 0.88 (0.78-0.99) • Association of low ECMO volume (≤ 50/year) with complications (bleeding, stroke, abdominal ischaemia, and limb ischaemia) in comparison with high ECMO volume (> 100/year): ○ aOR** (95CI): 1.46 (1.29-1.66) * adjusted on age, sex, prior cardiopulmonary resuscitation, indication categories (post-heart transplantation, acute coronary syndrome, acute heart failure), duration of VA-ECMO support, and complications (bleeding, stroke, abdominal ischaemia, and limb ischaemia) ** adjusted on the same variables except complications and with the time to 30-day in-hospital mortality



Study	Design and Sample Size	Study population	Results
		1 987 (> 100/year)	
Huesch M.⁸² (2018)	Retrospective study using administrative discharge data in one US state (no medical records available) n = 2 948	Adults patients who received ECMO from 2007 to 2015	Limited positive association between greater experience (cumulative ECMO volume over time) or annual ECMO volume and risk-adjusted mortality: above 50 cumulative cases or 10 annual cases, there is no more relationship with risk-adjusted mortality (curve essentially flat)
Tay et al.⁸⁸ (2019)	Retrospective study using a nationwide healthcare administrative database (Korean National Health Insurance) n = 5 751	Adults patients who received ECMO from 2009 to 2014 Number of patients per annually ECMO volume category: 2 186 (< 20/year) 1 818 (20-39/year) 1 747 (≥ 40/year)	- Association of low ECMO volume (< 20/year) with higher in-hospital mortality in comparison with high ECMO volume (≥ 40/year): - aOR* (95CI): 1.70 (1.01-2.88) - aOR* (95CI): 1.82 (1.05-3.16) * adjusted on age, gender, Charlson Comorbidity Index and the need for continuous renal replacement therapy ** adjusted on the type of hospital (tertiary or general), and experience: an experienced ECMO center was defined as one that had at least a year of experience since its first ECMO case).
Muguruma et al.⁸⁹ (2020)	Retrospective study using a Japanese nationwide inpatient database n = 1 277	Adults patients who received ECMO for respiratory failure from 2010 to 2018 Number of patients per yearly ECMO volume category: 400 (< 8/year) 419 (8-16/year) 458 (≥ 17/year)	- Association of high ECMO volume (≥ 17/year) with lower hospital mortality (in comparison with low-volumes centres (< 8/year)^{\$}: - aOR* (95CI): 0.58 (0.39-0.87) ^{\$} aOR were also calculated with redefined cut offs similar to those from ELSO (reference centres < 6 ECMO/year): - aOR* (95CI): 0.87 (0.59-1.28) 6-14 ECMO/year - aOR* (95CI): 0.60 (0.40-0.91) 15-30 ECMO/year - aOR* (95CI): 0.78 (0.41-1.46) > 30 ECMO/year * adjusted for age, immunocompromised status, duration of mechanical ventilation, use prior to initiation of ECMO (0–2, 3–6, and ≥ 7 days), acute respiratory diagnosis group, central nervous system dysfunction before ECMO, acute associated non-pulmonary infection, neuro-muscular blockade agent before ECMO, bicarbonate infusion before ECMO, cardiac arrest before ECMO



Study	Design and Sample Size	Study population	Results
Aguayo et al.⁸⁰ (2020)	Retrospective multicentre study (from national registry in US-National Inpatient Sample) n = 11 408	Adult patients who were transferred to ECMO centres and placed on ECMO at the receiving hospital from 2010 to 2016 Number of patients per annual ECMO volume terciles: • 2 818 (low) • 4 214 (medium) • 3 776 (high)	- Association of low ECMO volume with hospital mortality in comparison with high ECMO volume: - aOR* (95CI): 1.35 (1.02-1.79) - In the subgroup of patients with cardiogenic shock aOR* (95CI): 2.25 (1.03-5.03) - No statistically significant differences in renal, respiratory, cardiac, infectious, or overall complications high and low-volume centres (no multivariate analysis performed)
Jang et al.⁸⁷ (2021)	Retrospective study using a nationwide healthcare administrative database (Korean National Health Insurance) n = 14 689	Adult patients who received ECMO between 2004 and 2017 • Tertiary hospitals 70% • General hospitals 30%	- High-volume hospitals showed statistically significant higher survival than low-volume hospitals. In-hospital mortality per annual ECMO volume: 76.5% (<10/year) 72.9% (0-19/year) 70.9% (20-49/year) 60.5% (50/year)

*age, gender, and comorbidities

Legend: aOR: adjusted odds ratio; 95CI: 95% confidence interval; ECMO: extracorporeal membrane oxygenation; ELSO: Extracorporeal Life Support Organization; PaCO₂: arterial partial pressure of carbon dioxide; PF ratio: ratio between arterial partial pressure in oxygen and inspired fraction of oxygen; SOFA score: Sequential Organ Failure Assessment score; VA-ECMO: veno-arterial extracorporeal membrane oxygenation; VV-ECMO: veno-venous extracorporeal membrane oxygenation

5.3.3 International guidelines and experts position

In this section we refer to the guidelines from the Extracorporeal Life Support Organization (ELSO) on the organization of ECMO centres.⁵

In addition, our search in the medical literature identified two articles ('position paper') on respiratory⁹² and cardiac failure⁹³, resulting from the opinion of experts of international groups of ECMO specialists. The position paper on respiratory failure has been included in the ELSO guidelines. The results of this section are presented in a table format (See Table 30, Table 31 and Table 32).

**Table 30 – Guidelines from Extracorporeal Life Support Organization (ELSO) on the organisation of ECMO centres⁵**

Components	Recommendations
General structure and ECMO volume	ECMO centre should be located in tertiary hospitals and in geographic areas that can support a minimum of 6 ECMO per centre per year
Staffing issues	A multidisciplinary ECMO team should be available and coordinated by a medical director (responsibility for the overall operation of the centre) and a ECMO coordinator (nurse, physiotherapist or perfusionist) in charge of the supervision and training of the technical staff, maintenance of equipment, and collection of data
Physical facilities and equipment	• ECMO equipment should be readily available (components and back up components of the ECMO system and supplies for all circuit components) • Device for monitoring the level of anticoagulation • 24/7 availability of laboratory, imaging, blood bank, cardiovascular operating room with cardiopulmonary bypass capabilities
Staff training and continuing education	ECMO centre should have a well-defined program for ECMO staff training (didactic lectures, bedside training, emergency training)
Selection criteria	Formal policy and procedures outlining indications and contraindications for ECMO, clinical management and maintenance of equipment should be available.
Data collection	ECMO centre should be actively involved in the ELSO, including participation to the ELSO registry
Mobile ECMO	A team for interhospital transport should be 24/7 available in each centre ^a

Table 31 – Summary of international experts consensus on the organisation of ECMO services for respiratory failure, included in ELSO guidelines⁹²

Components	Recommendations
General structure and ECMO volume	• ECMO should be organised in expert high-volume tertiary centres. • Annual volume should be at least 20 ECMO per year with a minimum of 12 ECMO cases for respiratory failure. • ECMO for cardiac and respiratory indications should be located in the same centre (not necessarily in the same ICU department) • Emergency access (<30 minute) to cardiovascular or thoracic surgery, abdominal surgery, oesophagogastroduodenal endoscopic interventions and interventional radiology.
Staffing issues	The ratio nurses to patient should be at least 1:1 to 1:2
Physical facilities and equipment	Equipment (and primed circuit) should be available for immediate use
Staff training and continuing education	• Continuing education and training for interhospital transport should be routinely performed. • Physicians should be trained in vascular and cardiac Doppler echography

^a According to ELSO guidelines, the team should include a cannulating physician, ECMO physician, a ECMO specialist (responsibility for ensuring equipment and priming/preparation of transport ECMO circuit and management of ECMO circuit), a transport nurse and ideally (if vehicle space allows) a transport respiratory therapist.



Selection criteria	Standardised protocols outlining indications and contraindications for ECMO, along with optimisation of conventional treatments before consider ECMO should be available.
Data collection	ECMO centre should be actively involved in the ELSO, including participation to the ELSO registry
Mobile ECMO	Mobile ECMO team should be implemented in a networks of hospital (regional or interregional level) transferring patients to the reference centre, and 24/7 available.

Table 32 – Summary of international experts consensus on the organisation of ECMO services for cardiac failure⁹³

Components	Recommendations
General structure and ECMO volume	• VA-ECMO for cardiac failure should ideally be performed at experienced, high-volume centers capable of providing other forms of advanced cardiac support, including percutaneous coronary interventions and long-term heart replacement therapies (e.g. ventricular assist devices and heart transplantation). • Centres should achieve at least 30 ECMO per year (substantial proportion of VA-ECMO for cardiac failure).
Staffing issues	Every team member should receive a specific ECMO training and demonstrate competencies on an ongoing basis.
Physical facilities and equipment	Centres should have a continual access to the facilities, equipment, and staffing necessary for both routine ECMO management and management of unanticipated emergencies of ECMO complications
Staff training and continuing education	ECMO staff should receive regular training and education on theoretical and practical aspects of ECMO, including simulation training whenever available.
Selection criteria	The use of pre-specified inclusion and exclusion criteria for consideration of ECMO should be used to facilitate a standardized approach that can be implemented expeditiously
Data collection	• Participation in national or international databases provides a standard against which programs can benchmark their performance. • Given the relative lack of high-level evidence for ECMO in cardiac failure, ECMO centers are encouraged to participate in large, multicenter registries
Mobile ECMO	Both local centers that may or may not have percutaneous coronary interventions capabilities but without the capabilities of ECMO management, should have affiliations with reference centers in order to have appropriate access to ECMO



5.4 Discussion and main findings

Because ECMO is a complex and high-risk technique, it has been hypothesised that limiting its use in high volume centres would increase the expertise required to safely and successfully implement its utilisation. Factors that would potentially lead to better outcomes include the development of highly skilled teams along with the development of specialised infrastructures and technologies. Besides, gathering cases in a limited numbers of centres facilitates the training and could contribute to standardise the management of patients. Organisational aspects in specialized centres, such as a high ratio nurse-to-patient ratio, may also play a role.

A relationship between volume and outcome has already been described in various medical fields also including intensive care medicine.^{94, 95} Historically, regarding the use of ECMO, two studies revealed that the strategy of gathering patients with respiratory failure to specialised ECMO centres was associated with a better survival.^{9, 41} Since then, many clinicians started to use the technique. The number of ECMO was used as a surrogate for expertise. However, the required threshold volume to gain sufficient expertise was not determined.

- In this review, we identified many publications reporting on a beneficial relationship between ECMO volume and outcome. The majority of publications offer retrospective analyses of national or international registries. One of the most important studies conducted with the data from the international ELSO registry on a considerable number of patients.⁹⁰ Its main limitation is that hospitals joining this registry do not necessarily account for a sample representative of all hospitals performing ECMO. Providing data in the ELSO registry is indeed made on a voluntary basis by hospitals that are ELSO members. However, we noticed that similar results were also observed in other studies not conducted on national registries.^{84, 86} This supports a favourable volume-outcome association. In this line, the study Tay et al showed that even after adjustment for type of hospital and experience, the association was clearly in favour of high volume centres.⁸⁸ It should be mentioned that the duration of ECMO runs is generally lacking in studies and could also participate to the expertise of ECMO

management, since longer ECMO runs duration gives more opportunity to gain knowledge (weaning, technical aspects such as oxygenator replacement, complications management,...).

Nevertheless, the positive connection between volume and outcome is not uniformly observed in studies. One study showed no clear association and two others⁸¹⁻⁸³ reported an inverse relationship with higher mortality in high-volume compared to low-volume centres (See Table 29). This results is difficult to compare with the studies that showed a benefit of gathering ECMO cases in high-volume centres. Indeed, it is important to emphasize that those studies were conducted on administrative registries comprising few clinical data. Therefore, their multivariate analysis was not adjusted to important clinical variables (in contrast to the studies that showed a benefit of centralisation). For instance, the type of cannulation (VV versus VA-ECMO), the use of mechanical ventilation or clinical parameters related to the global severity were lacking. Authors of those studies conceded that this was a substantial limitation and mentioned that they could not exclude a selection bias. Moreover, no clear threshold was mentioned since the categorisation of centres was based on percentiles of institutional ECMO volume. Another explanation suggested by the authors is that high volume centres have a more liberal utilisation of ECMO and include generally more severely- ill patients. In this line, a study⁸² suggested that patients admitted in low-volume centres appeared less severely sick, but it should be mentioned that this was based on the results of laboratory tests, which clinical relevance is considerably limited.

- We noticed that the cut- off values on ECMO volume were approximately similar in the retrieved studies showing a beneficial outcome-volume relationship. Overall, the minimum annual cut-off ranges from 15 to 20 to observe an effect on outcome. An exception would be the German study by Becher et al. that contrasted considerably from other studies and in which the lowest cut-off volume was set at 50 ECMO/year.⁸⁵ No comparison can be made with other studies since this minimal value exceeds the maximal threshold of other studies.



- Finally, it is worth noting that an ECMO volume threshold should not be the only surrogate marker to be considered to assess expertise. As mentioned by Barbaro et al., such a minimum volume threshold may introduce a perverse incentive for centers to provide ECMO support to patients whose clinical circumstances may be marginally indicative for ECMO.⁹⁰ In addition to the annual ECMO volume, other organisational factors certainly play a key-role in the optimal development of an ECMO program and should be taken into account. They include:
 - The development of standardised protocols for the eligibility of patients.
 - The development of strict protocol for the clinical process of care.
 - Continuous education for team members.
 - The presence of a registry and an analysis of outcomes with benchmarking to other centres.
 - The presence of hospital networks with mobile ECMO ensuring interhospital transfers.

Two recent publications on the organization of ECMO during COVID-19 outbreak have controversial results. In a retrospective analysis of ELSO registry including 4 812 ECMO patients, Barbaro et al investigated the relationship between survival and the time at which ECMO was started, by defining ECMO early-adopting centres (centres that adopted ECMO for COVID-19 patients early during the pandemic, i.e on or before May 2020) and late-adopting centres (centres that only provided ECMO for COVID-19 after May 1, 2020).⁹⁶ Authors showed that the mortality at 90 days was lower in centres with greater experience providing ECMO to COVID-19 patients. Conversely, another multicentre retrospective study reported the outcome of patients admitted in 19 centres located in Middle East or India. Among those, 14 centres were already using ECMO before the pandemic.⁹⁷ Four were high-volume centres (> 20 ECMO/year) and new 5 centres started

ECMO in 2020 for covering the demand of COVID-19 patients. The recommendation of ELSO were rigorously applied in the newly-launched centres (training program, patient selection by national experts, high nurse-to-patient ratio, supervision by telemedicine programs). In multivariate analysis, authors showed that there was no statistically significant relationship between the type of centres (new versus established) and outcome.^a Although this second publication emphasized that newly established centres benefiting from a close supervision may provide favourable outcome, it should be noted that the sample size was rather limited (307 patients). In addition the rate of prone positioning prior to ECMO was considerably low (52%) and authors recognized that they cannot exclude that some patients would have improved with this therapy and might have avoided ECMO.

^a Adjusted odds ratio for 60-day discharge: new centre (reference=established centre): 1.65; 95%CI: 0.75-3.67



6 PATIENT PERSPECTIVES AND ETHICAL ASPECTS WITH ECMO USE

6.1 Introduction

The general context in which ECMO is used, implies urgent medical decisions, in situations in which the life of the patient is at risk, and thus, physicians' must act on the best interest of the patient (art. 8, §5 patients' rights law).

Patients eligible for ECMO treatment are severely ill, and unable to participate in treatment decisions. Even in those cases in which an "advanced negative directive" exists, the patients' rights law requires that a well-defined intervention is refused, (i.e. in this case the ECMO) for this to be valid (art. 8 § 4 in fine Patients' rights law). A too general description of the refused treatment or a refusal of any action, would not meet this requirement. This is also the case if there are situations that patients could not foresee. Under these circumstances, given the incapacity of these patients to offer their consent, surrogate decision-makers, which may not necessarily always be family members or carers, often play an important role (art. 14 Patients' rights law).

Although studying patient and family/carers perspectives, as well as ethical aspects linked to the use of ECMO was thought to deserve consideration, a conscious decision was made not to involve patients or family members in this research mainly for two reasons:

First, the complexity and efforts that would imply their identification and involvement would deserve a broader analysis on ethical aspects surrounding highly-invasive potentially lifesaving interventions in the ICU, (and not only ECMO) in those situations, in which patients are most often unable to actively participate in clinical decisions. Second, the selection of patients for such research would be unavoidably biased towards survivors,

who would be more positive towards ECMO, while covering the views of family carers of those who did not survive would be highly complex.

6.2 Methods

Instead, and in order to still cover or highlight important aspects, from a patient or family/carers perspective, a search for good quality HTA reports (including such component) was carried out. With this in mind, the websites of HTA institutes listed on the INAHTA (International Network of Agencies for Health Technology Assessment) and the EUnetHTA (European network of Health technology agencies) websites were consulted (search date: February 2022) via their respective databases^a to capture recent (published from 2010) reports on ECMO for patients with respiratory or cardiac failure.

The MESH term used for the search in the INAHTA database was: "Extra Corporeal membrane Oxygenation". In the EUnetHTA database, the search terms used were : ECMO OR "Extracorporeal Membrane Oxygenation".

6.3 Results

The two Canadian HTAs already described in our review of the clinical literature^{26, 46} both included the patients/family carers perspective, with INESSS focusing on a review of the literature on this regard for both VA and VV-ECMO, and Ontario including interviews to four patients and four family carers for VA-ECMO.

The Ontario HTA⁴⁶ interviewed patients or family carers mostly connected to lung or heart transplantation programmes. No cases of ECMO being used as ECPR for cardiac arrest were identified. Generally, the selection bias of these patients or family carers resulted in a positive view of ECMO, as temporary support to stabilise their severe medical conditions. Patients relied mainly on the expertise and judgement of health care providers given the life threatening medical conditions they suffered from. Two family carers of patients who died after having received ECMO were included in this

^a INAHTA: <https://database.inahta.org/>

EUnetHTA: <https://eunethta.eu/pop-database/> . This database covers HTAs that are ongoing, planned, or published in the last 3 months.



interviews, but the cause of death in these cases was not considered to be due to the ECMO and thus, their impressions were nevertheless, positive towards the device.

The HTA by INESSS²⁶ focused primarily on the literature and identified four SRs and a cohort study, of variable quality. The authors of this HTA found that most of the available studies focused on approaches that could improve communication and support to family members or carers of severely ill patients. Outcomes were mainly subjective, mostly measuring satisfaction, stress or anxiety levels. None of these studies were specifically linked to ECMO use and were instead broader in their scope.

Finally, one very recent study by the Canadian HTA agency CADTH⁹⁸, specifically on ECMO was identified. The focus of this study was on experiences and perspectives of both survivors (and/or family carers) and healthcare providers confronted with ECMO support for respiratory failure.

The authors of the review performed a search on multiple databases, including Medline and EMBASE, but limited their search to English language studies published between January 2010 and May 2021.

The studies identified were critically appraised according to Krefting's methods for assessing trustworthiness in qualitative research and were considered to have a level of trustworthiness from high to moderate.⁹⁹

Overall 9 studies were identified and their findings were described narratively. The main conclusions were the following:

When family members were asked to act as surrogate decisionmakers for patient, regarding the possible initiation of ECMO, this was not perceived by them as a choice, but rather as a necessity, given the urgency and the fact that the alternative was an almost certain death. They therefore, saw ECMO as a hope and a lifesaving intervention and accepted the decision from physicians. Physicians based such decisions on the clinical prognosis of each individual patient.

Once the patient was on ECMO, both family carers and physicians faced great uncertainty regarding the changes of recovery. When patients did not respond to ECMO, family members felt they had done everything they could

to save their lives. while physicians, on the contrary, considered it a failure (wrong patient selection).

Family carers expressed experiencing important challenges linked to the need to be close to the ICU services during the ECMO intervention. Financial and logistical support was thought to be important for them during those moments.

Clear, frequent information was thought to be crucial for the reassurance of family members, although information needs varied from one situation to another. The role of formal or informal peer-support was thought to be of great value.

Family carers and providers differed in their views on the limits of ECMO support and time for withdrawal, as well as on who should have the authority and responsibility to decide whether to continue ECMO. Standardise protocols on this regard that could bring transparency and clarity in decision making and could even be helpful to solve some of those discrepancies.

The transfer of ECMO patients from one centre to another was perceived by family members to be disruptive and in those situations, effective coordination and communication was thought to be of great value. Some providers mentioned also the importance of involving family carers, or even deferring the decision to withdraw ECMO to them, instead of purely informing them, given their better knowledge of patients and their wishes.

Patients and family carers continue to suffer from anxiety and emotional (or physical) distress even once discharge home. Supporting programmes could be beneficial in these circumstances.

The limitations mentioned in this review, mirrored those of the previous HTAs, with only one study including family members of non survivors and a potential bias towards healthier participants in these exercises versus other "sicker" survivors, which poses questions on the potential transferability of these results.



7 INTERNATIONAL COMPARISON ON THE USE AND THE FUNDING OF ECMO

With the contribution of F. S. Taccone^a as co-author

Key-points

- Among the selected countries in the international comparison, only the UK and Italy have a centralized organization of ECMO services. This type of organization is based on expert high-volume ECMO centres to which peripheral hospitals refer patients through mobile ECMO units. Such countries have a limited number of ECMO centres that are distributed according to the geography and population density.
- In accordance to international guidelines, countries with centralized ECMO services have defined the requirements for ECMO centres including the composition, the skills and the training of ECMO teams, the characteristics of hospitals providing ECMO (cardiothoracic surgery), the continuous education and the assessment of outcomes (compulsory participation to national and international registries).
- All selected countries have developed the capacity to transfer patients requiring ECMO through mobile ECMO teams. The level of organization and availability varies considerably between countries.
- Funding mechanisms for ECMO vary substantially between countries. They include daily lump-sums, in the UK and in Belgium, fixed single lump-sums in the Netherlands and Belgium, time dependent single lump-sums in Italy, and DRGs

(non-ECMO specific) in France. Funding amounts also vary greatly between the studies countries

7.1 Introduction

In many countries, despite limited evidence supporting the effectiveness of extracorporeal life support (ECLS) (See Chapter 4), its use in healthcare services has increasingly grown over the last decade.⁵ This rise followed the H1N1 flu epidemic, in the course of which ECMO was successfully used, and the results from a RCT conducted in the UK, showing potential benefits of veno-venous ECMO (VV-ECMO) in the setting of respiratory failure.²

This growing interest and eagerness for VV and VA-ECMO could also be associated with improved techniques and equipment on the one hand⁷⁸, and with accumulated expertise of treating physicians on the other. ICUs have also been developing over time and improving the quality of care and outcomes.¹⁰⁰

This has subsequently led to an increased utilisation of intensive care medical resources¹⁰¹ and to a significant growth in expenditure in this field, across healthcare systems.^{102, 103} The organisation of ECMO varies considerably among countries and there still remains a need to determine the most optimal way to set up ECMO services.

Belgium has also experienced a similar increase in ECMO use as seen internationally (See Chapter 2), while data on its outcomes remain scarce. Its organisation varies from one centre to another and it remains unclear whether the current reimbursement of ECMO covers the real costs linked to its use.

In order to draw insights for the Belgian healthcare system, an international comparison was conducted across a panel of European, neighbouring countries (France, Italy, the Netherlands and the UK), with similar health care systems to that of Belgium, but different organisation and funding

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methods for ECMO. The selection of countries and the identification of foreign experts was done with the help of a Belgian ECMO expert, and by reviewing scientific publications and grey literature.

7.2 Methods

Information gathering was performed by means of a written questionnaire that was sent to experts, in July 2021. One expert per country was invited to fill in the questionnaire, which was elaborated in partnership with a Belgian expert (see Table 33 for more details). The names of the consulted experts are mentioned in the colophon of this report. These international experts did not take part in the drafting of this chapter and cannot be held responsible for its content. They did not receive a fee for their contribution.

Complementary relevant information was sought by consulting governmental websites, epidemiological institutes and healthcare organisations, in each country. Regarding the organisation of ECMO services in Belgium, we consulted a Belgian expert along with members of the Belgian Society of Intensive Care Medicine (SIZ)^a. Costs data and reimbursement rules were extracted from the National Institute for Health and Disability Insurance national sickness fund (compulsory insurance) (NIHDI/RIZIV/INAMI^b).

Table 33 – International comparison of ECMO management and funding in Belgium, France, Italy, the Netherlands and the UK.

- The identification of experts and the country selection was developed together with a Belgian expert by reviewing scientific publications, grey literature, through personal European contacts of Belgian experts and via other contacts suggested by the European experts originally identified.
- A questionnaire was elaborated and sent to international experts in ECMO, in July 2021. It was written in English and included 10 questions requiring a response in free text. Sections included the clinical organisation (centralisation and regulations at national level, requirements for implementation, mobile ECMO program) and funding (global costs, reimbursement/financing rules). For the questions regarding costs or funding/reimbursement, specific instructions were given to ask for an opinion from financial managers or economist-colleagues, if required. The full questionnaire is available in Appendix 6.1. In addition, some experts were contacted through video-conference meetings.
- The responses received were analysed by KCE researchers. Respondents were re-contacted if any clarification was necessary and their answers were completed by data retrieved from national guidelines or official administrative documents of the different countries.

^a <https://www.siz.be/>

^b <https://www.inami.fgov.be/fr/Pages/default.aspx>;
<https://www.inami.fgov.be/nl/Pages/default.aspx>



7.3 Results

7.3.1 Countries with a centralisation of ECMO services

7.3.1.1 The concept of centralisation

Among the countries included in our analysis, ECMO services are centralised in the UK and Italy. In the UK, the centralisation is nationally organised, while in Italy, this was also the case until 2018, but it is now managed at the regional level. In such centralised so-called 'Hub and Spoke' model, the ECMO centre is considered as the hub to which peripheral centres refer patients requiring ECMO.⁹² Transfer of patients is performed by specialised teams, called retrieval teams, able to implant ECMO cannulas at the bedside from the referring hospital, before safely transporting patients on ECMO (or postponing its initiation until the patient is deemed able to be rapidly transferred to the reference ECMO centre).^{8, 104, 105}

This way to set up ECMO services was largely promoted by the results of two studies performed in the UK.¹⁰⁶ The CESAR trial, published in 2009⁹ showed that the strategy of transferring patients with respiratory failure to ECMO centres brought about benefits in terms of survival. The other study was conducted during the influenza A (H1N1) pandemic and demonstrated a significantly lower mortality in patients who were referred for ECMO to one of the nationally designated ECMO respiratory centres, when compared to non-ECMO patients (For more information on these, see Chapter 4).⁴¹

The literature specifically considering the impact on the centralization of ECMO on outcomes is discussed in detail in Chapter 5. Nevertheless, hereunder, we provide a summary of the main advantages based on key-references of literature from specific studies^{9, 27, 90}, or resulting from expert-based consensus.^{5, 78, 92, 93} According to these sources, the centralisation of ECMO services could be associated to the following advantages:

- Since ECMO is a complex therapy with high risk of adverse events, its centralisation allows to promote the development of skilled teams and maintain a high level of experience. As such, increasing the volume of cases fosters a safe and efficient level of care.

- Centralisation allows to gather and promote the access and availability of ancillary resources required for a successful practice of ECMO (surgery services, interventional radiology, imaging, blood bank).
- Specialised ECMO consultants can be reached 24/7 for referral, but also for provision of advice (phone consultation).
- The variability of clinical practice is reduced: the access to ECMO is regulated according to standardised eligibility criteria, based on national standards.
- The transfer of patients to reference centres can be optimally organised through the development of mobile ECMO teams (being part of the reference centres). Teams with ECMO-skilled members (intensivist, nurse, perfusionist, surgeon) are dedicated to initiate ECMO at peripheral centres and safely transfer patients under ECMO to the reference centres. They are 24/7 available. These teams are equipped with devices (monitoring, ventilator, pumps,...) specifically adapted to the transport that is custom made for the provision of ECMO during the journey (ground ambulance, helicopter, aircraft).
- A real-time nationwide registry is easier to implement. It allows to manage bed capacity and anticipate an appropriate and rapid response in case of surge demand of ECMO.
- Communication of data in registries facilitates the improvement of care, research and education.
- Centralisation could allow to better control the costs and optimise the utilisation of resources.

In contrast, the literature has also highlighted possible disadvantages that critical care services centralization could present and that could apply to ECMO¹⁰⁷:

- a delay in access to ECMO;
- an increased risk of complications during the transfer, or clinical worsening (mainly if the patient is transferred without an ECMO) ;
- a loss of skills and clinical experience in peripheral centres.



7.3.1.2 Description

United Kingdom

In 2010-2011, the UK public health care system (National Health Service-NHS) drew up a large structured and centralised VV-ECMO network service¹⁰⁸, covering the whole territory.^a The overall organisation is endorsed by NHS England/NHS Scotland^b Highly specialised services commissioning. The oversight consists of commissioners and NHS Medical directors.

- There are six commissioned centres for the provision of VV-ECMO, each covering a specified geographical area: two in London (Royal Brompton and Harefield Hospital, Guy's and Thomas' Hospital), Cambridge (Papworth Hospital), Leicester (Glenfield Hospital), Manchester (Wythenshawe Hospital) and Aberdeen (Aberdeen Royal Infirmary). The last centre is used as a surge centre, when the capacity of the other centres is exceeded. Referrals of patients are organised according to the geographical location of the hospital asking to transfer a patient. Each of these commissioned centres cover a population from 10 to 15 million people.^c (See Appendix 6.2) Factors that were used to recognize centres as reference ECMO centre are presented in Table 34.
- Websites (referral pathway-NHS) have been set up and clearly mention what patients are eligible for ECMO, and all the required information.^d Specialised care givers can be reached by phone 24/7 for referral and also for provision of advice.

- The required minimum number of ECMO per year has been set at 20 ECMO/year. Each centre generally treats 30 patients with VV-ECMO per year, on average.
- Surge demand of ECMO is managed through a national guideline. A planned and structured strategy of management of surge demand of ECMO services has been established at a national level, through a standardised operating procedure form.^{109, 110} It aims at giving fast access to ECMO services and maximizing the capacity.

Table 34 – Key-factors in the recognition as adult ECMO centres across the UK¹¹¹

- Being a member of (and reporting data to) the Extracorporeal Life Support Organisation (ELSO)^e
- Formal team management composed by a clinician ECMO director (responsibility for the overall operation of the centre) and a coordinator (responsibility for the supervision and training of the technical staff, maintenance of equipment, and collection of data).^e
- ECMO specialist nurses and multidisciplinary ECMO team including intensivists specialised in ECMO, perfusionists and surgeons
- Each centre to provide its own dedicated mobile ECMO team, which must be capable of providing mobile ECMO retrieval
- Collaboration between centres when capacity is reached (national plan of surge demand in ECMO)¹⁷

^a <https://www.signpost.healthcare/ecmo-referral-pathway>

^b Referrals from North Wales are made to Manchester. Referrals from South Wales are made to London (St Thomas' Hospital) and referrals from Northern Ireland are made to Leicester.

^c Other ECMO centres are specifically dedicated for indications of ECMO in the paediatric population

^d Example of referral pathway: <https://www.rbht.nhs.uk/our-services/clinical-support/critical-care-and-anaesthesia/ecmo-and-severe-respiratory-failure/ecmo-referrals-and-transfer-pathway>

^e <https://www.elseo.org/>



- Participation to biannual national collaborative clinical governance meetings to present and discuss the results (indication, outcome,...) of centres.

Italy

In the setting of the H1N1 outbreak in 2009, the Italian Ministry of Health set up a national network of intensive care units¹¹² that included 14 ECMO centers (See Appendix 6.3) for adults and two centers for neonatal/paediatric ECMO, mainly located in tertiary centres (ECMOnet, today called Rete Respira).¹¹³ The network covers all Italian regions, each area referring primarily to one ECMO center. It remained organised at the nationwide level until 2018 and is now managed at the regional level.¹¹⁴

- The board leading the network is made up of two intensivists that coordinate the communication between the Health Ministry and the ECMOnet, and lead its organisation and functioning.¹¹³
- A 24/7 national Call Center Service sorts out and directs any request for transfer to the closest ECMO center (and/or the transportation ECMO team)
- There is no determined minimum number of ECMOs required per year.

7.3.1.3 Teams and resources

Staff characteristics

- In both countries, teams include staff members specifically trained for ECMO (physicians, nurses and perfusionist), who are 24/7 available in the ICU^{a, 108, 113}
- In the UK, having followed a specialised training is compulsory¹⁰⁸ for both physicians and nurses, while an annual certificate renewal is mandatory for nurses. Accredited ECMO training programs are run in several references centres in the UK^b. Courses are held over several days and are organised for all members of the multidisciplinary team involved in the care of patients supported with ECMO.
- In Italy, when the network was created, ten sessions of a 3-day ECMO training course, open to physicians, perfusionists, and nurses of the ECMOnet were organised¹¹³ and master classes are still organised in the country.
- In the UK, the ratio of nurses per patient is 1:2 (no physician-to-patient ratio), while in Italy, no specific ratio (physician or nurse to patient ratio) was communicated by the consulted expert.

Resources and interdependence with other hospital departments

In both countries, centres have to be based within units with expertise in the management of severe respiratory failure, and must be collocated with a cardiothoracic surgery department. The centres are generally tertiary hospitals.

^a In the UK, a respiratory therapist is also included in the ECMO team

^b For instance, theoretical and practical/interactive courses are run in Royal Papworth Hospital in Cambridge ([https://royalpapworth.nhs.uk/health-professionals/papworth-professional-development/critical-care-](https://royalpapworth.nhs.uk/health-professionals/papworth-professional-development/critical-care-courses/ecmo-courses)

[courses/ecmo-courses](https://royalpapworth.nhs.uk/health-professionals/papworth-professional-development/critical-care-courses/ecmo-courses)) or Glenfield Hospital in Leicester (<https://www.leicestershospitals.nhs.uk/aboutus/departments-services/heart-services/ecmo/ecmo-training/>)



In the UK, ECMO centres must be part of a local critical care ODN (operational delivery network). ODNs are networks focused on coordinating patient pathways between providers over a wide area, to ensure access to specialist resources and expertise.^a

In Italy, both VV and VA-ECMO have to be performed in the same centre (both techniques cannot be used separately in distinct centres).

Mobile ECMO

In both countries, mobile ECMO services cover interhospital transportation throughout the whole country, and are performed by road or air, according to the distance to be travelled.^{112, 114-116} After ECMO is weaned, patients are generally repatriated to the referring hospital.

- In the UK, the provision of mobile ECMO is particularly structured. The covered area has been determined according to the transport time needed to reach the ECMO centre and the population covered. All reference centres provide their own integrated ECMO Mobile Units including a physician, a nurse and a perfusionist. If the ECMO team considers initiating ECMO from the referring hospital, it asks for an available operating theatre (or interventional radiology) with theatre team and a radiographer capable of operating the radiological devices (C-arm/fluorography), an ultrasound machine and provision of crossmatched blood. The patient is transported afterwards on extracorporeal support.^{b c 117}
- In Italy, there is no defined covered area, but patients are generally transferred to the nearest ECMO centre. Five of the centres assured interhospital transportation throughout the Italian territory, whenever the

nearest ECMO net centre can not receive the patient (See Appendix 6.4).¹¹³ There is no specific requirement regarding the composition of the retrieval team (mobile ECMO team) but it usually includes ICU doctors and nurses, along with a perfusionist. Some teams may include a cardiothoracic surgeon.¹¹²

7.3.1.4 Regulatory frame in terms of data collection and quality of care

- In both countries, the reporting of data to the health authorities is mandatory (to the NHS in the UK or to the Health Ministry and reimbursement office in Italy). In the UK, a register is continuously updated, but not publicly available. It may nonetheless become available via the Intensive Care National Audit and Research Centre (ICNARC) in the future.^d
- Reporting all outcomes to the Extracorporeal Life Support Organisation (ELSO), to allow international benchmarking, is mandatory in the UK, whereas this is not the case in Italy^e. Nevertheless, 13 out of the 14 Italian ECMO reference centres provide data to the ELSO registry at present.
- The UK ECMO centres have to specifically fulfil other requirements:
 - Centres must adhere to the standard operating procedures for management of surge and escalation in critical care (See Table 34) and support NHS England Emergency Preparedness, Resilience and Response (EPRR) planning, which is a strategic national framework aiming to organise the response in case of any incident, event or outbreak of disease.^f

^a <https://www.england.nhs.uk/ourwork/part-rel/odn/>

^b Sometimes, the patient can be transferred without ECMO for further assessment at the ECMO centre (if sufficiently stable to be mobilised).

^c <https://www.londonccn.nhs.uk/training-research/transfer-videos/ecmo-transfers/>

^d ICNARC is a clinical trial unit from the NIHR (National Institute of health research) that aims to improve the care and outcomes of critically ill patients through national clinical audits. (<https://www.icnarc.org/About/Overview>)

^e Sixteen centres are registered in ELSO in Italy.

^f <https://www.england.nhs.uk/ourwork/epr/>



- Centres have to present their data on accepted and declined referrals, and outcomes of patients (survival, morbidity) during meetings biannually organised at the national level, with all ECMO centres. In each centre, those statistics are also discussed during meetings held monthly (morbidity-mortality discussion).

7.3.1.5 Funding

- ECMO services are funded through lump-sums in both countries. Experts mentioned that there is no separate specific reimbursement for the disposables or additional expenditure (imaging, lab tests, surgery,...) used for ECMO. The billing can only be performed by medical specialities authorised to implant ECMO (mainly intensivists and cardiothoracic surgeons).
 - In the UK, healthcare expenditures consumed for ECMO are fully covered by NHS Tariffs, and are set out at the national level (although slight differences exist between hospitals): ECMO services for adults with respiratory failure is being commissioned by NHS England^a. Only designated specialised centres that are commissioned may provide adult VV-ECMO and the related intensive care services. Currently, there is no commissioned pathway for ECMO for acute cardiogenic shock or cardiac arrest^b.^{118, 119} While centres may provide ECMO for other indications, this is not funded by the healthcare system. Tariffs are not in the public domain. Average reimbursement communicated by the expert is of approximately £5000 per day for an inpatient stay. It should be noted that this lump-sum is paid instead of a

normal bed tariff and thus, covers all other general hospital costs along with the costs related to the use of ECMO.

- In Italy, no single national tariff exists, and instead reimbursement varies among regions. These regional tariffs are not publicly available. In Lombardy, for instance, for each ECMO implanted, the reimbursement is linked to the duration of the ECMO run: for < 24 hours the amount is €27 800, while it reaches €37 000 for an ECMO run >24 hours and < 30 days and €74 200 for an ECMO run > 30 days. It should be noted that this is, similar to what we saw in the case of the UK, a global lump-sum covering all costs associated with the ICU stay, and not only those specifically linked to the use of ECMO.
- Patients retrieval by ECMO mobile teams are fully covered by the Italian and UK healthcare systems. In the UK, an amount of approximately £3000 is paid for the retrieval of patients. In Italy, this lump-sum is €5000.

7.3.2 Countries without centralised ECMO services

In the other countries of our analysis, ECMO services are not currently centralised and their organisation varies considerably. This implies that ECMO is used in many ICUs throughout the countries, with no formal particular requirements or restrictions for centres that are willing to develop the technique. As such, contrary to what is recommended in national and international guidelines, and in contrast with centralised systems where these guidelines are respected and closely followed, ECMO can be

^a Specialised services aim at supporting people with a range of rare and complex medical or surgical conditions and are delivered by specialised healthcare providers. They are usually provided in few hospitals and accessed by a small number of patients (rare and complex conditions). Those services also support pioneering clinical practice in the NHS. The Clinical Priorities Advisory Group (CPAG) determines which services are

commissioned. Prioritisation is made according to the clinical benefits and costs (<https://www.england.nhs.uk/commissioning/>).

^b Success with VV-ECMO transfer has resulted in some centers to similarly consider transfer of patients with refractory cardiogenic shock who are too unstable to transfer without mechanical circulatory support.²⁸



implemented in centres regardless of hospital structure and the availability of resources and equipment, such as cardiothoracic surgery.

7.3.2.1 Description

Belgium and France

- In Belgium and France, there is no guidance on how to develop an ECMO program, nor particular prerequisite or condition for centres that are carrying out such a program. Theoretically, each ICU is allowed to use ECMO. There is therefore, no determined minimum yearly threshold of ECMO patients.
- In Belgium, although ECMO is used in several hospitals without cardiothoracic surgery, the technique is mainly implemented in ICUs located in larger hospitals (but not necessarily tertiary care university centres). As such, patients can be referred from hospital without ECMO to those larger centres.
- In addition to this, some ICUs have specifically developed the VV-ECMO technique and are able to run and wean uncomplicated ECMO. According to interhospital collaborative networks, patients are secondarily transferred under ECMO to tertiary centres, if necessary (e.g. in case of severe complications or difficult weaning).

Based on the specific nomenclature billing codes (See Table 2), the Belgian National Institute for Health and Disability Insurance has shown that, the number of individuals receiving ECMO and subsequent expenditures have substantially increased between 2011 and 2019 in Belgium^{a,10}

^a It should be noticed that this amount corresponds exclusively to the specific nomenclature billing codes and does not take into account all related costs such as staff or hospitalisation costs.

The Netherlands

- In The Netherlands, the use of ECMO in adults has not yet been structurally organised,¹²⁰ but one of the consulted experts explained that the SARS-CoV-2 pandemic has led the medical community to start thinking about how ECMO services could be reorganised and centralised in the near future. This new vision will probably lead to build a structured planification of surges in demand of ECMO. There are many hospitals currently using ECMO, with some of them being low-volume centres (5 to 6 ECMO per year). The majority of patients requiring ECMO are nonetheless, treated in high-volume tertiary centers.
- In 2016, the ECLS (Extracorporeal Life Support) study group from the Dutch Society for Intensive Care Medicine (NIVC-Nederlandse Vereniging voor Intensive Care)^b published national guidelines on the indication of ECMO and organisation among centers.¹²¹ The recommendations were based on expert opinion. The study group advocated for centres to fulfill those requirements and to implement ECMO in centers where cardiothoracic surgeons and perfusionists are available. They made the distinction between centers according to the volume and the cardiac surgery activity:
 - Cardiac centres where only VA-ECMO is performed.
 - ECMO center where VV and VA- ECMO are performed with a minimal threshold of 6 ECMO/year.
 - ECMO expert centers where VV and VA- ECMO are performed with a least 30 ECMO/year.

The study group discouraged from using ECMO in small volume centres (described as less than 6 ECMO cases per year) and emphasized the lower mortality rate described in high-volume centres (See Chapter 5).^{90, 121}

^b <https://nivic.nl/>



Authors were of the opinion that clear agreements within regions were necessary to gather patients in expert centres, so that sufficient expertise can be gained.¹²¹ These guidelines have mainly an advisory value and do not represent a legal duty.

7.3.2.2 Teams and resources

Staff characteristics

Belgium and France

- In both countries, certified intensive care specialists must be 24/7 present in ICU but there is no other particular legal skill-requirement neither for physicians nor for nurses or perfusionists. Nurse staffing is legally defined since 1998 in Belgium, when a federal law set up the minimal level at 1 nurse per 3 patients^a. In France, the legal ratio nurse-to-patient was set up at 2 nurses for 5 ICU patients in 2006^b. There is no specific nurse or doctor ratio defined for ECMO patients, and such ratio varies highly between ICUs. In France, high volume ECMO ICUs have ECMO-qualified staff combined with a 24/7 available perfusionist and the nurse to patients ratio is 1:2.
- In practice, although ECMO certification is not legally required for healthcare givers, staff members of ICUs using ECMO follow generally education programs that are organised by some experts centres, mainly in France. This training is generally endorsed by universities in the form of a complementary diploma (See Appendix 6.5).
- In both countries, perfusionists are nurses who complemented their education with a specific training provided by professional

organisations: Belgian Society for Extra-Corporeal Circulation Technology (BELSECT^c) and Société Française d'Assistance Circulatoire et de Circulation Extra-Corporelle^d. Two schools provide training to become a clinical perfusionist, both for Dutch and French-speaking nurses in Belgium (Leuven^e, Liège^f), while several training courses are organised in France^g.

The Netherlands

- There is no specific guidance on the composition of the staffs using ECMO. However, the guidelines from the NIVC published in 2016 (See above), recommended that an ICU team specifically trained in ECMO procedures has to be available 24/7.¹²¹ This team should include ICU physicians and ICU nurses along with perfusionists, and should be competent with the ECMO equipment used (the ICU physician or the perfusionist must be able to prepare the device immediately at bedside). The nurse-to-patient ratio varies between 1:1 to 1:2.
- The study group advocated for continuous training. Although continuous education or annual formal certification are not required for healthcare givers, many centers have set up local training programs for their staff including lectures, hands-on training and simulation exercises that aim to appropriately react in case of emergency issues.¹²⁰ In some teams, nurses have been trained to help perfusionists to ensure an appropriate operational functioning of the ECMO (circuit, membrane, pumps,...).
- There is no fixed yearly minimal threshold of ECMO. The ECLS study group from the NIVC suggested 6 ECMO per year as a threshold and 30/year to be recognised as expert centers (See 2.1.2).¹²¹

^a https://www.ejustice.just.fgov.be/cgi_loi/change_lg.pl?language=fr&la=F&cn=1998042740&table_name=loi

^b https://www.legifrance.gouv.fr/codes/article_lc/LEGIARTI000006917013

^c <https://www.belsect.be/>

^d <https://www.sfaccec.fr/>

^e <https://www.belsect.be/education/leuven>

^f <https://www.belsect.be/education/liege>

^g <https://www.sfaccec.fr/cms/index.php/la-formation>



7.3.2.3 Resources and interdependence with other hospital departments

In countries that do not centralise ECMO services, there is no specific obligation to perform VV or VA- ECMO in centres with a cardiothoracic surgery. Neither the availability nor the proximity of cardiothoracic and/or vascular surgery are legally specified. VV and VA- ECMO can be individually used in centres.

Mobile ECMO

Belgium

Patients requiring ECMO are generally transferred by private ambulance companies to centres that perform ECMO. Since they are generally too unstable to be safely transported by conventional ambulances (or need to be transferred on ECMO), a retrieval team from the referral hospital is organised to complement the standard transport. The composition of the team varies according to the availability of members when the transfer is organised (in general, experienced ICU doctors, nurses, perfusionists). Despite the fact that there is no structural mobile teams in Belgium, some centres have set up these teams (e.g. nearly all centres registered to ELSO).

France

- Having a mobile ECMO service is not an obligation for hospitals providing ECMO. However, high-volume centers (mainly university hospitals in major cities) have organised ECMO mobile units in the major cities of France (UMAC-Unité mobile d'assistance cardiocirculatoire; UMAR-Unité mobile d'assistance respiratoire). Seven structured mobile ECMO depending from expert centers have been set up throughout the country. The retrieval team commonly includes an ECMO consultant, a nurse and a perfusionist. Ground

transportations is commonly used and long-distance air transport has successfully been organised with military or private aircrafts, for transfers from remote overseas French territories.^{91, 122} An information telephone line for retrieval and transfer is, for instance, available 24/7 at the University Hospital of Martinique^a.

- At the beginning of the SARS-CoV-2 pandemic, the surge in demand for ICU beds and ECMO drove the ECMO services to urgently self-reorganise and centralise the access: a network in the region of Ile de France ('Great Paris') was developed: 17 ICUs able to manage ECMO were designated as ECMO centres and were supported by six mobile ECMO teams with the ability for cannulation of patients at non-ECMO ICUs and to transfer them to the seventeen referral centres (See Appendix 6.6 and 6.7).⁸⁶ Fifty-nine percent of the centres were cardiothoracic centers and 53% were university hospitals. An inventory of all ECMO devices available in the region was made. A taskforce of ECMO experts established guidelines in order to homogenise the indications and management of ECMO services and an ECMO-hub was set up in one referral hospital (La Pitié Salpêtrière^b). Regular reports and data on the capacity were shared with healthcare providers and health authorities, or other stakeholders (via email and digital appa). Other similar initiatives were reported in the north of France.¹²³ This initiative included also the needs for VA-ECMO and VV-ECMO for other causes than COVID-19.

The Netherlands

The transfer of patients between ICUs is regionally organised in The Netherlands, through a network of seven Mobile Intensive Care Unit (MICU) across the country. The transfer of patients under ECMO is also supported by MICUs that have ECMO-trained staff members available. MICUs are nevertheless available for a limited time period, i.e. extended office hours. Hospitals that provide ECMO can also organise an urgent transfer with their

^a <http://www.universityhospitalmartinique.fr/about-Circulatory-support-mobile-unit-CHU-Martinique-Caribbean-ECMO-ECLS>

^b <http://pitie-salpetriere.aphp.fr/>



own team members outside the available hours. The retrieval team generally includes an ICU specialised- physician, a nurse, a perfusionist, and can also include a cardiovascular surgeon.

7.3.2.4 *Regulatory frame in terms of data collection and quality of care*

The transfer of data to health authorities is not organised in countries without centralisation of ECMO services. As such, the ECMO bed capacity (registry of available ECMO devices) at the nationwide level is difficult to determine when there is a surge demand for ECMO. Moreover, although centres can organise local meetings to discuss the outcomes (survival, complications) of their own patients, such statistics are not available at the national level. In the same way, the reporting of data to international databases such as ELSO is made on a voluntary basis^a.

- In 2012, a publication from the French Society of Anesthesia (SFAR-Société Française d'Anesthésie-Réanimation^b) reported a capacity of 180 ECMO devices in France (10% of them outside university hospitals).¹²⁴ During the SARS-CoV-2 pandemic, initiatives to assess the global ECMO capacity were launched. For instance, in the region of Ile de France ('Great Paris'), a registry of available ECMO (See Mobile ECMO) was held to coordinate and rationalise the access to ECMO (strict and standardised eligibility criteria).¹²⁵
- In The Netherlands, although there is no official national registry, some centres collaborate by sharing their data for research purposes. The National Intensive Care Evaluatie registry provides continuous ICU data from participating ICUs, with the aim to monitor and optimise the quality of care.^c We did not retrieve ongoing or past projects related to ECMO

organisation. The national intensive care society (Nederlandse Vereniging voor Intensive Care) recommends to schedule regular meetings to discuss patients outcomes, and advocates for reporting data to ELSO database.

- In Belgium, eight hospitals report their data to ELSO. There is no official registry of ECMO capacity. However, during the SARS-CoV-2 pandemic, the Hospital Transport Surge Capacity Committee^d (depending from the Risk Management Group of the Health Ministry^e) drew up an inventory of the ECMO beds capacity across the country. Each hospitals had to report the number of patients mechanically ventilated and on ECMO combined with the availability of ventilators and ECMO machines. This registry was performed in collaboration with Sciensano^f (Scientific Institute of Public Health).

7.3.2.5 *Funding*

Belgium

- Fees for patients on ECMO are covered under several billing codes including intervention (cannulating) and the surveillance (monitoring), during the first five days. The billing code for monitoring patients on ECMO during the first day differs from the following days. Billing codes for VV- ECMO are existing since 2017. Total amount related to billing codes from 2010 to 2019 are presented in Figure 33 and Figure 34.

The cannulations for VA and VV-ECMO are covered by lump sums of €863.11 (codes 229703-229692) and €265.57 (code 229725-229714), respectively.

Lump-sums are allocated for the monitoring of both VA and VV-ECMO:

^a In Belgium, 9 centres are registered in ELSO while there are 6 in France and 10 in The Netherlands

^b <https://sfar.org/>

^c <https://stichting-nice.nl/>

^d <https://organesdeconcertation.sante.belgique.be/fr/comite-hospital-transport-surge-capacity-htsc>

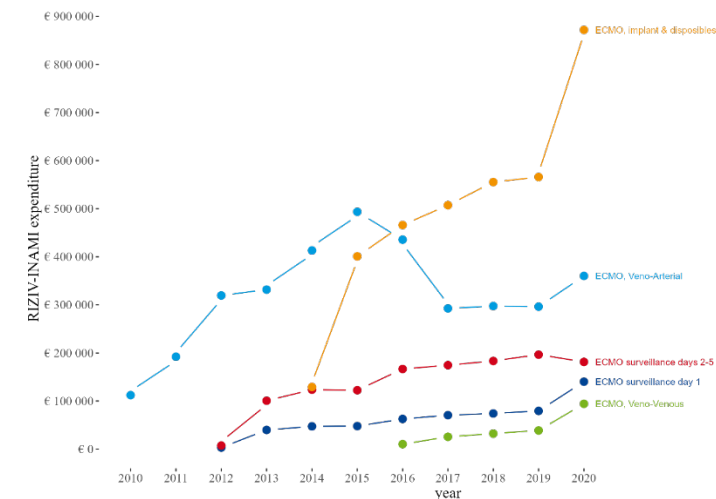
^e <https://www.health.belgium.be/en/node/35662>

^f <https://www.sciensano.be/en>



- On the first day, the lump sum allocated for ECMO monitoring is €149.98 (code 211363)
- From the second day, the surveillance of ECMO is reimbursed at the rate of €131.23 per day until the fifth day (code 211385).
- In the setting of the SARS-CoV-2 pandemic, the limitation of billing to the fifth day is no more taken into account and a new billing nomenclature code has been set up^a. This code (211982) is not limited to the fifth day to be in adequacy with the larger length of stay in the ICU of COVID-19 patients who require ECMO. It corresponds to an amount of €130.06 per day.
- In addition to this, the consumables needed for the use of the device are covered by a lump-sum of €1023.34 (codes 159935-159946). This is a conditional reimbursement, since several conditions are required: the prescription must be signed by a specialist physician and can be applied once per hospital stay.

Figure 33 – Expenditures associated with nomenclature billing codes for VA and VV-ECMO over time for patients ≥ 16 years old

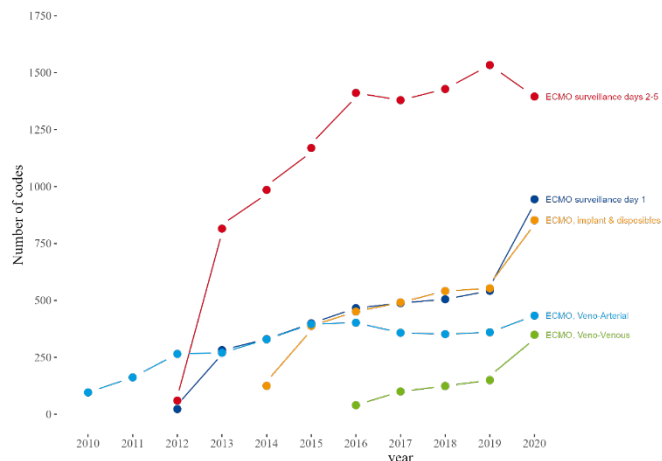


Legend: ECMO implant and disposables (code 159946-159935); ECMO Veno-Arterial (code 229703-229692); ECMO Veno-Venous (code 229725-229714); ECMO surveillance day 1 (code 211363); ECMO surveillance days 2-5 (code 211385)

^a <https://www.inami.fgov.be/fr/covid19/Pages/urgences-soins-intensifs-unites-covid19-hopitaux.aspx>



Figure 34 – Numbers of nomenclature billing codes over time for patients ≥ 16 years old



Legend: ECMO implant and disposables (code 159946-159935); ECMO Veno-Arterial (code 229703-229692); ECMO Veno-Venous (code 229725-229714); ECMO surveillance day 1 (code 211363); ECMO surveillance days 2-5 (code 211385)

- Yearly expenditures (See Figure 33 and Figure 34) for VV-ECMO cannulation have been rising from 2016 due to a volume effect (increased number of patients), while expenditure for VA-ECMO cannulation has decreased in 2016, remained stable until 2019, and is rising from 2020. Yearly expenses for the monitoring of ECMO (first day) have also progressively gone up over the years. We noticed a decrease of expenses associated with the monitoring day 2 to 5 from 2019. Finally, expenditures associated with the ECMO device rose from 2014 onwards.

- In case of inter-hospital transfer, the transport cost is not reimbursed and is paid by the patient but sickness funds or voluntary insurances can partly contribute in the costs. The refund substantially varies among sickness funds and private insurances.
- There is no separate funding for associated costs (such as transfusions, need for extra-surgery, biological analysis,...). However, the reimbursement of global hospitalisation fees follows the third-party payer system, where the sickness fund pays the provider directly and patients only pay supplements or non-reimbursed services. It should be noted that the billing codes specific for ECMO are limited to the fifth day (outside the period of SARS-CoV-2 pandemic) and that can generate important costs for hospitals when the need for ECMO is prolonged. A maximal sum of € 102,33 can be billed to the patient and corresponds to the fees for the hospital pharmacist related to purchasing, stocking and guaranteeing the sterility of the device.^a

France

- To date, the ECMO device is not registered in the list of reimbursed products and services ('liste des produits et prestations remboursables'), meaning that no specific reimbursement exists for its funding. Therefore, hospitals finance ECMO services through payments allocated for their funding: GHS tariffs (Groupe Homogène de Séjour^a) are based on the medical activity (type of disease and related management) during the hospitalisation. An additional funding can be obtained through the fundings dedicated to the missions of general interest (mission d'intérêt général^b) that is a lump-sum granted to cover research and innovation.
- There is no extra-funding associated with ECMO placement or monitoring. The funding of ECMO services is determined by the GHS tariffs (diagnosis of cardiogenic shock- R570 for VA-ECMO and septic shock- R572 in the case of VV-ECMO) and the hospital length of stay.

^a afleveringsmarge / marge de délivrance

^b <https://www.igas.gouv.fr/spip.php?article89>



- Emergency transport is generally used for patients retrieval by ECMO mobile teams and is covered by the healthcare insurance system.

The Netherlands

- The funding of ECMO is organised through a fixed lump-sum payment and depend on which type of ECMO has been used. VA-ECMO is covered by a Diagnostic Treatment Combination (Diagnose Behandelcombinatie-DBC) whose amount is currently approximately €2000 (DBC 39610). The billing of ECMO procedure is limited to a single particular specialty since it has to be placed by a cardiothoracic surgeon and is then only billed in cardiothoracic centres approved for implementing VA-ECMO. There is no separate reimbursement for the disposables or other resources associated with the use of ECMO.
- Conversely, VV-ECMO is not within the scope of funding through DBC. In this case, the cannulation is performed by specialists other than surgeons (intensivists), outside of approved cardiothoracic centres, and is subsequently not reimbursed. The costs of VV-ECMO are therefore charged to the hospitals.
- Fees for retrieval by ECMO mobile teams (MICU) are also fully covered by the healthcare system (lump-sum of about €2000-DBC 190132 for

transfer duration less than 2 hours and about €3000- DBC 190133 for transfer duration more than 2 hours^{b)}).

- In 2016, an estimation of hospital costs was assessed in the University Medical Center Groningen by the Dutch Extracorporeal Life Support Study Group, on a sample of 67 patients. The costs of ECMO were differentiated in costs of procedures (devices and disposables, costs of additional human resources, surgery hours) and costs of daily surcharge of therapy (work of the perfusionist and daily depreciation of ECMO). Indications for extracorporeal support were large and included VA and VV- ECMO. The mean total hospital costs were €106 263 (95% CI: 83 841- 126 266) per patient, corresponding to daily expenditures of €2 796.¹²⁶ Nursing costs accounted for 52% of the total while the costs related to ECMO (procedures and daily surcharge) per se were €11 948 and accounted for 11% of the global expenses (See Appendix 6.8). The duration of ECMO support was highly heterogeneous with a mean of 135 hours (standard deviation: 163 hours) and the in-hospital mortality reached 68%. This preliminary project gave rise to an ongoing prospective observational cohort study conducted at the nationwide level and aiming at performing a cost-effectiveness analysis of ECMO (NCT02837419).¹²⁷

Table 35 – Summary table on main characteristics of the organisation of ECMO in each country

Characteristic s		UK	Italy	Belgium	France	The Netherlands
Level of centralisation		National	Regional	/	/	/
Teams organisation	Nurse-to-patient ratio	1:2	/	/	/	/
	Mandatory specialised training	Yes	Yes	No	No	No
	Colocalisation of the ECMO centre with	Yes	Yes	No	No	Only for cardiac centres



	cardiothoracic surgery department					
	Structured mobile ECMO	Yes	Yes	No	Partially (UMAC- UMAC in major cities)	Partially (Mobil Intensive Care unit limited to office hours)
Yearly ECMO volume threshold		20	Not determined	Not determined	Not determined	- Only for cardiac centres - Suggested minimum threshold 6/year
National data collection regulation		Yes	Yes	No	No	No
Funding of ECMO	£5000/day* Cover hospital costs and ECMO related expenditure		Depends on the ECMO duration*: <24 hours: €27 800 <30 days: €37 000 > 30 days: € 74 200 Cover hospital costs and ECMO related expenditure	Single or daily lump- sums specifically for the use of ECMO*: - consumables for the use of the device: single payment of €1 023.34 - cannulation: Single payment of €863.11a/265.57b - Monitoring 1st day: Single payment of €149.98 - Monitoring after 1st day (until 5th day): Daily lump-sum of €131.23	Funded by the GHS tariffs (diagnosis of cardiogenic or septic shock)	Single lump-sum specifically for the use of VA-ECMO\$: €1 945.39 (minimum) to €2 139.93 (maximum)
Funding of mobile ECMO		Yes £3000	Yes €5000	No (partly sickness funds or voluntary insurance)	Yes (use of emergency transport services)	Yes €2000 to €3000#

Legend: ECMO : Extracorporeal membrane oxygenation ; UMAC : unité mobile d'assistance circulatoire ; UMAC : unité mobile d'assistance respiratoire* tariffs are not even in the country and vary according to hospitals. Those amounts were communicated by the consulted experts and correspond to their centre; \$ lump-sum are specific for the use of ECMO and does not cover expenditure associated to the ICU resources; # depending on the distance travelled; a VA-ECMO; b VV-ECMO



7.4 Discussion

From our international comparison, we identified that the organisation of ECMO among healthcare systems varies considerably and is sometimes not evenly structured within the same country. The organisation of ECMO services is a challenge for healthcare systems since mortality remains high (See Chapter 4). For instance, in Germany, a recent epidemiologic study demonstrate that the use of ECMO has been increasing for the two last decades, and that despite a decrease in hospital mortality, over time, mortality remained high, particularly in older patients.¹²⁸

The main findings of the organisational characteristics are the following:

- The UK and Italy have built a structured organisation of ECMO services, based on the so-called 'Hub and Spoke' model. For this purpose, they had to develop a robust referral and retrieval coordination, given that a structured transport system for patients requiring ECMO (mobile ECMO) is one of the key-elements in such an approach.^{92, 104}
- In countries that have no centralised ECMO services, we found out that local experience, healthcare culture or availability of resources contribute to how ECMO services are implemented. In such systems, every ICU can develop its own local ECMO program regardless of the expertise or the hospital structure and resources. As a result, some ICUs may provide ECMO a limited number of times and patients requiring ECMO are consequently not grouped in high-volume centres. This contributes to the great heterogeneity (including within the same country), and goes against the recommendation from international ECMO societies that advocate for a centralised use.^{5, 16} The degree of organisation of retrieval teams/mobile ECMO also varies substantially according to the country.
- The SARS-CoV-2 pandemic has recently increased awareness about the need to centralise ECMO services in case of surge in demand.^{16, 129, 130} Notably, the global strain on the healthcare system has presented a challenge to organise ECMO, and has risen many questions regarding the planning, the allocation and the pooling of resources or equipment. Since ECMO is a resource consuming technique requiring highly skilled staffing, setting up 'Hub and Spoke' models, appeared to be the best option in countries, such as France.⁸⁶ As already described, ECMO services were centralised in the region of 'Great Paris'. This type of organisation had already been launched in the UK⁹ or Italy^{113, 114} during the previous H1N1 pandemic, and has been maintained and adapted over time. It gave rise to their current centralised structure. In this setting, a global overview on the ECMO capacity (inventory of equipment and teams) at the regional/national level is of utmost importance to build a well-planned care strategy, particularly during infectious disease outbreaks.¹³¹ Up to now, non-centralised systems do not allow to have clear overview on the capacity and availability of ECMO beds. National registries including those characteristics could certainly be a point of improvement in the future.
- In our international comparison, we noticed that the funding and reimbursement vary according to the national health care systems but, overall, ECMO is, for a large part, financed in each country by health authorities. It should nevertheless be noted that due the low level of evidence, the reimbursement of ECMO varies widely among countries. For instance, health authorities do not offer specific funding for VV-ECMO in The Netherlands, or for VA-ECMO in the UK. Expenditure associated with ECMO is difficult to appraise since it includes the procedural costs of ECMO (device, disposables), combined with additional costs related to extra resources utilisation: ICU staff (nursing workload), supplemental examinations (imaging, laboratory tests) or procedures (transfusions, surgery, anesthesia, costs related to complications).¹²⁶ The additional costs caused by extra resources utilisation (along with the ICU stay) are generally covered, according to the payment mechanisms determined by each healthcare system, i.e. no specific funding mechanisms. These details are considered in Chapter 8.



8 SYSTEMATIC LITERATURE REVIEW OF COSTING STUDIES

8.1 Introduction

This chapter provides an overview of cost studies on VV and VA-ECMO. The aim is to identify the key cost factors linked to the use of this therapy as well as its approximate mean cost. This information will serve as input to our comparison between the costs specifically attributed to the use of ECMO, and its current reimbursement in Belgium.

8.2 Methods

8.2.1 Search strategy

A systematic search for relevant cost evaluations published from 2010 was carried out in Medline (through OVID), EMBASE, NHSEED (CRD) and NHSHTA (CRD) to retrieve primary cost studies or economic evaluations and SRs of economic evaluations or cost studies (i.e. secondary economic evaluations). An overview of the search strategy is given in an appendix.

No restrictions were imposed for language but to keep it as relevant as possible for Belgium, only European, Australian or Canadian studies were included in this review. The reason behind the inclusion of Australia and Canada is the similarity of their health system, to those of European countries. The search strategy was performed by an expert information analyst and checked by a second researcher.

In addition to these primary studies, a search for good quality HTA reports (including an economic component) on our topic of interest was carried out. First, the websites of HTA institutes listed on the INAHTA (International Network of Agencies for Health Technology Assessment) and the EUnetHTA (European network of Health technology agencies) websites

were consulted (search date: Dec 2021) via their respective databases^a to capture recent (published from 2010) reports on ECMO for patients with respiratory or cardiac failure. The MESH term used for the search in the INAHTA database was: “Extra Corporeal membrane Oxygenation”. In the EUnetHTA database, the search terms used were : ECMO OR “Extracorporeal Membrane Oxygenation”.

8.2.2 Selection procedure

To identify potentially relevant studies for our analysis all titles and abstracts were checked, in order to exclude any obvious studies that did not match our research subject. All articles that appeared to be interesting, or for which there were some doubts, were read in full in order to select those pertinent for inclusion in our review.

Reference lists of the selected evaluations found via our search were checked for additional studies worth adding to our analysis.

Study selection was completed by one researcher, but any doubts that came up during the exercise were discussed and solved in collaboration with a second reviewer.

A description and short critical appraisal of all individual studies included in our review is provided. This follows the checklist designed of Drummond et al.¹³² in the case of full economic evaluations, while for cost studies, the focus was put on the costs included, the sources consulted, any assumptions made for estimating them, as well as any sensitivity analyses undertaken or the consideration of the uncertainty and limitations surrounding the results obtained.

^a INAHTA: <https://database.inahta.org/>

EUnetHTA: <https://eunethta.eu/pop-database/> . This database covers HTAs that are ongoing, planned, or published in the last 3 months.



8.2.3 Selection criteria

All costing studies focusing on ECMO for adult patients with cardiac and/or respiratory failure were included in our review. Thus, cost descriptive analyses or detailed cost comparisons, full economic evaluations taking into consideration effectiveness, as well as cost consequences analyses (considering costs and effects separately), were considered.

A decision was made to exclude publications in the form of letters, editorials or notes and abstracts, since these would not offer enough information to include them in our analysis.

Regarding the geographic scope, only European, Australian or Canadian studies were included in this review.

An overview of the inclusion/exclusion criteria is given in Table 36.

Table 36 – Selection criteria for costing studies

Selection criteria	Inclusion criteria	Exclusion criteria
Population	Adults (≥ 18 years) with cardiac or respiratory failure, refractory to conventional management	Children or neonates
Intervention	VV-ECMO (respiratory failure) VA-ECMO (cardiac arrest, cardiogenic shock)	- Programmed ECMO (high risk cardiac procedure/surgery) - Specific rare conditions (intoxications, hypothermia, post-partum/pregnancy, phaeochromocytoma, stress cardiomyopathy, graft dysfunction) - Extracorporeal CO₂ removal (ECCO₂R)
Comparator	For VV-ECMO : Conventional	No exclusions

		mechanical ventilation
		- For VA-ECMO: usual care with specific therapies (such as temporary mechanical support), - No comparator (for detailed cost studies on VA or VV-ECMO).
Design	CCA, CUA, CEA, CMA, detailed costing studies	Studies offering no detailed costing
Type of publication	Articles or reviews	Letters, editorials, notes, abstracts and posters
Country	All European countries, Australia and Canada	Any other countries

CCA: Cost consequences analysis; CEA: Cost-effectiveness analyses; CMA: Cost-minimisation analyses; CUA: Cost-utility analyses;

8.2.4 Results:

8.2.4.1 Search for primary and secondary costing studies

Our systematic search for primary and secondary cost studies for cardiac and respiratory failure adult patients returned 506 citations, after eliminating duplicates. Of those, 483 did not meet our inclusion criteria, based on a review of their title and/or abstract. Of the 23 citations left, 9 were excluded because of their country of origin (6 carried out in the USA, 2 in Asia and 1 in Brazil), which make their cost less relevant for the Belgian context than those shown in European, Australian or Canadian studies. A further 6 were excluded after reading their full text, 3 because of their referral to an earlier study already included in our review and the other 3 because their indication, which left us with 8 relevant studies to be considered. Further exploration of the references of the selected articles did not result in the identification of

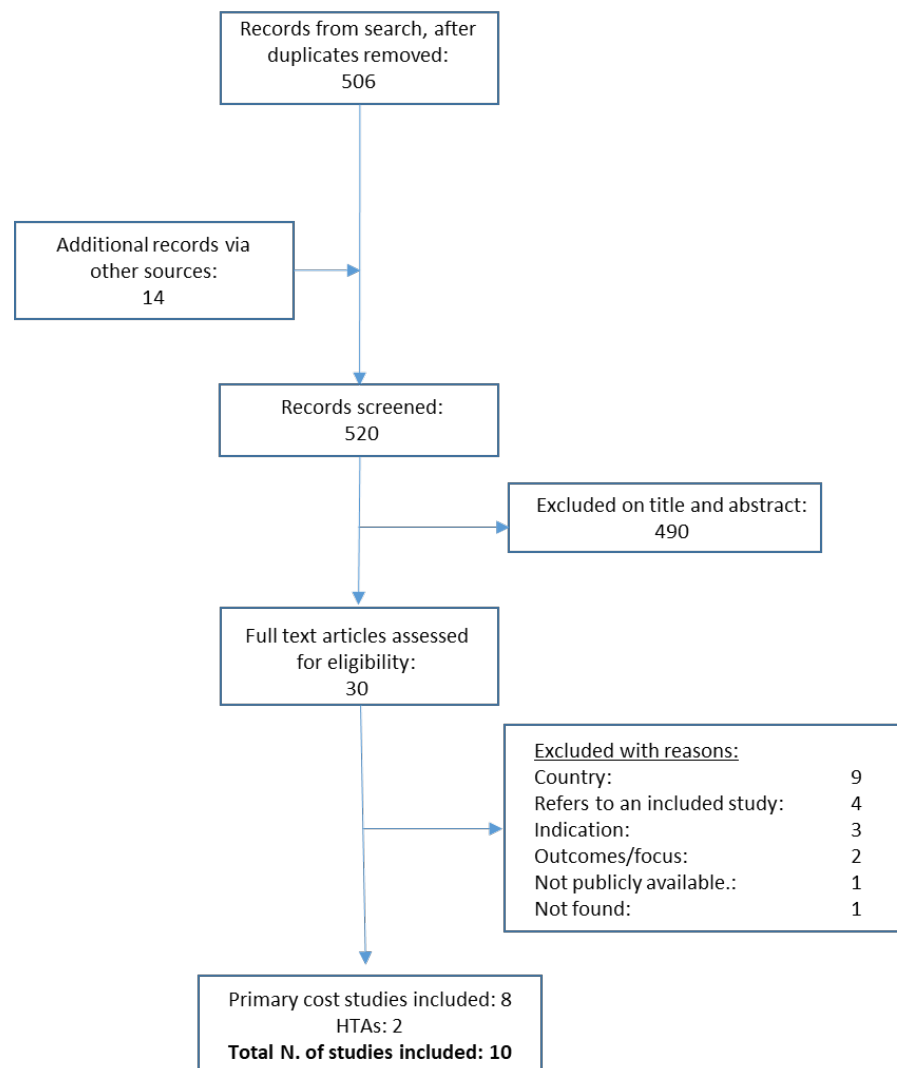


any additional study that could be of interest to our research. Therefore, 8 costing studies were included in our review.

8.2.4.2 Search for HTAs

The search for HTAs in the EUnetHTA POP database did not identify any studies. It is important to highlight that this European database was conceived with the purpose to highlight possible collaborations between European HTA agencies and as such, it includes only planned, ongoing or very recent reports (published in the last 3 months). The search on the INAHTA returned 14 studies published from 2010. From these, 7 were excluded after reading their title and abstracts. From the remaining 7, 2 from the CADTH published in 2014 focused purely on clinical outcomes and guidelines and were therefore excluded.^{133, 134} A further one from 2014 by HAYES Inc. consisted of a private report requiring payment.¹³⁵ One Canadian report by MUHC, dating from 2017 could not be found,¹³⁶ and a 2010 Scottish report by QIS referred to the CESAR study already included in this review.¹³⁷ This left us with two relevant HTAs, both Canadian, one published by Ontario Health in 2020,⁴⁶ and the other by INESSS in 2019.²⁶ Both were used for reference checking purposes, in order to ensure no relevant costing/economic studies had been missed from our search.

Our literature selection process is illustrated in a flow chart (see Figure 34).

**Figure 35 – Flow-Chart Selection Process Costing Studies ECMO for respiratory and cardiac failure**



8.3 Overview of costing studies on ECMO

As shown in Table 37, two studies were undertaken in Canada,^{102, 138} one in Australia,¹³⁹ three in the Nordic countries,¹⁴⁰⁻¹⁴² two of which were carried out by the same author,^{141, 142} one in the Netherlands¹²⁶ and one in the UK.¹⁴³

Two studies were published in 2010,^{142, 143} while the remaining six were more recent, with four studies published between 2019 and 2020^{102, 138, 140, 139}

Only one RCT with a cost component was identified.¹⁴³ Four consisted of retrospective cohort studies^{102, 126, 140, 141}, a further was a prospective cohort study¹⁴², while the two last ones carried out transition decision models.^{138,139}

Table 37 – Characteristics of selected costing studies

Author	Year	Country	Type of analysis	Perspective	Costing base	Costing horizon
Peek	2010	UK	RCT with economic component	Public Health System	RCT	6 months after randomisation
Mishra	2010	Norway	Prospective cohort study	Hospital	Prospective cohort study and retrospective overhead costing estimations	Overall hospital admission
Oude-Lansink	2016	Netherlands	Micro costing analysis	Hospital	Retrospective exploratory cohort (single centre)	Overall hospital admission
Minshra	2017	Norway	Retrospective single centre study	Hospital	Clinical pathways identified via hospital admin systems	1 year after admission, 3, 5 and 7
Barret	2019	Canada	Cohort state transition decision model	Public Health System	Literature	Lifetime
Fernando	2019	Canada	Retrospective cohort study	Public Health System	Administrative databases	1 year after admission
Dennis	2019	Australia	Cohort state transition decision model	Hospital	Retrospective/prospective cohort (2 centres)	10 years after admission
Jaamaa-Holmberg	2020	Finland	Retrospective cohort study	Hospital	Retrospective cohort in a single transplant centre	1 year and lifetime



8.3.1 Type of cost analysis

Three of the studies identified performed a cost-utility analysis (CUA),^{140,138, 143,139} with a further one presenting both a CUA and a cost-effectiveness analysis (CEA).¹³⁰ The three CUAs expressed their outcomes in QALYs, while the CEA did so in life years gained (LYG). The remaining studies all used micro-costing techniques to estimate their costs. They therefore, collected resources utilisation and unit costs data and combined them in their estimations. Only one of the studies was based on a prospective case series,¹⁴² while the other three were based on retrospective cohort studies: two single-centre studies,^{126, 141} and one population based cohort.¹⁰²

8.3.2 Perspective

Five of the studies were carried out from a hospital perspective,^{126, 140-142, 139} even if one of them presented their analysis as having been carried out from a health systems perspective.¹³⁹ The remaining three were performed from a public health system perspective.^{102, 138, 143} (See Table 37 for details).

8.3.3 Time frame of analyses and discounting

Table 37 also summarises the time frame of the cost studies included in this review. Two studies considered costs over the hospital admission period.^{126, 142} The oldest of all analysis, the only RCT, looked at a horizon of 6 months after randomisation.¹⁴³ Fernando et al. 2019, considered costs over one year after admission,¹⁰² while Mishra et al. included a horizon of 1, 3, 5 and 7 years.¹⁴¹ The Australian study looked at a time frame of 10 years, although they varied this period in their sensitivity analysis (SA).¹³⁹ Only two studies^{138, 140} looked at a lifetime horizon, with one purely focusing on that time frame.¹³⁸

Regarding the studies covering a horizon of over a year and their inclusion or not of discounting, Mishra et al.¹⁴¹ offered primarily a cost analysis at one year. Estimations of costs at 3, 5 and 7 years were also presented in a table, but no detailed explanation was given as to how the costs were estimated or whether any discounting was applied. The other three,^{138, 140,139} discounted costs and offered information on the rates used. Thus, the Canadian study by Barret et al.¹³⁸ used 1,5% for both costs and outcomes

in their base case scenario, reflecting Canadian recommendations.¹⁴⁴ The Finish study, offered estimations with and without discounting at 3,5% and mentioned that although there are no official recommendations regarding discounting in Finland, a discount rate of 3,5% for both costs and outcomes was used, following recommendations by NICE.¹⁴⁵ Similarly, discounting in the case of the Australian study was also set at 3,5%.¹³⁹

Table 38 – ECMO type and population sample in selected studies

Author	Type of ECMO	Population
Peek	VV-ECMO (n=90)	180 adults with ARDS (mean age: 39.9+/-13.4). Exclusion criteria: high pressure (>30 cm H ₂ O of peak inspiratory pressure) or high FiO ₂ (>0.8) ventilation for more than 7 days; intracranial bleeding; any other contraindication for active treatment.
Mishra	VV-ECMO (n=2); VA-ECMO (n=13)	15 consecutive ECMO procedures for 9 adult patients (16+) and 5 paediatric patients (0-5 years) with respiratory or cardiac failure, from Jan to Dec 2007.
Oude-Lansink	VV-ECMO (n=38), VA-ECMO (n=15), ECLS (n=14)	67 adult patients admitted to the ICU requiring ECMO between 2010-2013. Mean age: 46+/-15.
Minshra	VA-ECMO (n=15)	278 patients, mostly male. Most common diagnosis: dilated cardiomyopathy before end-stage HF. All eligible for HTx or LVAD. Mean age for ECMO as bridge to urgent HTx: 38 +/-21.
Barret	VV-ECMO	Hypothetical cohort of patients with ARDS. Modelled age: 45



Fernando	VV-ECMO (n=321); VA-ECMO (n=303)	692 adults (mean age: 51.3+/-16) receiving ECMO from Oct 2009 to March 2017
Dennis	VA-ECMO (ECPR) (n=62)	62 patients on refractory cardiac arrest. 61,3% IHCA and 38,7% OHCA. Mean age: 51,9+/-13,6
Jaamaa-Holmberg	VA-ECMO (n=102)	102 adult patients (mean age: 52.1+/-11.7) admitted to the hospital with cardiogenic shock (n=78) or cardiac arrest (n=24) between 2013 and 2017.

ARDS: Acute Respiratory Disease Syndrome; HF: Heart failure; HTx: Heart Transplant; ICU: Intensive Care Unit; IHCA: In-hospital cardiac arrest; LVAD: Left Ventricular Assist Device; OHCA: Out of hospital cardiac arrest; VA: Veno-arterial; VV: Veno-venous

8.3.4 Type of ECMO and Population

Table 38 summarises the populations reflected in the different evaluations. Overall, five studies identified in our review, covered just one type of ECMO, with Peek et al.¹⁴³ and Barret et al.,¹³⁸ focusing on patients suffering from ARDS and on VV-ECMO; while the other three considered VA-ECMO,^{140, 141, 139} one of them, ECPR.¹³⁹ Given the scope of our study, all studies but one covered only an adult population. The exception, a relatively old Norwegian study,¹⁴² presented a very low sample size (n=14), and mixed adults (n=9) with paediatric ECMO patients (n=5).

Although all studies which reported the gender of patients showed to have more males than females, in three cases the difference was very small presenting well-balanced populations on that respect. The others, showed a proportion of males accounting for over 60%,^{102, 139-141} with one having a population of 78% males.¹⁴⁰ The latter covered a population with cardiogenic shock or cardiac arrest.

The mean age mentioned in these studies varied from 38 to 52 years, reflecting the fact that ECMO is used in relatively young populations.

8.3.5 Comparator

Overall, four studies, were comparative.^{138, 143, 140, 139} Two of these, followed a cohort of patients on VA-ECMO or ECPR, and assumed the comparator would be imminent death. The other two, both on VV-ECMO, used standard supportive mechanical ventilation as their comparator.^{138, 143}

A further study,¹⁴¹ on VA-ECMO carried out on terminal heart failure patients in the waiting list for a heart transplant, compared patients listed for HTx who died on the waiting list, those who underwent HTx, those who had ECMO as bridge to HTx and those who received LVAD treatment, either isolated, or bridging to HTx. However, comparisons of ECMO patients versus non ECMO patients were in this case not possible, since although in one group all patients received ECMO, some patients in the other groups were also treated with ECMO and a separation of results was not performed.

The remaining three, consisted of non-comparative costing studies^{102, 126, 140, 142}

8.3.6 Cost and outcome inputs

Costs were derived from different sources depending on the study, including the published literature, national tariffs, administrative data, hospital reimbursement claims or hospital accounting.

With regard to outcomes, all studies but one¹³⁸ captured mortality from their populations, most of which did so retrospectively,^{102, 126, 140, 141} while the two oldest studies did so prospectively^{142, 143} and a further combined retrospective and prospective analyses.¹³⁹ The exception was the CUA carried out by Barret et al, for which mortality data was extracted from the literature,¹³⁸ and more specifically from a MA carried out by Munshy et al.,¹⁴⁶ which included 10 studies overall and a population of 496 patients on ECMO and 752 on mechanical ventilation. Despite the relatively high number of studies included, 6 were observational studies, with sample sizes ranging from 18 to 245 patients, and from the four RCTs identified, two focused on extracorporeal CO2 removal.^{147, 148} One of the remaining RCTs included in the MA by Munshy et al.¹⁴⁶ was already included in our review,¹⁴³ and the other was a study from 1979. All RCTs identified were on VV-ECMO.



While most studies focused on studying mortality, four also considered patients quality of life (QoL).^{138, 140, 143, 139} QoL values for the only RCT here included¹⁴³ were captured during the study by means of different instruments, including the SF-36^a and the EQ-5D questionnaire,^b while the Finnish retrospective cohort study¹⁴⁰ used the questionnaire EQ-5D-3L for capturing this important outcome. In the case of the Australian study, health related QoL was derived from cerebral performance category (CPC) scores at hospital discharge.¹³⁹ Finally, the evaluation by Barret et al,¹³⁸ which based their analysis on the available literature, used as their key source for utilities, the study by Skinner et al.,¹⁴⁹ which captured their data via the questionnaires AQoL^c and SF-6D in order to measure utilities for ARDS survivors (no specific QoL measurement on ECMO patients).

8.3.7 Results

8.3.7.1 Costs:

Table 39 shows the costs captured in the studies included in our review. Comparisons between studies are difficult primarily because of the different costs considered, as well as differences in indications and time horizons used for the calculations. Overall, the five studies undertaken from a hospital perspective,^{126, 140-142 139} limited their costs to hospital costs, even if two of these^{140, 141} considered a one year time horizon, and one¹³⁹ a 10 year horizon in their analyses. The other two^{126, 142} focused purely on the hospital

admission period. All studies independently of their perspective, included ICU costs, reflecting the setting in which these patients are treated. In addition to this, laboratory and imaging costs were commonly specified, as well as surgical costs. Transplantation costs were specifically covered in two studies.^{126, 141} While transportation to and from the hospital was included in four.^{138, 141, 143, 139} The inclusion of capital equipment was not always made explicit, and the costs of disposables were in some cases counted for as a separate item, and in others included in the ECMO procedural costs.

From the three studies which considered a health services perspective and looked at time horizons longer than the hospital admission time,^{102, 138, 143} Barret et al.¹³⁸ used the costs covered in the study by Peek et al.¹⁴³ These three studies included costs linked to the use of outpatient health services (eg GP or nurse consultations), physiotherapy, long-term care and home care.

Two of the four comparative studies included in our review presented the overall costs of VV-ECMO patients and the incremental costs of those patients over the cost of patients on standard mechanical ventilation.^{138, 143} The other two comparative studies, assumed imminent death if no ECMO was used and thus, captured only the costs for patients on VA-ECMO and ECPR.^{140, 139}

The overall mean costs over the study period are highly variable as seen in Table 39.

^a https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/scoring.html

^b <https://euroqol.org/eq-5d-instruments/>

^c <https://www.aqol.com.au/index.php/aqolinstruments>



Table 39 – ECMO costs captured on included studies

Author	Costing yr	Time horizon	Costs included	Capital equipment	Cost source	Mean/Median cost over study period
Peek	2005	6 months	<u>During hospital stay:</u> Transport; ICU stay, N. of organs to support (0-1, 2 or 3+), hospital LoS. <u>After discharge:</u> Outpatient and inpatient visits to nurses, physiotherapists and GPs, surgery, residential care, home care from families and carers, transport and other hospital services.	Included	Consumption from RCT (n=180) and from large, multicentre study of ICU expenditure	GBP 73 979 for ECMO group (vs GBP 33 435 with standard treatment). Mean incremental costs of ECMO per patient: GBP 40 544
Mishra	2007	Hospital admission	ICU stay and costs, OR costs, drugs, blood products, lab and radiology services and disposable equipment	Not specified	Patient records and time motion studies. Retrospective examination and estimation of overhead costs.	Mean incremental costs per ECMO procedure in the ICU: US\$ 67 000. From overall hospital costs, personnel accounted for 82%, blood products for 7%, lab and radiology for 2.5%, disposable items for 3% and drugs for 1.5%.
Oude-Lansink	2013	Hospital admission	Nursing days, medication, functional examinations (i.e., bronchoscopy, ECGs, and lung function testing), imaging, transplantation, renal replacement therapy, screening, surgery and anaesthesiology, lab tests, microbiology, blood products, and procedural costs of ECMO.	Included	Dutch reference prices applied to resource consumption captured via retrospective single centre cohort study	Mean costs: € 106 263: 52% nursing costs; 11% cost of ECMO procedures and daily surcharge; 37% other resources. Non-comparative, so no incremental ECMO costs available.
Minshra	2012	1 year, 3, 5 and 7	<u>Pre-surgical period:</u> all hospital costs over 3 months prior to intervention. <u>Surgical stay costs:</u> organ procurement, transport and staff, device purchasing, ICU. All <u>post-surgical and follow-up costs</u>	Included	Consumption and patient-specific costs from cohort study (patient records)	Overall hospital costs for ECMO as bridge to HTx at 1 year: US\$ 292 078+/-101 915; at 3 years: US\$ 338 903 ± 108 501; at 5 years: US\$ 346 241 ± 135 149; at 7 years: US\$ 457 627 ± 457 627.
Barret	2016	Lifetime	Taken from Peek et al (2009) - (see entry above)	Included	Literature	Mean incremental lifetime cost for ECMO: CAN\$ 145 697. Mean incremental ECMO costs over 6 months: CAN\$ 117 370.
Fernando	2016	1 year	Inpatient costs, ED costs, complex continuing care, rehabilitation, long term care, home care, outpatient care:	Not specified. Cost of ECMO considered to be already	Administrative databases.	Median overall ECMO costs at 1 year: CAN\$ 130 157; inpatient costs: CAN\$ 91 192. <u>After discharge</u> median costs for continuing care, lab costs and drug costs: 0, Median costs for



			outpatient costs, lab costs, drugs, physicians' fees.	included in the inpatient costs		outpatient visits: CAN\$ 2 321; Median costs for physician billing: CAN\$ 22 191
Dennis	2016	10 years	Medical and nursing costs, ambulance, pharmacological, therapeutic and diagnostic procedures, renal replacement, consumables, ECMO circuits, complications, blood products, hospital overheads, surgery	Not specified	Hospital DRGs, Australian Medicare Benefits Schedule and Pharmaceutical Benefits Scheme	Mean costs per patient for an ECMO run: AU\$21 758± 23 059; ICU LoS costs: AU\$26 716±44 201; Hospital LoS: AU\$13 893±25 576
Jaamaa-Holmberg	2017	1 year and lifetime	Ward day costs in different units, surgical procedures, lab costs and imaging costs.	Not specified	Consumption of resources from cohort (n=102), and unit prices from hospital tariffs.	Median hospitalisation cost: € 129 967. Mean ICU day of VA-ECMO treated patients: €3 363/day. ICU price of VA-ECMO (over 6 days): € 20 178.

ECG: electrocardiogram; ED: Emergency department; HTx: Heart Transplant; OR: operating room; VA: Veno-arterial

Table 40 summarises the outcomes obtained in the different studies which considered both costs and outcomes, included in this review.

Table 40 – Outcomes in the included studies

Author	Outcomes considered	Hospital LoS (in days)	ICU LoS (in days)	ECMO (in days)	Duration	Mortality (in %)	Mean incremental LYQ/QALYs	Source outcomes	of
Peek	Mortality; QoL, LoS in hospital, LoS in ICU	Median (IQR): with VV-ECMO: 35 (58.4); w/o VV-ECMO: 17 (40.5)	Median (IQR): with ECMO: 24 (27.5); w/o ECMO: 13 (5)	Median (IQR): 9 (10)††		with VV-ECMO: 37% (33/90) at 6 months; w/o VV-ECMO: 47% (41/87)	↑QALYs (95%CI) with VV-ECMO at 6 months: 0.03 (0.00–0.06); ↑QALYs with VV-ECMO in a lifetime: 3.66	Multicentre RCT (n=180); Utilities from EQ-5D	
Mishra	Mortality, LoS in hospital	Mean (range): LoS in hospital: 51.5 (6-123 days).	NA	Mean (range): 9.5 (4-23)		Overall: 42.8% (6/14); 21.4% (3/14) at 30 days; and 21.4 (3/14) during follow up. 57.1% (8/14) survived.	NA	Cohort (n=14)	
Oude-Lansink	Mortality, LoS in hospital, LoS in the ICU	Mean ± SD: LoS in hospital: 38 ± 45	Mean ± SD: 18 ± 22	Mean ± SD: 5.6 ± 6.79		68% (44/67) in-hospital	NA	Cohort (n=67)	



Minshra	Mortality, LoS in hospital, LoS in ICU	For those on VA-ECMO as bridge to HTx (n=15) Mean ± SD: LoS in hospital: 35±15; Time from day on waiting list to HTx: 39 ± 85	Mean ± SD: 17±13	Mean ± SD: for bridge to HTx: 9.1 ± 8.5 days. Weighted mean duration for all patients on ECMO: 7.9 days	13.3% (2/15) at 30 days; 30% at 1, year	NA	Retrospective single centre study (n=15)
Barret	Mortality, AEs, QoL	NA	NA	NA	with VV-ECMO: 33%; w/o VV-ECMO: 52%	↑ LYG with VV-ECMO: 5.2, ↑ QALYs with VV-ECMO: 4.05	Literature. Mortality: MA by Munshi 2014, Utilities: Skinner 2013
Fernando	Mortality, LoS in hospital	Median (IQR): 22 (36); In respiratory failure: 26 (39); In cardiac failure: 15 (30)	NA	NA	Over hospitalisation: 30.5% (98/321) for respiratory and 50.5% (153/303) for cardiac patients). <u>At year 1:</u> 37.1% for respiratory and 53.8% for cardiac.	NA	Retrospective cohort study (n=692)
Dennis	Mortality, QoL, LoS in hospital, LoS in ICU	Mean ± SD: 12±21.8	Mean ± SD: 5.8± 9.6	Mean ± SD: 3.8±4.0	60% (37/62)	↑ QALYs with ECPR: 3.0	Cohort study (n=62)
Jaamaa-Holmberg	Mortality, QoL, LoS in hospital, LoS in ICU	Median (IQR): 32 (38)	Median (IQR): 12 (16)	Median (IQR) VA-ECMO: 6 (6)	Overall: 35% (36/102), <u>In CS:</u> 20.5% (16/78), <u>In refractory CA:</u> 79%(19/24)	LYG: 26.2, QALYs: 20.9	LoS, days on VA-ECMO and mortality from cohort study (n=102); utilities from EQ-5D-3L

AEs: Adverse events; CS: cardiogenic shock ; CA: cardiac arrest; HTx: Heart transplant; LoS: Length of stay; LYG: Life years gained; MA: Meta-analysis; QALYs: Quality adjusted life years; QoL: Quality of life; VA: Veno-arterial; VV: Veno-venous



8.3.7.2 Outcomes and ICERs

Table 40 shows that the economic evaluations comparing VV-ECMO with standard supportive mechanical ventilation, identified in our review, found a reduction in mortality with VV-ECMO, with the oldest of these studies showing a mortality rate of 37% with ECMO versus 47% without it, and the Canadian evaluation presenting a mortality of 33% with ECMO versus 52% without it.^{138, 143} The mortality rates found in the remaining studies ranged from a low of 30,5%¹⁰² to a high of 68%.¹²⁶ Differences appear to be due to the type of ECMO, with studies on VV-ECMO presenting lower mortality rates, as well as on indications and length of the study.

The overall LoS shown in the studies was around 30 days, although great variations existed. Studies reporting on ICU LoS varied from 24 (for VV-ECMO)¹⁴³ to 5.8 days (for ECPR).¹³⁹ Finally, the duration of ECMO appeared to be of around 9 days.

The two comparative studies, which performed a CUA for VV-ECMO, showed a gain in QALYs with VV-ECMO versus conventional ventilation of 3,66¹⁴³ and 4,05¹³⁸ over a life span. Barret et al.,¹³⁸ also estimated an incremental gain in LYs of 5,2. The two CUAs on VA-ECMO and ECPR, also showed gains in QALYs with ECMO, of 20,9 over a lifetime (in Jaamaa et al.), and of 3,0 in the Australian study by Dennis et al.¹³⁹

ICERs obtained for VV-ECMO were CAN\$ 36 000¹³⁸ and GBP19 252 (95%CI: 7 622 to 59 200);¹⁴³ with both studies concluding that VV-ECMO is likely to be cost-effective at their respective willingness to pay thresholds. The Australian study on ECPR also found it to be cost-effective at commonly used thresholds, reporting an ICER of AU\$25 212 (€16 890) per QALY.

8.3.7.3 Sensitivity Analyses

The majority of the studies^{102, 126, 140-142} did not include a sensitivity analysis or put their costs to the tests, since their aim was descriptive and no modelling was necessary. Only the studies by Peek et al.,¹⁴³ Denis et al.¹³⁹ and that of Barret et al.¹³⁸ (given their full economic evaluation nature), put their assumptions to the test. Thus, Peek et al.¹⁴³ performed a univariate analysis during which the values of different variables were changed. This analysis, showed hospital cost estimates to be sensitive to the methods

used in the estimations of ICU costs (i.e. NHS reimbursement charges versus case-mix-adjusted costs), with significantly lower costs (and ICERs practically cut in half) when NHS reimbursement charges were used. The authors also checked the robustness of the results with and without discounting costs, but in this case the results did not change noticeably.

Dennis et al,¹³⁹ carried out both scenario analysis and probabilistic sensitivity analysis. In the scenario analysis, the time horizon for the estimations was varied to 5 and 15 years (being 10 the base case scenario). Modelling estimates were sensitive to survival rates, length of ICU and hospital stay, length of survival post arrest and neurological outcomes. The scenario analysis also showed the time horizon to be an important variable.

Barret et al,¹³⁸ performed both univariate and probabilistic sensitivity analyses. These analyses showed the results to be highly variable and sensitive to changes in the efficacy of VV-ECMO (mortality source used as input) and to costs. Variations in costs showed a proportional variation on ICERs, while small variations on mortality inputs, resulted in larger variations in the ICER.

8.3.7.4 Conflict of interest

Four of the studies included in this review declared to have a conflict of interest having received payments from manufacturers.^{102, 140, 143, 139} From the remaining, three declared no conflict of interest,^{126, 140, 141} while the smallest of all studies did not include a declaration of conflicts of Interest.¹⁴² The existence of conflicts of interest may introduce a bias which could affect the validity of the study results, although there is, up to date, no hard evidence on this.

8.3.8 Discussion and limitations

Despite the fact that the four full economic evaluations identified via our search (limited to European, Australian and Canadian studies), showed positive results for ECMO, it is important to highlight that only the two that studied VV-ECMO, had a comparator arm, since as already seen in our clinical review, there is more evidence of higher quality (RCTs available). The two full economic evaluations that studied VA-ECMO and ECPR,



assumed patients that were not put on ECMO, died. The remaining of the studies were non-comparative cost analyses, most of which were based on small sample cohort studies ranging from 14¹⁴² to 102 patients,¹⁴⁰ with the exception of a Canadian retrospective cohort study¹⁰² which considered a population of 692 patients with respiratory or cardiac failure. Despite the higher sample size of the latter, both costs and indications relied on administrative databases and assumptions had to be made regarding coding. In addition to this, no separate data was available for VV and VA-ECMO, so a separation was made bearing in mind the indications registered in the database. No data on complications related to ECMO were available, and thus, these were not considered in the analysis.

A further important limitation linked to the generalisability of the results from the studies included in this review, is that centralisation exists in the countries/regions where some of these studies were carried out, and thus, the validity of their findings, for other countries where not such organisation is in place, could be questioned. Further important limitations, linked to the clinical data and the design of the existing clinical studies have already been detailed in our clinical chapter (See Chapter 4)

Given the focus of this research, more on the use, organisation and reimbursement of ECMO in Belgium, the aim of this chapter was to identify relevant costs for ECMO, as well as summarising the finding from the published literature. In view of the lack of Belgian specific studies, a decision was made to still analyse the costing studies carried out in countries with similar health systems to that in place in Belgium, in order to inform a survey to be sent to Belgian hospitals (i.e. what costs are more important and have more weight in this particular field). In addition to this, an attempt was made to extract from the literature the most relevant costs only, which would be specifically linked to the use of ECMO, and not general costs in which any ICU patient would incur, and that are often, as in the case of Belgium, funded and reimbursed separately.

To increase comparability between the different studies, the costs extracted from the literature were presented as daily costs. In order to do so, some assumptions had to be made for those studies for which, not all information necessary to calculate these costs was given in the article. The assumptions made (eg regarding the duration of ECMO) are detailed in a table in appendix.

No currency conversion or updating of these costs was performed.

A summary of the results is presented in Table 41. There is a wide range of costs, mostly due to the differences in the factors, perspective, patient populations, and time horizons considered. These differences, may also reflect some of the assumptions made regarding the duration of ECMO (whenever these were necessary). It is important to note that, while in some studies it was easy to extract the ECMO-specific costs, in others, only a global cost (including in some cases, large time horizons and general ICU costs) were presented, and not surprisingly, the latter presented much higher estimations. For example, the studies by Mishra et al.,¹⁴² and Oude-Lansink et al.¹²⁶ were the only ones focusing purely on the hospital admission period, while others looked at a 6-month, one year or even lifetime-horizons, and in some cases, the latter covered not only hospital costs, but also outpatient costs, making comparisons difficult.

Table 41 – Mean Costs per patient of VV and VA-ECMO from the literature

Author	Costing yr	Time horizon	Mean costs over study period	Mean daily cost*	Type of ECMO
Peek	2005	6 months	GBP 40 544	GBP 4 505	VV-ECMO
Mishra	2007	Hospital admission	US\$ 67 000	US\$ 7 053	VV (n=2) and VA-ECMO (n=13)
Oude-Lansink	2013	Hospital admission	€11 948	€ 2122	VV-ECMO (n=38), VA-ECMO (n=15), ECLS (n=14)
Minshra	2012	1 year	US\$ 120 000	US\$ 15 000	VA-ECMO
Barret	2016	Lifetime	CAN\$ 117 369	CAN\$ 13 041	VV-ECMO
Fernando	2016	1 year	CAN\$ 91 192	CAN\$ 12 159	VV-ECMO and VA-ECMO



Dennis	2016	10 years	AU\$ 21 758	AU\$ 5726	VA-ECMO (ECPR)
Jaamaa-Holmberg	2017	1 year and lifetime	€ 20 178	€ 3363	VA-ECMO

VA: Veno-arterial; VV: Veno-venous

**Not all articles presented daily costs, or provided duration of ECMO. Some assumptions were made regarding these estimations. A detailed explanation regarding how daily costs of ECMO were derived for each study, is provided in an appendix.*

8.4 Key Points

- **Four (European, Australian or Canadian) full economic evaluations identified via our search showed that ECMO is likely to be cost-effective at commonly used thresholds.**
 - The two full economic evaluations on VV-ECMO were both based on the same data source (i.e. the RCT by Peek et al.)
 - The two full economic evaluations for VA-ECMO and ECPR assumed all patients who were not on ECMO had an imminent death. This assumption was made given the scarce clinical evidence for VA-ECMO (see chapter on clinical review for more details).
- **The remaining of the studies were non-comparative costing analyses, based on small sample, cohort studies.**
- **Generally, there was a lack of detailed data, allowing the extraction of incremental ECMO-specific costs, over those of a non-ECMO ICU patient.**
- **Great differences were found in costs. These were mostly due to the differences in the factors considered, but the perspective used, patient populations included, and time horizons studied also influenced these differences.**

9 SURVEY OF BELGIAN HOSPITALS ON COSTS OF ECMO

9.1 Introduction

Given the lack of Belgian costing studies in this field, this section reports on a survey carried out amongst Belgian hospitals aimed at gathering costs linked to the use of ECMO in this country. The final objective was to compare these costs to the current reimbursement available for ECMO use. Thus, the focus was on any incremental costs specifically linked to ECMO, compared to those of a non-ECMO ICU patient. No consideration was given to any costs incurred in for which separate reimbursement exists (eg additional transfusions or tests needed for an ECMO patient).

9.2 Methods

With this in mind, two separate questionnaires were drafted. The first one was addressed to hospital managers and was structured in five separate sections.

Section 1, gathered general information including the type of hospital (i.e. general, university or general with academic component), and the mean cost of an ECMO console.

Section 2, captured the number of ECMO machines and patients on ECMO during each of the last 3 years (2019, 2020 and 2021)

Section 3, covered disposable costs linked to cannulation/placement of ECMO (per patient)

Section 4, focused on cost of treatment/monitoring of ECMO (per patient)

Section 5, listed other general costing questions.

The second questionnaire was addressed to the head of ICU in charge of ECMO and was structured in four sections:

Section 1, gathered, once more, information on the type of hospital.



Section 2, collected information on the specialties and time involved in the placement of ECMO (VV and VA), and the stabilisation of the patient.

Section 3, captured data on the specialties and time required for monitoring patients on ECMO (VV and VA)

Section 4, covered the availability or not of an ECMO mobile unit, its composition and time requirements.

Section 5, registered data on the ratio nurse-to-patient in the ICU for a non-ECMO patient versus an ECMO patient.

At the end of each section, a free text question was added to allow respondents to add any comments or clarifications they considered helpful for the interpretation of the information provided or for our research in general.

These questionnaires were sent both as Lime surveys and word documents to hospital managers in Belgium.

In order to identify the most appropriate recipients of these surveys, a list of all hospital managers was drafted after searching for their information online. From these, contact addresses (i.e. emails) were identified for a total of 94 hospital managers. Since not all centres were ECMO users, TCT data for the two latest available years (2018-2019) was used to extract from the list, hospitals that had used ECMO in less than three occasions over the period 2018-2019. These were excluded from our list, to avoid the inclusion of centres with only exceptional ECMO use. The questionnaires were finally sent to a total of 36 hospitals. Copies of these questionnaires are available upon request in both French and Dutch. Hospitals managers were asked to fill the questionnaire addressed to them, and forward the second questionnaire to the head of the ICU unit, in charge of ECMO. No information that could possibly facilitate the identification of a centre was asked, and results were grouped and analysed by one researcher, with the collaboration and input of a second researcher. Responses were received in February 2022 and gathered in a excel sheet to facilitate their analysis.

Contributions were done on a voluntary basis and no financial recognition was offered.

9.3 Results

Overall, 18 hospitals managers and 18 heads of ICU replied. The response rate was therefore, 50% for both. All questionnaires were completed in full, and detailed, clear information was provided.

There was a evenly distributed balance between university and general hospitals amongst respondents, with 8 university hospitals and 9 general hospitals, as well as 1 general hospital with an academic component. The latter, was grouped with the university hospitals for the purpose of this analysis.

9.3.1 Overall number of ECMO machines and patients on ECMO 2019-2021

The number of ECMO machines in the 18 centres who responded to our questionnaire grew from 57 in 2019 to 78 in 2021 (+37%), with a mean of 3 consoles per centre in 2019 and 4 in 2021. The mean number of consoles in general hospitals was below that of university hospitals throughout the period studied (1,78 versus 3,33) and in 2021 (4,56 versus 5,33). In addition to this increase, two respondents mentioned they temporarily rented 2-3 additional consoles in 2020 and 2021 over a period of high demand due to the COVID-19 crisis, while a further centre explained they converted pump consoles, used in the operating theatre into ECMO units, for a limited period of time in 2020.

Similarly, the number of patients placed on ECMO over those three years increased greatly for VV-ECMO, reflecting an important use of VV-ECMO during the COVID-19 crisis. Thus, while the number of patients on VV-ECMO in the 18 respondent centres was 170 in 2019, it went up to 397 in 2021 (+134%). The mean number of patients treated with VV-ECMO per hospital, in 2019 was 9,44 (range 0 to 34) compared to 22,06 in 2021 (range 3 to 62). These figures depended on the type of hospital studied, with a mean of 27 (range 3 to 62) in university and general hospitals with an academic component, and 17 (range 4 to 32) in general hospitals, in the year 2021.



The number of patients placed on VA-ECMO over the same period decreased. Thus, while the number of patients on VA-ECMO in the 18 respondent centres was 306 in 2019, it decreased to 219 in 2021 (-28%). The mean number of patients treated with VA-ECMO in 2019 was 17 (range 0 to 56) compared to 12,57 (range 0 to 41) in 2021. These figures varied, once more, depending on the type of hospital, with a mean of 17 (range 3 to 41) in university and general hospitals with an academic component, and 8 in general hospitals (range 0 to 29) in the year 2021. It is interesting to note that three centres which were not doing ECMO in 2019 started placing some patients on VV-ECMO in the period 2020-2021.

9.3.2 Costs of ECMO

9.3.2.1 Console

Our survey gave a mean cost per ECMO unit of €79 983, with most estimates falling close to that mean, despite the large range of costs presented (from €32 973 to €109 000). Bearing in mind the mean life span of these consoles mentioned in our survey, (i.e. 15 years) and assuming the console would need to be replaced by a new one after that time, a cost of the console per patient was estimated. In order to do this, the mean number of patients (on VV or VA-ECMO), and the mean number of consoles in the latest year for which data was reported (2021) was extracted from our survey. This resulted on a mean annual number of patients treated per ECMO console, of 7,90. This was lower than the mean in 2019, in the pre-COVID-19 period, which was 8,33. Despite a higher number of patients treated with ECMO, in 2021, the increase in the number of consoles per centre during the COVID-19 period, resulted in this lower patient rate per machine.

The mean overall cost per patient of the console was estimated to be of approximately €675. We will use this estimate as our base case. However, during a consultation with experts, these explained that the lifetime of the console may vary, and although 15 years appeared to be a reasonable assumption, for hospital accounting this time horizon is most often set to 10. There is also the possibility that if an improved version of the console is launched, the hospital may decide to replace the units earlier. Assuming a

shorter lifespan for the console of 10 years, the mean cost per patient would be of €1012. This value would be used in our sensitivity analysis to ensure a possible shorter lifespan is considered.

9.3.2.2 Disposables

In addition to the ECMO unit, the use of this intervention incurs also in disposable costs, which according to our survey consist mainly of the cannulae, as well as the oxygenator plus circuit. The reported mean cost per patient of drainage cannulae was €501 (from €330 to €734), while it was €390 (from €56 to €665) for arterial or reinjection cannulae. Nevertheless, others were mentioned by some of the responders, such as double lumen cannulae (mentioned by 2 respondents), with an estimated mean cost of €2721 (range from €2350 to €2850), and PROTEK-DUO cannulae (mentioned by 4 respondents), with a mean cost of €5488 and a range from €4850 to €6050.

Other disposables mentioned included the oxygenator and circuit, which had a reported mean cost per patient of €2628, but presented a much wider range (from €850 to €5445).

The overall mean cost of disposables per patient was estimated at €3519. For this mean, only the most common cannulae (drainage and arterial/re-injection) were considered, and therefore, these costs represent the most common approached used, but also a potentially conservative estimate.

A point was made that ECMO use is in general very costly for hospitals. In addition to this, a respondent mentioned that some tests required for these patients are not reimbursed such as AC tests (one every 2 hours) or ROTEM tests (once per day). The extent to which these tests are performed in ECMO patients in Belgium, remains unknown.



9.3.2.3 Time per staff type

Important costs are attached to the high staff resources required for ECMO use. In order to capture these, questions were posed to the heads of ICU regarding the staff involved during both the placement/cannulation phase and the monitoring of ECMO, and the (ECMO-specific) time required for each of the staff categories involved. Responses received were assumed to be representative of the situation at that point in time, (February 2022).

A costing exercise using the KCE costing manual¹⁵⁰ was pursued to be able to attach a cost to each specialty and thus, estimate an overall ECMO-specific resource cost (incremental to that of non-ECMO ICU patients).

According to respondents, the staff involved during the cannulation phase (including the stabilisation of the patient) to place a VA-ECMO, consisted of:

Perfusionists (16/18 respondents), surgeons (15/18), intensivist (16/18), ICU nurse (17/18), and others (8/18). The specialties mentioned under the “others” category, were most commonly cardiologists or anaesthetists.

The staff involved during the cannulation phase (including stabilisation of the patient) to place a VV-ECMO, consisted of:

Perfusionists (16/18 respondents), surgeons (12/18), intensivist (18/18), ICU nurse (18/18), and others (5/18). When specifying the “others”, two responders mentioned an instrumentalist nurse, one an anaesthetist, one a cardiologist and the last respondent, a second intensivist.

The mean times per specialties are listed in Table 42, separately for VA and VV-ECMO.

In order to estimate a personnel cost for the cannulation/placement of VA and VV-ECMO, we applied costs from our costing manual,¹⁵⁰ to each specialty and multiplied this by the estimated mean time required for placing a patient on ECMO. Given the differences in VA and VV-ECMO cannulation time reported in our survey, estimations were made separately.

It is important to highlight that the costs per minute for a surgeon used in our exercise represent those of a cardiac surgeon, while the cost of a perfusionist was assumed to be equal to that of an ICU nurse. Nursing costs were based on a working day of 7,6 hours. Physicians’ costs were based on an estimation of their gross hospital income, minus deductions. All the details explaining the methodology used to calculate these costs can be found in our costing manual.¹⁵⁰

The costs (per specialty) extracted from our costing manual, dated from march 2012 and were thus, updated to February 2022 costs, by means of the Belgian wage revaluation coefficient (“verhogingscoëfficiënt”/“coefficient d’augmentation”)^a in the case of nurses. Given the fact that physicians in Belgium are not salaried, the update of physicians’ costs (intensivists and surgeons, in our specific case), was done by means of the Health Index.^{bbbb} Although estimating the indexation of fees by means of medical-mutualist agreements would have been possible, no indexation of “deductions” could have been applied, and thus, the Health Index was identified as the best option, being more specific to our field of interest than the consumer price index, often used by researchers for updating purposes.

Costs and times were weighted by the proportion of respondents who mentioned each specialty, in order to calculate a mean cost reflecting the group of respondents to our survey. Given that the majority of hospitals replied that no “other” specialties were included in the cannulation of VV or VA-ECMO or its monitoring, and that amongst those who did mentioned “other” specialties, there was great variation in the specialties mentioned, as well as on the estimations of time, it was decided to exclude this category from our valuations. Our estimates reflect therefore, the costs linked to the base team involved in ECMO use and are likely to offer a conservative estimate.

^a [Bureau fédéral du Plan - Indice des prix à la consommation & prévisions d'inflation](#)



Table 42 summarises the mean costs obtained for both VV and VA-ECMO during the cannulation (and patient stabilisation) time. Overall, these amounted to €772,45 for VA-ECMO, while they were lower for VV-ECMO (€663,24).

Table 42 – Mean personnel costs for cannulation/placement of ECMO

ECMO VA Specialty	N. of respondents	Mean time (in min)	Cost/mi n (2012)*	Cost/mi n (Updt Feb 2022)	Mean cost per specialty Feb 2022	Mean total cost Feb 2022
Perfusionist	16	121	€0.64	€0.74	€88.96	€772.45
Surgeon	15	69.23	€2.92	€3.52	€243.66	
Intensivist	16	143.08	€2.27	€2.74	€391.49	
Nurse	17	205	€0.64	€0.74	€150.71	
ECMO VV Specialty	N. of respondents	Mean time (in min)	Cost/mi n (2012)*	Cost/mi n (Updt Feb 2022)	Mean cost per specialty Feb 2022	Mean total cost Feb 2022
Perfusionist	16	124	€0,64	€0,74	€91.16	€663.24
Surgeon	12	66	€2,92	€3,52	€232.29	
Intensivist	18	114	€2,27	€2,74	€311.92	
Nurse	18	157	€0,64	€0,74	€115.42	

*From Swartenbroekx N, Obryn C, Guillaume P.¹⁵⁰

Regarding the monitoring period, medical staff involved in this phase consisted mainly of:

Perfusionists (16/18 respondents), surgeons (5/18), intensivist (18/18), ICU nurse (18/18), and others (5/18). Under “others”, two respondents mentioned physiotherapists, two others a post-graduate medical student, and a final one, a cardiologist in case of VA-ECMO, who was responsible for checking the base problem which made it necessary to use VA-ECMO.

The mean (daily) time reported per specialty for this monitoring period can be seen in Table 43. Regarding the nursing time during this monitoring phase, most respondents mentioned that nurses were continuously monitoring ICU patients in general, during their shift. Thus, in order to identify and refer only to the incremental nursing time required for ECMO over non-ECMO ICU patients, information provided by the respondents regarding the ratio nurse-to-patient, with and without ECMO was used. Respondents gave a mean ratio nurse-to-patient, for non-ECMO ICU patients of 1:2,47 (range from 1:2 to 1:3). Fourteen out of the 18 respondents to our survey mentioned this ratio decreased in the case of ECMO patients, while a further respondent was unsure. Only three respondents mentioned the ratio did not change. The mean adapted ratio for ECMO patients was 1:1,21 patients (range from 1:1, as recommended in the ELSO guidelines¹³ to 1:2). This confirms the need for a more resource intense monitoring of ECMO patients in the ICU. Assuming a day of 7,6 hours,¹⁵⁰ this would translate into a need for 3,20 extra hours per day of nursing time (192 minutes).

Regarding the time for the intensivist to monitor ECMO patients, one respondent mentioned the intensivist was continuously monitoring ECMO patients and a further two, gave a mean time per ECMO patient per day between 4-6 hours. These three responses were excluded from our estimations, since they were thought to represent the overall time spent monitoring ECMO patients, instead of the incremental daily time required for an ECMO patient when compared to a non-ECMO ICU patient. It is important to note that these costs are aimed at representing an average ECMO patient. The mean (daily) time for the intensivist was estimated using the remaining responses, and was of 86 minutes.



Overall mean (daily) personnel costs during the monitoring phase amounted to €422,01 (See Table 43 for details).

Table 43 – Mean daily costs of monitoring for ECMO (VV and VA)

Specialty	N. of respondents	Mean time (in min)	Cost/minute (2012)*	Cost/minute (Updt to Feb 2022)	Mean cost per specialty Feb 2022	Mean (daily) costs Feb 2022
Perfusionist	16	44	€0.64	€0.74	€32.35	€422.01
Surgeon	5	17	€2.92	€3.52	€59.83	
Intensivist	18	86	€2.27	€2.74	€235.31	
Nurse	18	192	€0.64	€0.74	€141.33	

*From Swartenbroekx N, Obyn C, Guillaume P.¹⁵⁰

In addition to the overall costing exercise some additional questions were asked in order to better interpret and understand the information.

When asked whether the current reimbursement system in place in Belgium was appropriate to cover all ECMO costs, all respondents thought it was not. Reasons for this discrepancy, were mainly linked to three factors:

1. the lack of reimbursement payment for the monitoring of ECMO after the 5th day, since the mean ECMO duration is thought to be longer and thus, any additional costs need to be covered by the hospital budget, which is thought already to be stretched, menacing the sustainability of ECMO use.
2. the low (and non-renewable) lump-sum available for disposables and ECMO units, which does not cover their cost and does not recognise the need to change some of the circuit components.
3. intensive monitoring by nurses and medication required, which need to come out of the BFM

The respondents to our survey thought that the most costly factors linked to the use of ECMO were staff costs, which appear to be non-negligible when we look at the personnel costs previously reported, as well as the disposable costs linked to the use of the ECMO machines. In two instances, hospitals mentioned the need to close some ICU beds when they have ECMO patients, to ensure enough nursing time can be devoted to them.

9.3.2.4 Mobile retrieving ECMO units

Concerning mobile retrieving ECMO units, 12 respondents mentioned to have one, and in most cases, it was the case in academic hospitals (or general with an academic component), with only one of these types of centres not having such mobile unit. Nevertheless, three general hospitals, out of the eight that responded to our survey, also mentioned to have one. For those who did mention having a retrieval team, the staff involved and time required was captured and described. The mobile team was composed in all cases of "1 intensivist, 1 perfusionist, and at least 1 nurse". In 6 cases, a surgeon was also part of the team, and in one case, a cardiologist was also included. Regarding the mean time required for this team to engage in retrieving activities each month, this was estimated to be 6,89 hours, with a range from 2 to 12 hours.

The overall mean cost of personnel per month linked to these activities would be estimated at a minimum of €1739, according to the figures provided in our survey, when taking into consideration a team composed of 1 perfusionist, 1 nurse and 1 intensivist. When two nurses are in the team, this mean monthly cost goes up to €2043. In those cases in which the presence of a surgeon would be needed (as mentioned by 6 respondents), the mean cost of personnel for this team, per month, would be of €3194 with one nurse and of €3498, if two nurses are part of the team.

9.4 Overall costs per ECMO treatment

For the purpose of our Belgian costing exercise, the monitoring costs were only estimated per day, due to the lack of reimbursement for the monitoring of ECMO after the 5th day, which resulted in a lack of data regarding the



duration of (VV and VA) ECMO. Therefore, an overall cost per episode could not be calculated based on the registered Belgian data.

Assuming a duration for VV-ECMO of between 8 and 28 days, based on the Quartiles 1 and 3 reported for COVID-19 patients in Belgium (See chapter 3 for details), the overall VV-ECMO costs would be between €8233 and €16 674. It is important to note that COVID-19 patients are particular, and may present longer ECMO durations than other types of patients requiring VV-ECMO. Nevertheless, the median duration of ECMO for these patients found in our data analysis was the same as the mean captured in the EOLIA trial (15+/-13)²⁷ and thus, the COVID-19 Belgian data was considered relevant for the purpose of these purely illustrative estimations. The costs of VA-ECMO, based on a median duration of 4 days (Quartile 1: 2,0; Quartile 3: 6,8)¹⁵¹ would be between €5810 and €7836. The extent to which these duration estimates identified via our review of ECMO costing studies, could represent Belgian reality, remains unknown.

Table 44 – Mean costs of ECMO (February 2022)

Mean costs per ECMO patient in Belgium	
VA-ECMO	
Console	€674.96
Disposable costs	€3 519.00
Personnel costs (placement/cannulation)	€772.45
Personnel daily costs (monitoring)	€422.01
VV-ECMO	
Console	€674.96
Disposable costs	€3 519.00
Personnel costs (placement/cannulation)	€663.24
Personnel daily costs (monitoring)	€422.01

9.5 Sensitivity analysis

In order to identify which aspects from our costing exercise had more weight on the overall costs and the extent to which variations on these could influence the overall results, a simple univariate sensitivity analysis was carried out. The baseline value was taken as the overall mean (incremental) ECMO costs assuming 9 days of ECMO.¹⁴³ Low and high estimates for each parameter were estimated as quartiles 1 and 3, (Q1 and Q3) for each tested variable.

Table 45 lists all variables tested, as well as the specific low and high values considered. It is important to note that in the case of the cost of the console, the high value covers, not only the Q3 of the costs reported via our survey, but also the assumption of a lower lifespan of the console (10 years as opposed to 15).

The specific weight of each variable can be observed in the tornado diagram presented in Figure 36. Our results show that the duration of ECMO, a variable for which no reliable Belgian data exists at present, has the most important weight, since these are patients who require a very intense monitoring and thus, the hospital continues to incur in high costs over the entire treatment episode. Similarly, for the same reason, the costs linked to the monitoring time of nurses and intensivists, also proved to have an important impact on the overall results. Finally, the weight of disposables was not negligible either.

While the time involvement of the different professionals in charge of placing patients on ECMO, appear to be less influential, it is important to highlight that these are one-off costs and thus, when estimating the costs over the entire treatment episode (here assumed to be of 9 days) they become less influential. If the mean duration of the treatment episode was very short, these costs would become more important.



Table 45 – Variables and values tested on sensitivity analysis for ECMO costs in Belgium

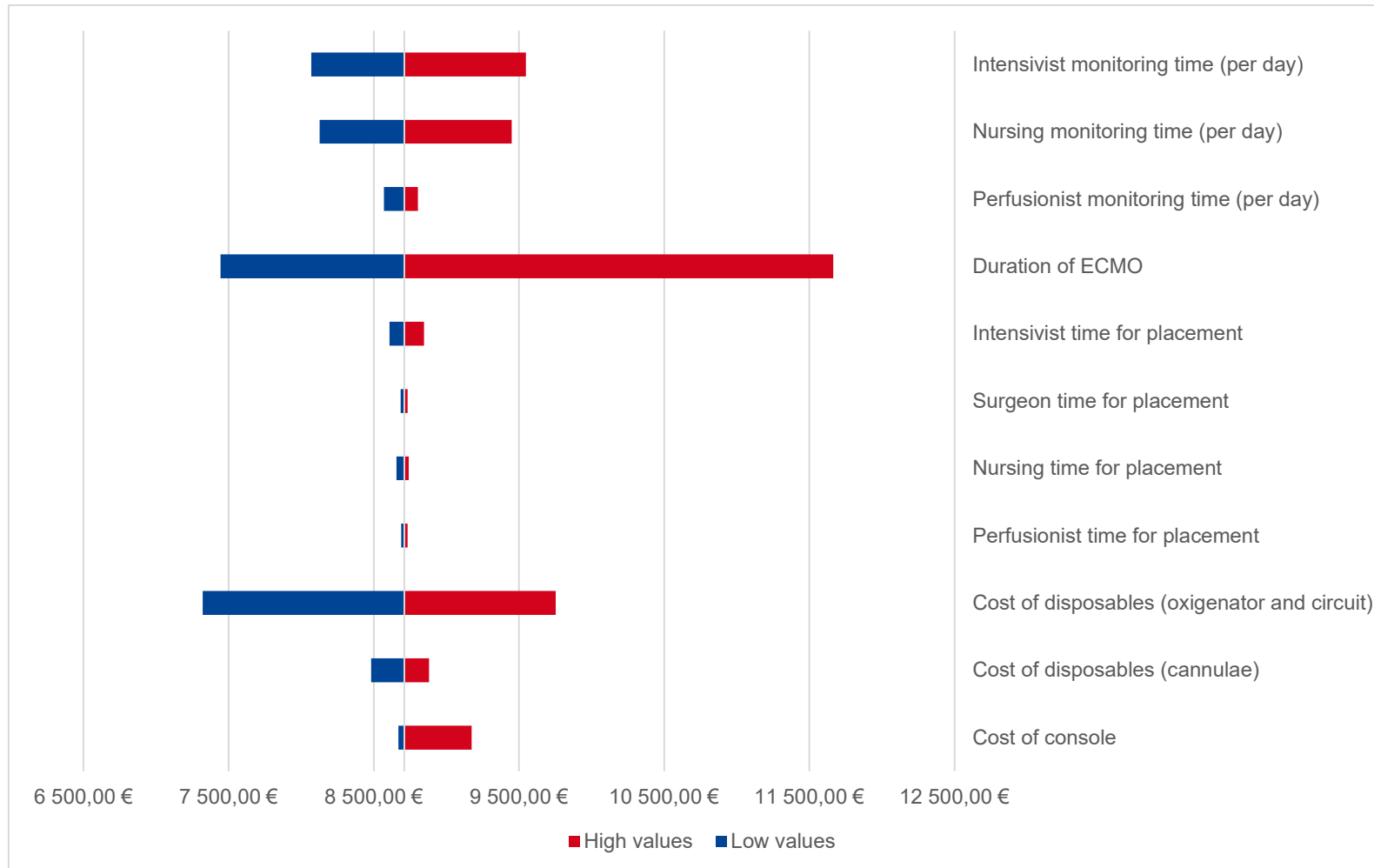
Variables	Values for variables		Total ECMO costs (excl. monitoring)	Total ECMO costs
Cost of console				
Baseline (mean)	79983.00		4911.81	8709.94
Q1	75100.00 (+ 15 years lifespan)		4870.60	8668.73
Q3	90000.00 (+10 years lifespan)		5376.08	9174.21
Cost of disposables (cannulae)				
Baseline (mean)	891.00		4911.81	8709.94
Q1	661.75		4682.56	8480.69
Q3	1061.52		5082.33	8880.46
Cost of disposables (oxygenator and circuit)				
Baseline (mean)	2628.00		4911.81	8709.94
Q1	1239.50		3523.31	7321.44
Q3	3670.30		5954.11	9752.24
Perfusionist time for placement	VA	VV		
Baseline (mean)	121.00	124.00	4911.81	8709.94
Q1	90.00	90.00	4890.57	8688.70
Q3	146.25	165.00	4933.45	8731.58
Nursing time for placement	VA	VV		
Baseline (mean)	205.00	157.00	4911.81	8709.94
Q1	120.00	90.00	4857.67	8655.80
Q3	270.00	180.00	4942.83	8740.96
Surgeon time for placement	VA	VV		
Baseline (mean)	69.23	66.00	4911.81	8709.94
Q1	60.00	56.25	4886.83	8684.96
Q3	90.00	60.00	4935.23	8733.36



Intensivist time for placement	VA	VV		
Baseline (mean)	143.08	114.00	4911.81	8709.94
Q1	120.00	60.00	4809.86	8607.99
Q3	180.00	180.00	5046.99	8845.13
Duration of ECMO				
Baseline (mean)	9.00		NA	8709.94
Q1	6.00		NA	7443.89
Q3	16.00		NA	11664.04
Perfusionist monitoring time (per day)				
Baseline (mean)	44.00		NA	8709.94
Q1	20.00		NA	8568.78
Q3	60.00		NA	8804.04
Nursing monitoring time (per day)				
Baseline (mean)	192.00		NA	8709.94
Q1	104.00		NA	8126.06
Q3	304.00		NA	9449.38
Intensivist monitoring time (per day)				
Baseline (mean)	86.00		NA	8709.94
Q1	60.00		NA	8069.68
Q3	120.00		NA	9547.19



Figure 36 – Tornado diagram for ECMO costs in Belgium





9.6 Limitations

Important limitations linked to our survey need to be recognised. First, ECMO centres to which the questionnaires were sent were identified on the basis of 2016-2019 TCT data, but some hospitals may have started using ECMO during the COVID-19 crisis and therefore, may not be represented in our sample.

Second, despite a response rate of 50% and a nice balance between the types of hospitals, hospital numbers remain low. Third, estimates provided are self-reported, which could differ from reality. In addition to this, responses were provided on a voluntary basis and no financial contribution was offered. This may have resulted in a sample of respondents representing those more interested in the use of ECMO. The extent to which their responses are also valid for other hospitals remains unknown.

While disposable and capital equipment costs are likely to be more generalisable, the staff (number and specialties) involved in ECMO use, or the ratio of nurse-to-patient could differ. Nevertheless, the inclusion of general hospitals, some of them with relatively low number of patients on ECMO in the period (2019-2021), as well as the consistency in most of the responses regarding the high human resources involved in ECMO use, could have reduced, to a certain extent, this potential risk of bias.

Fourth, the mean value has been used, for our estimations. However, variations in responses for some specific variables, such as the cost of the oxygenator and the circuit were large and therefore, subject to great uncertainty.

Fifth, the time required for “other” specialties, since mentioned by a minority of respondents, were excluded from the costing exercise, which was aimed at estimating a mean cost that could be representative of Belgian practice.

Sixth, the cost of ECMO mobile units is presented separately and not captured in our base case costing, since it was unclear to what extent some of these units and personnel time were also available for other patients needed to be brought from other hospitals (ie. Not ECMO specific retrieval units).

For all of the above mentioned reasons, and despite the fact that it represents the only source of Belgian cost information linked to ECMO use publicly available to this date, it is important to consider these results as an approximation not exempt from uncertainties, and thus, the reader should avoid taking any absolute figures here presented as real facts. With that in mind, the overall costs presented in Table 46

as ranges (using Q1, Q3) could be compared with the current reimbursement levels in Belgium. Table 46, shows that the costs obtained via our survey, appear to be well above the current reimbursement levels. Nevertheless, more, reliable data would need to be collected to gain a clearer understanding of the order of magnitude of these differences.

**Table 46 – Mean incremental hospital costs of ECMO (per patient) compared to current reimbursement in Belgium**

Mean incremental* costs per ECMO patient in BE	Range of estimated costs (low-high values)**	Reimbursement/funding received by the hospital	Source of reimbursement/funding***
VA-ECMO			
Console	€633.76-€1 139.24	Unknown	Federated subsidies (previously BFM-A1)
Disposable costs	€1 901.25-€4 731.82	€ 1 023.34	RIZIV/INAMI codes 159946-159935 and BFM-B2
Personnel (physicians and nurses) costs for ECMO placement, start and withdrawal	€609.97-€984.79	€ 863.11	RIZIV/INAMI codes 229703-229692
Personnel (physicians and nurses) daily costs for monitoring patients	€263.47-€610.59	€ 134.98	RIZIV/INAMI codes 211363 (1st day); 211385 (2nd-5th day)
VV-ECMO			
Console	€633.76-€759.49	Unknown	Federated subsidies (previously BFM-A1)
Disposable costs	€1 901.25-€4 731.82	€ 1 023.34	RIZIV/INAMI codes 159946-159935 and BFM-B2
Personnel (physicians and nurses) costs for ECMO placement, start and withdrawal	€421.13-€873.45	€ 265.57	RIZIV/INAMI codes 229725-229714
Personnel (physicians and nurses) daily costs for monitoring patients	€263.47-€610.59	€ 134.98	RIZIV/INAMI codes 211363 (1st day); 211385 (2nd-5th day)

* Over a non-ECMO ICU patient.

** Low: Quartile 1, High: Quartile 3 of responses for each variable captured in the survey.

*** The codes RIZIV/INAMI here represented exclude the codes for children and neonates.



9.7 Key Points

No Belgian costing study or data on ECMO use is currently (publicly) available.

Our survey to Belgian hospitals showed:

- **An increase in the number of patients on VV-ECMO, and in the number of consoles from 2019 to 2021.**
- **Mean costs per patient of console/capital equipment of €675 or €1012, (depending on the lifetime of the console).**
- **Mean costs per patient of disposables of around €3519.**
- **Mean personnel costs per patient during the cannulation/placement of ECMO of approximately €772 for VA-ECMO and €663 for VV-ECMO.**
- **Mean personnel costs per patient during the monitoring of ECMO of approximately €422, for both VV and VA-ECMO, although differences exist between the two types of ECMO, in complex cases (more intense monitoring required for VA patients and therefore, more costly).**
- **No Belgian data on the duration of ECMO (VA or VV) was available and thus, a mean overall cost per ECMO episode could only be estimated on the basis of the ECMO durations mentioned in the literature (between €7389 and €11609 for VV-ECMO and between €5810 and €7836 for VA-ECMO).**
- **Costs obtained via our survey appear to be above the current reimbursement levels.**
- **The limited data obtained via our survey is subject to important uncertainties. More reliable data would need to be collected to gain a clearer understanding of the order of magnitude of these differences between reimbursement levels and real costs of ECMO.**

10 CONCLUSIONS AND GENERAL DISCUSSION

Our research represents the first attempt to offer a complete overview of ECMO use in Belgium, the current trends, organisational challenges, reimbursement, and costs.

Despite the important limitations that surround this research, it highlights a number of important points:

The use of ECMO has grown in the last years and continues to grow, with a marked increase in the use of VV-ECMO during the SARS-CoV-2 pandemic, and a slight decrease in the number of VA-ECMO over that same period. This general growth confirms a trend seen worldwide and makes it important to review this complex and high-risk technique.

Although the available clinical evidence in support of ECMO remains limited and of variable quality, for both VA- and VV-ECMO, RCTs are available for VV-ECMO only. For VA-ECMO, there are four ongoing studies comparing it with standard therapies for cardiac arrest or cardiogenic shock. Despite the fact that, these ongoing studies are likely to be subject to the similar biases/limits, already seen in the published data (eg. selection bias, cross-overs) and which have been detailed in our clinical review chapter, this is an area where an increased use of ECMO is likely to be seen in the near future. In particular, some of the consulted experts, saw ECPR, as a field likely to increase VA-ECMO use in the next few years. With regard to the future use of VV ECMO, this appears to be well established, and new studies are not expected given the existence of RCTs and the severity of these patients. What could increase in the future would be the number of centers offering VV ECMO, and the distribution of patients across these, since new centres that were not using ECMO prior to the COVID-19 pandemic, may continue using it after it, having invested already in the ECMO machines, and having developed an experience in the field.

Our review of factors which could have some weight on the effectiveness of ECMO, identified a number of studies linking patient volumes with better outcomes. Once more, these presented some important limitations which are covered in the relevant chapter.



An important point to make in this regard is that it is unlikely that patient volume, in isolation could result in better patient outcomes and thus, the volume of ECMO cases should not be seen as the single surrogate marker of clinical experience. Improving outcomes would most likely rely in a combination of structural and organizational factors in centres performing ECMO, allowing to improve the quality and expertise of care. These would include the development of standardized protocols for the eligibility criteria for ECMO and for the overall process of care. In addition to this, building up a teams through systematic educational programs (including simulation training) is considered as a crucial step to improve skills and confidence. Finally, an analysis of clinical data and outcomes through registers, along with the possibility to make comparisons between centres would also be a crucial step to improve the quality of care. Our data analysis highlights a wide spread of use between different Belgian centres, including both academic and general hospitals, amongst which, some, perform low number of ECMOs on a yearly basis. This contrasts with the situation in countries that have developed a centralised approach of ECMO services, in which the offer of ECMO centres is limited and adjusted to the population needs. In such a centralised approach, the numbers of ECMO centres per habitant is substantially much lower than Belgium. Nevertheless, the limited data registration available at present in Belgium does not allow to assess the appropriateness of the current use, but does highlight the need for improving (and encouraging) data registration, setting up standard protocols and quality measurements.

Although detailed clinical data is available for some hospitals which were willing to share these with us, our data analysis was instead based on the existing administrative databases. These suffer from important weaknesses such as their retrospective and administrative (non-clinical) nature, their limited variables, and the fact that the latest data available refer to the year 2019. Nevertheless, the focus on these data was the only approach that allowed for exhaustiveness, covering all hospitals and avoiding any generalisation of data from highly specialised, larger hospitals where resources, or organisational factors, as well as patient volumes, could differ greatly from those seen in smaller hospitals.

A further data source which was discussed and considered was the ELSO registry. However, few Belgian hospitals appear to contribute to this, and thus, results and conclusions would, once more, lack of generalisability.

A more complete data registration focusing on relevant patient characteristics and comorbidities, specific indications, duration of treatments, and complications could bring great value to an area currently lacking transparency, and offer a first step towards an optimisation of ECMO use. The specific data parameters to be captured should be discussed and agreed upon with professionals, and could include variables such as:

- Specific patient characteristics (e.g. age and sex) and relevant comorbidities
- Detailed indication for which ECMO (veno-venous or veno-arterial) is used
- Days in ICU pre-ECMO placement
- Days on mechanical ventilation pre- veno-venous ECMO
- Severity score (organ dysfunction) at ECMO placement
- Proportion of patients transferred specifying if already on ECMO, or to be placed on ECMO at arrival to the new centre
- ECMO duration
- Complications
- Hospital survival
- Death within 48h of ECMO placement...

Our survey to Belgian hospitals fills in an important gap despite its limitations, since no publicly available studies on Belgian ECMO costs are available up to this date. Responses showed that costs appear high, confirming similar overall results of studies performed in other European countries. Nevertheless, comparisons of the order to magnitudes between the Belgian data and the European or Canadian studies captured in our review are not appropriate, mainly because our survey was aimed at



identifying incremental ECMO-specific costs, while all but two studies from the published literature were non-comparative. Therefore, the separation of incremental costs was not possible. Even when looking at the comparative studies, these covered very wide costs (transport, ambulatory costs, physiotherapy...) and performed their analysis over a six-month period, so their overall costs would not offer an appropriate comparator for the results obtained via our Belgian survey, where the focus was purely on the hospitalization period during which ECMO was used.

Although a global view on costs of ECMO would have been interesting, this would have made our survey too complex and thus, a conscious decision was made to focus purely on the incremental costing aspects that could then be compared with the ECMO-specific reimbursement/funding currently available.

Such comparisons show that the current costs of placing/starting a patients on ECMO as well as those of monitoring those patients are above the current reimbursement levels, with the exception of the placement and start of VA-ECMO. Nevertheless, given the self-reported nature of the survey, as well as its voluntary aspect, means that its results should be interpreted with caution and the order of magnitude of the gap between costs and reimbursement should be further explored and confirmed.

An important data gap at present has impeded the estimation of the mean incremental costs of ECMO over the entire treatment episode, since at the moment, no good data on the duration of ECMO exists in Belgium. This is explained by the fact that the current reimbursement codes for monitoring ECMO patients can be charged only until the 5th day, after which the reimbursement stops, with the exception of the indication SARS-CoV-2, for which a new code was created to allow a daily reimbursement without any time limit. A similar approach could be thought for other indications of VV-ECMO and VA-ECMO to facilitate the registration of ECMO duration, a variable that is not only important from a financial perspective, but that can also in some cases serve as an indicator or quality of care.

Other clinical aspects linked to ECMO use, such as mechanical ventilation characteristics or the relevant patient comorbidities were not available either at the time of analysis. These could prove very informative for future considerations.

Regarding the patient perspective, the limited literature review performed highlighted in particular the need for effective and frequent as well as transparent communication between providers and patients and family carers, as well as the need for supporting both patients and family carers, not only during the ECMO intervention, but also after completing this.

Despite the unavoidable incompleteness of this report and its limitations, it provides a one stop view of this complex field and a first step towards the improvement of an area that could benefit from greater transparency, standardization and resources.



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