

Mechanical circulatory support for refractory out-of-hospital cardiac arrest: A Danish nationwide multicentre study

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Abstract

Background

Extracorporeal cardiopulmonary resuscitation (ECPR) has shown potential as a salvage therapy for patients with refractory out-of-hospital cardiac arrest (OHCA). The objective of this study was to describe the gradual implementation, survival and adherence to the national consensus with respect to use of ECPR for OHCA in Denmark, and to identify factors associated with outcome.

Methods

This retrospective, observational cohort study included patients receiving ECPR for OHCA at all tertiary cardiac arrest centers (n = 4) in Denmark between July 2011 and December 2020. Logistic regression and Kaplan-Meier survival analysis were used to determine association with outcome. Outcome was presented as survival to hospital discharge with good neurological outcome, 30-day survival and predictors of 30-day survival.

Results

A total of 259 patients were included in the study. Thirty-day survival was 26% and a good neurological outcome (Glasgow-Pittsburgh Cerebral Performance Categories (CPC) (CPC 1–2)) was observed in 94% of patients at discharge. Strict adherence to the national consensus showed a 30-day survival rate of 30% compared with 22% in patients violating one or more criteria. Adding criteria to the national consensus such as signs of life during cardiopulmonary resuscitation (CPR), pre-hospital low-flow < 100 minutes, pH > 6.8 and lactate < 15 mmol/L increased the survival rate to 48%, but would exclude 58% of the survivors from the current cohort. Logistic regression identified asystole (RR 1.36, 95% CI 1.18–1.57), pulseless electrical activity (RR 1.20, 95% CI 1.03–1.41), initial pH < 6.8 (RR 1.28, 95% CI 1.12–1.46) and lactate levels > 15 mmol/L (RR 1.16, 95% CI 1.16–1.53) as factors associated with increased risk of 30-day mortality. Patients presenting signs of life during CPR had a threefold higher survival rate compared to patients without signs of life (45% versus 13%, $p < 0.001$).

Conclusions

A high survival rate with a good neurological outcome was observed in this Danish population of patients treated with ECPR for OHCA. Stringent patient selection for ECPR may produce higher survival rates but potentially withholds life-saving treatment in a significant proportion of survivors, why optimization of the selection criteria is still necessary.

Background

Out-of-hospital cardiac arrest (OHCA) is a time-critical condition associated with a high mortality worldwide. Despite various initiatives to improve public engagement and ensure access to a sufficient number of external defibrillators, survival rates remain poor(1). Extracorporeal cardiopulmonary resuscitation (ECPR) has emerged as a rescue therapy in adult patients with OHCA that is refractory to conventional cardiopulmonary resuscitation (CPR). Short-term mechanical circulatory support (MCS) with Impella devices(2) or extracorporeal membrane oxygenation (ECMO) may ensure life-saving organ perfusion, lending clinicians crucial time to identify and treat the underlying cause of cardiac arrest. Several observational studies and recently one randomized clinical trial have demonstrated encouraging results after ECPR for refractory cardiac arrest(3–7). ECPR has been introduced gradually over the past ten years in Denmark, and a national consensus was adopted in February 2018(8). However, detailed knowledge of the full cohort treated remains scarce. Regional differences in triage of patients with OHCA may influence the availability of ECPR, which may in turn affect patient selection and outcome. The aims of this study were to describe temporal trends and regional variation in the use of ECPR in Denmark, to evaluate adherence to the national consensus on ECPR use and to identify factors associated with outcome.

Methods

This nationwide retrospective, observational cohort study was conducted at four tertiary cardiac arrest centres in Denmark (Aalborg University Hospital, Aarhus University Hospital, Odense University Hospital and Copenhagen University Hospital). In Denmark, ECPR is performed at these four centres exclusively.

National consensus

The Danish national consensus on the use of ECPR in patients with refractory OHCA was adopted in February 2018(8) (Fig. 1, Consensus A – National consensus). The most consistent criteria for inclusion were normothermic cardiac arrest with an underlying reversible cause, an initial shockable rhythm, witnessed arrest, bystander CPR and end-tidal CO₂ > 1.3 kPa. Regional differences in the inclusion criteria were present during the study period as shown in Fig. 1, Consensus B – Extended version, (Additional file 1, Table A1).

Study population

The study population included all patients aged ≥ 18 years receiving ECPR for refractory OHCA, which was defined as absence of return of spontaneous circulation (ROSC) despite resuscitation efforts for more than 15 minutes. Patients treated between July 2011 and December 2020 were identified from local ECPR databases and medical records. Due to regional differences in ECPR availability and updates to ECPR databases, the data collection period differed for each hospital: Aalborg University Hospital (February 2016 - December 2020), Aarhus University Hospital (July 2011 - December 2020), Odense University Hospital (November 2015 - December 2020) and Copenhagen University Hospital (November 2016 - December 2020).

Study setting

Patient selection, triage and implementation of ECPR were performed at the discretion of the treating ECPR team at the individual centres. The specialized ECPR teams, including anaesthesiologists, cardiothoracic surgeons, perfusionists, and invasive and general cardiologists managed all patients upon arrival. Ven-

arterial ECMO cannulations were inserted percutaneously using the Seldinger technique with ultrasound guidance or open cut-down technique with direct visualization of the femoral vein and artery. Vascular access was achieved by 15F-23F arterial cannulas and 19F-26F venous cannulas. In the majority of patients, a distal arterial perfusion cannula was inserted to ensure antegrade limb perfusion. Circuit flow was titrated until effective circulatory response was achieved. Fluid, inotropes and vasopressors were applied if necessary. In a minority of cases with visible spontaneous cardiac contractility observed on echocardiography during rhythm check, an Impella device was initially placed percutaneously in the femoral artery, and correct positioning was then confirmed by fluoroscopy or echocardiography. For both ECMO- and Impella-treated patients, unfractionated heparin was administered routinely to avoid systemic clotting and aiming for an activated partial thromboplastin time of 60–80 seconds or an activated clotting time of 160–180 seconds. Post-resuscitation care and management were performed according to local intensive care unit (ICU) standard protocols including targeted temperature management (TTM), neurological prognostication and procedures for withdrawal of treatment. Weaning from MCS was done if cardiac and respiratory function were considered to have recovered sufficiently or if further treatment was deemed futile.

Data collection

Study data were recorded in a uniform national database. A study coordinator from each hospital was assigned to manage the data collection. According to the Utstein recommendation for data collection(9), information on cardiac arrest was acquired from the pre-hospital emergency medical service logistic systems and included information on: time of cardiac arrest, witnessed arrest, bystander CPR, initial rhythm and pre-hospital care comprising inotropic usage and intubation. Patient demographics and in-hospital data on clinical parameters, known comorbidities, laboratory tests, intervention and outcome data were obtained from patient records.

Study end-points

The primary end-point was 30-day survival. Secondary end-points included survival to hospital discharge, neurological outcome at hospital discharge and regional differences in triage and outcome. Neurological outcome was evaluated by the Glasgow-Pittsburgh Cerebral Performance Categories (CPC), and a favourable outcome was defined as CPC scores 1 and 2(10).

Statistical analysis

Continuous data are presented as median and interquartile range (IQR, P_{25} - P_{75}) and categorical data as number and percentages. The Mann-Whitney U-test and the Kruskal-Wallis H-test were used for comparison of continuous data, whereas the chi-squared test and Fisher's exact test were used for categorical data. Logistic regression was performed to assess the association of risk factors on 30-day mortality. Results are expressed as risk ratio (RR) and 95% confidence interval (CI). Risk factors were identified *a priori* based on their clinical relevance and previously published literature. Survival analysis results are presented as Kaplan-Meier curves for various subgroups of patients and compared with the log rank test. In case of missing values, patients were excluded from the statistical analysis. Two-sided p-values of < 0.05 were considered statistically significant. Statistical tests were performed using STATA/IC 16, College Station TX77845, USA, for Mac.

Results

Figure 2 demonstrates the gradual implementation of ECPR in Denmark. Between July 2011 and December 2020, a total of 259 patients treated with ECPR for OHCA were enrolled in the study: (Aalborg University Hospital, n = 34, Aarhus University Hospital, n = 138, Odense University Hospital, n = 55, and Copenhagen University Hospital, n = 32). Survival to day 30 was seen in 67 (26%). A total of 65 (25%) patients survived to hospital discharge, and 61 (94%) of these patients were discharged with a CPC of 1–2.

Baseline and cardiac arrest characteristics

Baseline and arrest characteristics are summarized in Table 1. The median age of the study population was 53 years (IQR, 45–60 years), and 79% were men. No significant differences in comorbidities were seen between survivors and non-survivors. In most cases, arrest aetiology was of cardiac origin; and the three dominant causes were acute myocardial infarction (n = 142, 55%), primary arrhythmia (n = 42, 16%) and pulmonary embolism (n = 24, 9%). Significantly more survivors than non-survivors presented an initial shockable rhythm ($p = 0.002$) and signs of life during conventional CPR ($p < 0.001$). Witnessed cardiac arrest was present in 223 (86%) of the patients, and 246 (95%) patients received bystander CPR initiated immediately after recognition of arrest with a median no-flow time of 0 minutes (IQR, 0–1 minutes). Survivors experienced a significantly shorter total low-flow time from cardiac arrest to ECPR initiation than non-survivors (94 minutes versus 107 minutes, $p = 0.002$).

Table 1
Baseline characteristics and pre-hospital data stratified by 30-day survival status

Variable	Total (n = 259)	Survivors (n = 67)	Non-survivors (n = 192)	P-value
Age (years)	53 [45–60]	54 [46–62]	53 [43–59]	0.19
Male sex	205 (79)	50 (75)	155 (81)	0.29
Comorbidities				
History of ischemic heart disease	30 (12)	9 (13)	21 (11)	0.58
Previous myocardial infarction	28 (11)	8 (12)	20 (11)	0.75
History of congestive heart disease	19 (7)	4 (6)	15 (8)	0.62
Hypertension	65 (25)	18 (27)	47 (25)	0.73
Type 2 diabetes	26 (10)	3 (5)	23 (12)	0.06
Peripheral vascular disease	11 (4)	4 (6)	7 (4)	0.31
Previous chronic kidney disease	8 (3)	2 (3)	6 (3)	0.65
Previous stroke	10 (4)	0 (0)	10 (5)	0.05
Cause of cardiac arrest				
Acute myocardial infarction	142 (55)	42 (63)	100 (52)	0.13
Pulmonary embolism	24 (9)	8 (12)	16 (8)	0.26
Primary arrhythmia	42 (16)	10 (15)	32 (17)	0.85
Chronic heart disease	5 (2)	1 (2)	4 (2)	1.00
Cerebral	6 (2)	0 (0)	6 (3)	0.34
Toxic	10 (4)	3 (5)	7 (4)	0.72
Other	20 (8)	4 (6)	16 (8)	0.79
Unknown	13 (4)	0 (0)	13 (5)	0.02
Witnessed arrest	223 (86)	60 (90)	163 (85)	0.34
Bystander CPR	246 (95)	64 (96)	182 (95)	0.94
Transient ROSC	48 (19)	27 (40)	21 (11)	< 0.001

Abbreviations: **CPR** Cardio pulmonary resuscitation; **ROSC** Return of spontaneous circulation; **VT** Ventricular tachycardia; **VF** Ventricular fibrillation; **PEA** Pulseless electrical activity; **LUCAS** Lund University cardiopulmonary assist system

Values are stated as medians and interquartile range [IQR] or numbers and percentages. A p-value < 0.05 is considered significant.

Variable	Total (n = 259)	Survivors (n = 67)	Non-survivors (n = 192)	P-value
Signs of life during CPR	100 (39)	45 (67)	55 (29)	< 0.001
Initial presenting rhythm				
Shockable (VT/VF)	173 (67)	55 (82)	118 (62)	0.002
PEA	57 (22)	10 (15)	47 (25)	0.10
Asystole	28 (11)	2 (3)	26 (14)	0.02
End-tidal CO ₂	3.6 [2.8-5.0]	3.6 [2.9-5.0]	3.5 [2.5-5.0]	0.99
Mechanical compression (LUCAS)	235 (91)	61 (91)	174 (91)	0.97
No-flow (min)	0 [0–1]	0 [0–2]	0 [0–1]	0.77
Pre-hospital low-flow (min)	72 [58–90]	67 [46–90]	75 [60–90]	0.06
Total low-flow (min)	105 [86–125]	94 [73–120]	107 [90–127]	0.002
Abbreviations: CPR Cardio pulmonary resuscitation; ROSC Return of spontaneous circulation; VT Ventricular tachycardia; VF Ventricular fibrillation; PEA Pulseless electrical activity; LUCAS Lund University cardiopulmonary assist system				
Values are stated as medians and interquartile range [IQR] or numbers and percentages. A p-value < 0.05 is considered significant.				

In-hospital and outcome characteristics

In-hospital and outcome data are shown in Table 2. ECMO was established in 225 (86.9%) patients, whereas Impella assistance was commenced in 12 (4.6%) patients. Twenty-two patients (8.5%) received combined ECMO and Impella support. Acute coronary angiography was performed in 234 (90%) patients, and 124 (48%) of the patients received percutaneous coronary intervention. Survivors more likely presented advantageous blood gas analysis with higher median pH levels (7.01 versus 6.88, $p < 0.001$) and lower serum lactate levels (12.0 mmol/L versus 15.0 mmol/L, $p < 0.001$) prior to ECPR implantation. The majority of the patients ($n = 218$; 84%) were admitted directly to the ICU after ECPR commencement. However, in 41 (16%) patients, further resuscitation efforts were deemed futile and treatment was withdrawn at the catheterization laboratory. No differences between the groups were seen regarding renal replacement therapy or TTM, ($p = 0.27$ and $p = 0.46$, respectively). ECPR duration and ICU length of stay were longer in survivors, indicating rapid withdrawal of support in the case of treatment futility. Bleeding at the cannulation site was observed in 76 (29%) and limb ischaemia was seen in 24 (9%) of the patients. None of the patients without distal perfusion had limb ischaemia. The main cause of withdrawal of life-sustaining treatment in non-survivors was severe brain injury ($n = 88$, 46%), no cardiac recovery ($n = 25$, 13%), device failure ($n = 4$, 2%), multiorgan failure ($n = 49$, 26%) and other ($n = 26$, 14%).

Table 2
In-hospital data stratified by 30-day survival status

Variable	Total (n = 259)	Survivors (n = 67)	Non-survivors (n = 192)	<i>P</i> -value
ECMO (only)	225 (86.9)	55 (82)	170 (89)	0.18
Impella (only)	12 (4.6)	6 (9)	6 (3)	0.05
ECMO + Impella	22 (8.5)	6 (9)	16 (8)	0.88
Laboratory data upon arrival				
pH	6.90 [6.82–7.02]	7.01 [6.92–7.15]	6.88 [6.80–6.98]	< 0.001
Lactate (mmol/L)	14.4 [11.4–17.0]	12.0 [9.1–14.7]	15.0 [12.0–19.0]	< 0.001
Potassium (mmol/L)	4.4 [3.7–5.4]	4.1 [3.6–4.9]	4.6 [3.8–5.5]	0.06
Haemoglobin (mmol/L)	8.6 [7.5–9.6]	8.7 [8.1–9.6]	8.6 [7.3–9.6]	0.22
Creatinine (mmol/L)	114 [98–130]	109 [95–131]	115 [99–130]	0.86
CAG performed	234 (90)	62 (93)	172 (90)	0.48
Coronary intervention (PCI/stent)	124 (48)	37 (55)	87 (46)	0.20
Left main	22 (9)	5 (8)	17 (10)	0.73
Left anterior descending	76 (33)	27 (44)	49 (29)	0.02
Left circumflex	8 (3)	2 (3)	6 (4)	0.96
Right coronary artery	30 (13)	9 (15)	21 (12)	0.58
Intensive care stay				
No. of patients admitted to ICU	218 (84)	67 (100)	151 (79)	< 0.001
TTM	152 (70)	46 (69)	106 (70)	0.46
Renal replacement therapy	91 (42)	32 (48)	59 (31)	0.27
ICU length of stay (hours)	53 [13–238]	284 [163–528]	19 [10–63]	< 0.001
ECMO/Impella-related complications				
Bleeding at cannulation site	76 (29)	32 (48)	44 (23)	0.01

Abbreviations: **ECMO** Extracorporeal membrane oxygenation; **CAG** Coronary angiogram; **PCI** Primary coronary intervention; **ICU** Intensive care unit; **TTM** Target temperature management

Values are stated as medians and interquartile range (IQR) or numbers and percentages. A p-value of < 0.05 is considered significant.

Variable	Total (n = 259)	Survivors (n = 67)	Non-survivors (n = 192)	<i>P</i>-value
Limb ischaemia	24 (9)	5 (8)	19 (10)	0.31
Gastrointestinal bleeding	33 (13)	10 (15)	23 (12)	0.90
Gastrointestinal ischaemia	22 (9)	4 (6)	18 (9)	0.20
Time on ECMO (hours)	50 [27–95]	67 [40–98]	37 [8–77]	0.002
Time on Impella (hours)	74 [28–165]	62 [50–165]	84 [10–166]	0.46
Hospital length of stay (hours)	23 [7-358]	687 [496–1060]	13 [4–46]	< 0.001
Abbreviations: ECMO Extracorporeal membrane oxygenation; CAG Coronary angiogram; PCI Primary coronary intervention; ICU Intensive care unit; TTM Target temperature management				
Values are stated as medians and interquartile range (IQR) or numbers and percentages. A p-value of < 0.05 is considered significant.				

Predictors of 30-day mortality

Table 3 shows results from the binary logistic regression. Thirty-day mortality was significantly associated with initial presenting rhythm with asystole (RR 1.36, 95% CI 1.18–1.57, $p < 0.001$), pulseless electrical activity (PEA) (RR 1.20, 95% CI 1.03–1.41, $p = 0.02$), low pH levels < 6.8 (RR 1.28, 95% CI 1.12–1.46, $p < 0.001$) and high lactate levels > 15 mmol/L (RR 1.33, 95% CI 1.16–1.53, $p < 0.001$). Signs of life during CPR (RR 0.63, 95% CI 0.52–0.76, $p < 0.001$) and transient ROSC (RR 0.54, 95% CI 0.39–0.76, $p < 0.001$) were both associated with a lower risk of mortality. Kaplan-Meier curves and the log rank test demonstrated similar results (Fig. 3). A favourable 30-day survival was seen in patients with a pre-hospital low-flow time < 60 minutes and in patients with pre-hospital low-flow time > 80 minutes. Patients with a prolonged pre-hospital low-flow time (> 80 minutes) had a higher rate of signs of life during CPR than patients with a pre-hospital low-flow time of 60–80 minutes (41% versus 34%). For other subgroups, please refer to Fig. 3 and Additional file 2, Figure A1 for further 30-day survival data.

Table 3
Binary logistic regression analysis of risk factors associated with 30-day mortality

Variables	Univariate analysis		
	RR	95% CI	<i>P</i> -value
Age (years)	1.00	(0.99–1.00)	0.21
Male sex	1.10	(0.90–1.34)	0.34
Witnessed arrest	0.91	(0.76–1.08)	0.28
Bystander CPR	0.98	(0.70–1.38)	0.93
Initial presenting rhythm			
VT/VF*	1.00	-	-
PEA	1.20	(1.03–1.41)	0.02
Asystole	1.36	(1.18–1.57)	< 0.001
Signs of life during CPR	0.63	(0.52–0.76)	< 0.001
Transient ROSC	0.54	(0.39–0.76)	< 0.001
End-tidal CO ₂	0.82	(0.65–1.01)	0.07
Pre-hospital low-flow ≤ 60 min	0.80	(0.67–0.95)	0.02
pH ≤ 6.8	1.28	(1.12–1.46)	< 0.001
Lactate ≥ 15 mmol/L	1.33	(1.16–1.53)	< 0.001
Abbreviations: CPR Cardiopulmonary resuscitation; VT Ventricular tachycardia; VF Ventricular fibrillation; PEA Pulseless electrical activity; ROSC Return of spontaneous circulation; RR Risk ratio; CI Confidence interval			
*Reference group.			

Regional differences

Regional differences in patient selection and outcome are shown in Table 4. The ECPR activity per million inhabitants differed between centres. In most centres, younger age was a predominant factor for triage; nevertheless, 38 (15%) patients with age > 65 years did receive ECPR although the remaining inclusion criteria were met. Initial presenting rhythm differed significantly between centres ($p = 0.003$). Pre-hospital low-flow times were significantly longer (77 minutes versus 60 minutes, $p = 0.02$) in hospitals serving patients in remote and rural areas with a distance to centre > 100 km ($p = 0.001$). Thirty-day survival between centres varied from 15–28%; however, this difference did not reach statistical significance, $p = 0.41$.

Table 4
Regional differences in triage and outcome of ECPR patients

Variable	Aalborg University Hospital (n = 34)	Aarhus University Hospital (n = 138)	Odense University Hospital (n = 55)	Copenhagen University Hospital (n = 32)	P-value
No. of ECPR/mio inhabitants*year	11.6	11.2	8.9	2.8	< 0.001
Age < 65 years	26 (76)	113 (82)	51 (93)	31 (97)	0.03
Initial presenting rhythm					0.003
Shockable VT/VF	19 (56)	82 (59)	44 (80)	28 (88)	
PEA	11 (32)	38 (28)	4 (7)	4 (13)	
Asystole	3 (9)	18 (13)	7 (13)	0 (0)	
Witnessed arrest	31 (91)	114 (83)	49 (89)	29 (91)	0.38
Bystander CPR	31 (91)	134 (97)	52 (95)	29 (91)	0.42
No-flow \geq 10 min	0 (0)	10 (7)	0 (0)	1 (3)	0.07
Pre-hospital low-flow (min)	60 [43–77]	75 [60–90]	77 [65–99]	60 [48–70]	< 0.001
Total low-flow (min)	90 [62–110]	105 [88–125]	119 [105–127]	94 [81–130]	< 0.001
Distance to centre \geq 100 km	2 (6)	21 (15)	19 (35)	0 (0)	0.001
30-day survival	5 (15)	38 (28)	14 (25)	9 (28)	0.41
Abbreviations: ECPR Extracorporeal cardiopulmonary resuscitation; VT Ventricular tachycardia; VF Ventricular fibrillation; PEA Pulseless electrical activity; CPR Cardio pulmonary resuscitation					
Values are stated as medians and interquartile range (IQR) or numbers and percentages. A p-value of < 0.05 is considered significant.					

Analysis of selection criteria in the Danish national consensus

Patients meeting all of the selection criteria of the Danish 2018 national ECPR consensus (Fig. 1, Consensus A – National consensus) with respect to normothermic arrest of cardiac origin, age < 65 years, witnessed arrest, bystander CPR, initial shockable rhythm, no-flow time < 10 minutes and end-tidal CO₂ < 1.3 kPa (n = 125, 48%) were compared with those who failed to meet one or more of these parameters (n = 134, 52%) (Fig. 4). Thirty-day survival was 30% in patients who met the selection criteria compared with 22% in patients who failed to meet one or more criteria (p = 0.11).

A more refined assessment of selection criteria including parameters such as signs of life during CPR, pre-hospital low-flow < 100 minutes, initial pH > 6.8 and lactate \leq 15 mmol/L in addition to the consensus criteria showed significantly higher 30-day survival rates in patients meeting one or more of the extended criteria than in patients failing to comply with the criteria (48% versus 19%, $p < 0.001$) (Fig. 4). However, this also implied that 58% (39/67) of the 30-day survivors in this cohort would fail to meet the extended consensus.

Discussion

The present study is the first nationwide multicentre study of outcomes in patients receiving ECPR for refractory OHCA in Denmark. The main findings showed that one in four ECPR patients survive to hospital discharge with a good neurological outcome. Outcome was significantly associated with initial presenting rhythm, signs of life during CPR, transient ROSC, pre-hospital low-flow time, initial pH and lactate levels. By offering ECPR only to patients meeting the strictest criteria, survival exceeded 48%, but this occurred at the cost of withholding life-saving treatment in the majority of patients saved by ECPR in the cohort. Thus, a continuing need exists for optimization of the ECPR selection criteria.

ECPR has emerged as a salvage therapy for patients suffering from refractory OHCA. Although resource demanding, ECPR has been shown to be both feasible and cost effective(11). Several previous observational studies have demonstrated encouraging survival rates and a favourable neurological outcome from applying strict inclusion and exclusion criteria in distinctive patient populations(12–16). The first randomized clinical trial recently published by Yannopoulos et al. (the ARREST trial) revealed superiority of ECMO-facilitated resuscitation with a survival rate of 43% compared with 7% with standard advanced life support(7). Survival at six months was also greater in the ECMO group (hazard ratio (HR) 0.16, 95% CI 0.06–0.41, $p = 0.0001$). Whereas the trial was well-designed and supports use of ECPR in refractory OHCA, apparent limitations are present as this was an open-labelled single-centre study with a relatively small and highly selected patient population. Despite growing interest in and a growing body of literature on ECPR for refractory OHCA, robust evidence on patient eligibility is still lacking.

In Denmark, a number of initiatives to improve pre-hospital quality of care for OHCA patients have produced a remarkable increase in 30-day survival rates from 3.9% in 2001 to 16% in 2018(17). Concurrently, ECPR has been evolving steadily and is now an established treatment for selected patients with refractory OHCA in all Danish regions. However, given the formal inclusion and exclusion criteria defined in the Danish national ECPR consensus, one might assume that the results of our study would reflect a more homogeneous population. Despite our intention to select qualified candidates, violation of the national consensus was seen in a substantial proportion of patients, as patients with an initial presenting rhythm with asystole, unwitnessed arrests and no-flow time > 10 minutes were among those who were treated. In the present study, ECPR was more often reserved for younger patients. This may explain why no significant difference was detected in age between survivors and non-survivors. For patients of younger age, ECPR was initiated despite more frequent failure to meet the criteria, whereas patients with a more advanced age were considered for ECPR only if they were optimal candidates according to the remaining selection criteria.

Previous studies have proposed advanced age as a predictor of a poor outcome in patients with ECPR(18), and some studies have even suggested an age of > 75 years as a contraindication for ECPR(19).

The predictive value of pH and lactate levels in patients with cardiac arrest is well established. Controversy still exists regarding the ECPR population. In our study, initial arterial pH and lactate levels were found to be associated with mortality. This finding is consistent with previous findings(12, 20). Jung et al. retrospectively reviewed 93 patients with cardiac arrest undergoing ECPR and found results similar to our results(21). On the contrary, Leick et al. found no association between elevated lactate levels and mortality(22). Acidosis and high lactate levels indicate prolonged phases of anaerobic metabolism due to tissue oxygen deficiency, advocating that pH and serum lactates may serve as alternate indicators of low-flow times and CPR quality. Conversely, no well-defined cut-off levels exists to predict a poor prognosis. Our results support the inclusion of pH and lactate into our decision-making when considering patients for ECPR, whereas specific cutoffs still need conformation in other cohorts. Importantly, a stringent use of pH > 6.8 and lactate < 15 mmol/L as selection criteria, may result in denying life-saving therapy to a considerable number of the survivors present in this cohort.

In contrast to previously published results(14, 23), known prognostic factors such as witnessed arrest, bystander CPR and end-tidal CO₂ were not significantly correlated with survival in our patient population. The lack of statistical significance may be explained by the highly selected population in the present study. The high frequency of patients with witnessed arrest receiving bystander CPR and the low frequency of the number of patients with a low initial end-tidal CO₂ in our study hampers evaluation of the prognostic value of these factors. Although no association was found in our study, these factors remain of paramount importance.

Pre-hospital parameters are of great assistance the selection of appropriate candidates for ECPR. Initial shockable rhythm, transient ROSC and signs of life during CPR are considered favourable prognostic factors in ECPR(24–26). In a prospective registry study, Bougouin et al. compared conventional CPR with ECPR in 13,191 consecutive patients with OHCA(27). Prognostic factors in the ECPR group comprised an initial shockable rhythm and transient ROSC prior to ECPR implementation. One of the main findings in our study was that patients with signs of life during CPR had a threefold higher survival rate than patients without signs of life during CPR. This is in correlation with a study recently published by Debaty et al.(28) The authors found, that any signs of life before or during CPR substantially improved 30-day survival with favourable neurological outcome in a multivariable prognostic model (OR 7.35, 95% CI 2.71–19.97). Moreover, the absence of signs of life more likely precluded survival with a good neurological outcome in patients with non-shockable rhythm. This observation supports the evidence of incorporating signs of life as an important factor in the selection of patients for ECPR. The present findings do not allow us to determine whether any of the patients would have survived without ECPR. However, the long total low-flow times observed makes this unlikely.

In the present cohort, a pre-hospital low-flow time < 60 minutes was associated with an increased survival rate; however, patients exceeding pre-hospital low-flow times > 80 minutes also had an advantageous outcome. Patients with long pre-hospital low-flow times had a higher rate of signs of life during CPR than

patients with a pre-hospital low-flow time of 60–80 minutes, indicating the highly selected nature of this population. Our results suggest that prolonged resuscitation efforts in the field may not be futile, especially in patients showing favourable circumstances and where ECPR can be established within a reasonable timeframe.

Historically, the arrest-to-perfusion time has been linked to survival(14, 16, 29, 30). Wengenmayer et al. reported that among 133 patients with cardiac arrest treated with ECPR, low-flow time was an independent predictor of mortality(30). Bartos et al. demonstrated a significant association between time from arrest to sufficient ECPR flow and neurological outcome in a cohort of 160 patients(16). These results are similar to ours. In the present study, hospitals serving patients in remote and rural areas had longer arrest-to-perfusion time due to longer distances to the invasive centre. Implementation of systematic pre-hospital ECPR calls, more rapid allocation of helicopter-mediated transport and direct triage to the catheterization laboratory may improve the performance and facilitate a reduction in system delay for these patients.

In the present study, we assessed pre-hospital and in-hospital factors in relation to outcome, which may come in benefit for clinicians in the selection of appropriate candidates for ECPR. Our results suggest that a more refined assessment of the inclusion criteria, comprising additional criteria such as signs of life during CPR and lactate levels, may improve selection of patients for ECPR. Nevertheless, one must recognize that limiting patient selection to strict pre-defined criteria may exclude some patients in whom ECPR would have bought valuable time until the reversible cause could be treated. The fact that the national consensus was violated in 52% of patients, of whom some survived to hospital discharge with a good neurological outcome in 94% of the cases, indicates that there is likely room for individualized decision-making, especially in the young patients. Patient selection for ECPR continues to be a challenging part of real-world clinical practice and further randomized clinical trials are warranted.

Limitations

The present study has several limitations. Its retrospective nature makes it subject to patient selection bias. The national consensus was available and adopted to some extent in all centres. This produces risk of bias in the evaluation of the associations with outcome. Although we conducted a multicentre study using nationwide registry data, the heterogeneity of the study population with a mixed cohort of patients with OHCA hampers generalization of the results. Neurological outcome at hospital discharge is a fairly crude measure; it is, however, broadly used in cardiac arrest studies. Studies assessing long-term survival and neurological outcome are necessary.

Conclusion

Patients receiving ECPR for refractory OHCA presented promising survival rates with a favourable neurological outcome at hospital discharge. Even though a more stringent patient selection with additional criteria may produce higher survival rates, this would also limit the number of candidates and possibly exclude half of the survivors from treatment, why individualized decision making is also of the essence in the future.

Abbreviations

CPC

Cerebral performance category

CPR

Cardiopulmonary resuscitation

ECMO

Extracorporeal membrane oxygenation

ECPR

Extracorporeal cardiopulmonary resuscitation

ICU

Intensive care unit

MCS

Mechanical circulatory support

OHCA

Out-of-hospital cardiac arrest

PEA

Pulseless electrical activity

ROSC

Return of spontaneous circulation

TTM

Targeted temperature management

Declarations

Ethical approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Danish Data Protection Agency (Ref. 1-16-02-383-18) and the Danish Patient Safety Authority (Ref. 3-3013-2696/1). In Denmark, informed consent or ethical approval is not required for registry-based research.

Consent for publication

Not applicable.

Availability of data and materials

The data underlying this article were provided by the administrative Regions of Denmark under license from the Danish Data Protection Agency and the Danish Patient Safety Authority and cannot be shared publicly due to Danish regulations for data protection. Data are however available from the authors upon reasonable request and with permission from the five administrative Regions of Denmark.

Competing interests

Dr. Stengaard reports speaker's fees from Rosche Diagnostics, outside the submitted work. Dr. Møller reports personal fees and grants from Orion Pharma, Novartis, Astra Zeneca, Abbott and Abiomed and served at scientific advisory board for Boehringer Ingelheim, outside the submitted work. Dr. Freeman reports grants from St. Jude and Astra Zeneca and personal fees from Meril Lifesciences and Edwards Lifesciences, outside the submitted work. Dr. Hassager reports grants from the Lundbeck Foundation and speaker's honoraria from Abiomed, outside the submitted work. Dr.Kjaergaard reports non-financial participation in the advisory board for the CoCa Trial. Dr. Terkelsen is supported by an unrestricted research grant from the Danish Heart Foundation. The remaining authors have no conflicts of interest to declare.

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Authors' contributions

SRM, CS, SC and CJT conceived and designed the study. SRM, LL, JBA, EG collected data. SRM performed statistical analysis, interpreted the data and drafted the manuscript. CS, SC and CJT supervised the study. All authors critically revised and approved the final version of the manuscript.

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Not applicable.

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Figures

INDICATIONS	CONTRAINDICATIONS
<ul style="list-style-type: none"> • Cardiac aetiology • Normothermia • Age < 65 years • Witnessed arrest • Bystander CPR • Initial shockable rhythm (in carefully considered cases PEA) 	<ul style="list-style-type: none"> • Asystole as initial presenting rhythm • No-flow > 10 minutes • End-tidal CO₂ < 1.3 kPa • Moderate to severe comorbidity
<p>REGIONAL VARIANCES</p> <ul style="list-style-type: none"> • Prehospital low-flow time < 100 minutes • pH > 6.8 • Lactate < 15 mmol/L • Signs of life during CPR 	

CONSENSUS A
(National consensus)

CONSENSUS B
(Extended version)

Figure 1

National consensus and extended consensus with regional variances for selection of patients with refractory OHCA and possible candidates for ECPR. CPR Cardiopulmonary resuscitation; PEA Pulseless electrical activity

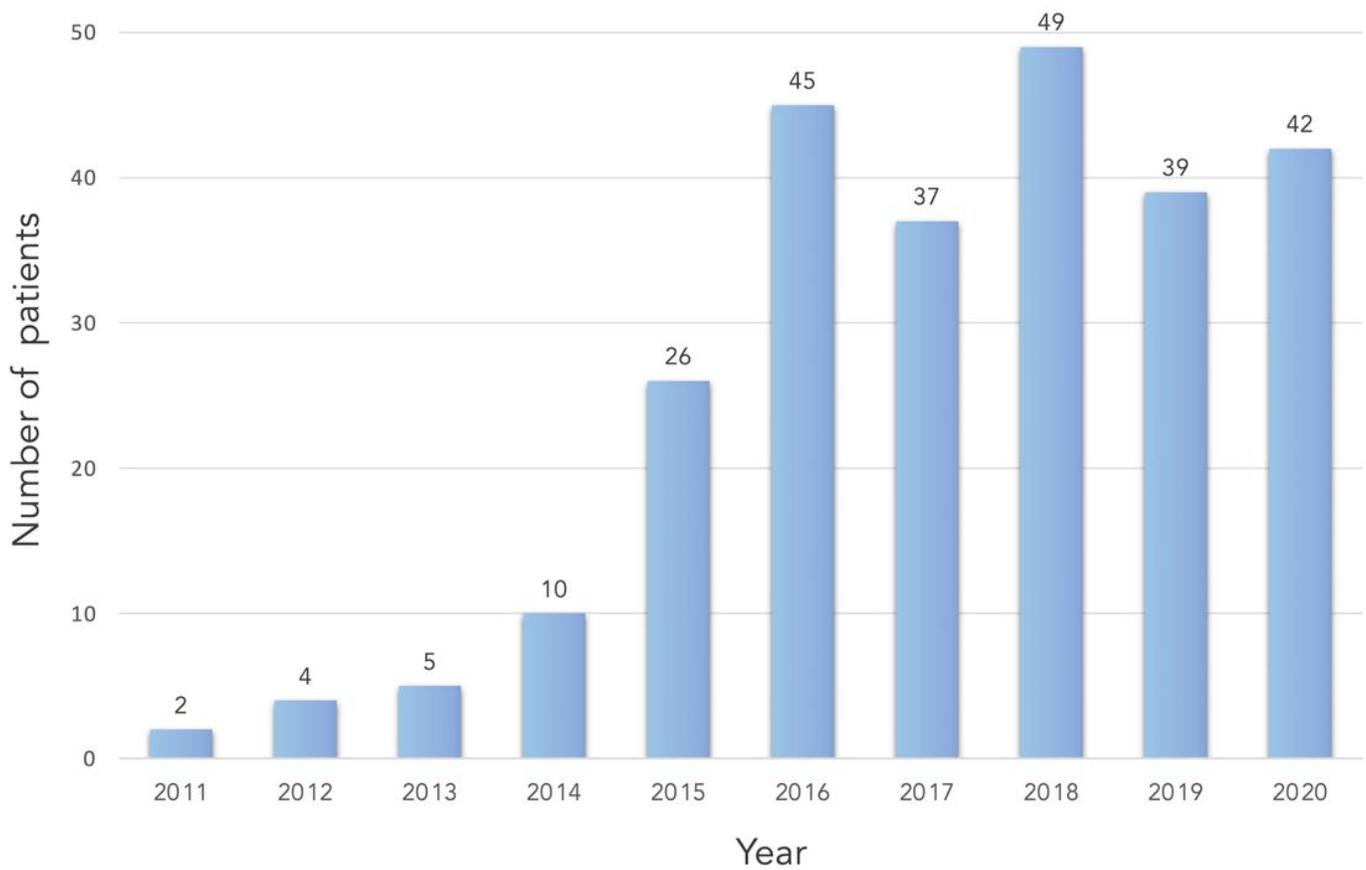


Figure 2

National trend in the use of mechanical circulatory support for OHCA in Denmark. Legend: The temporal use of mechanical circulatory support in four cardiac centres in Denmark from July 2011 to December 2020.

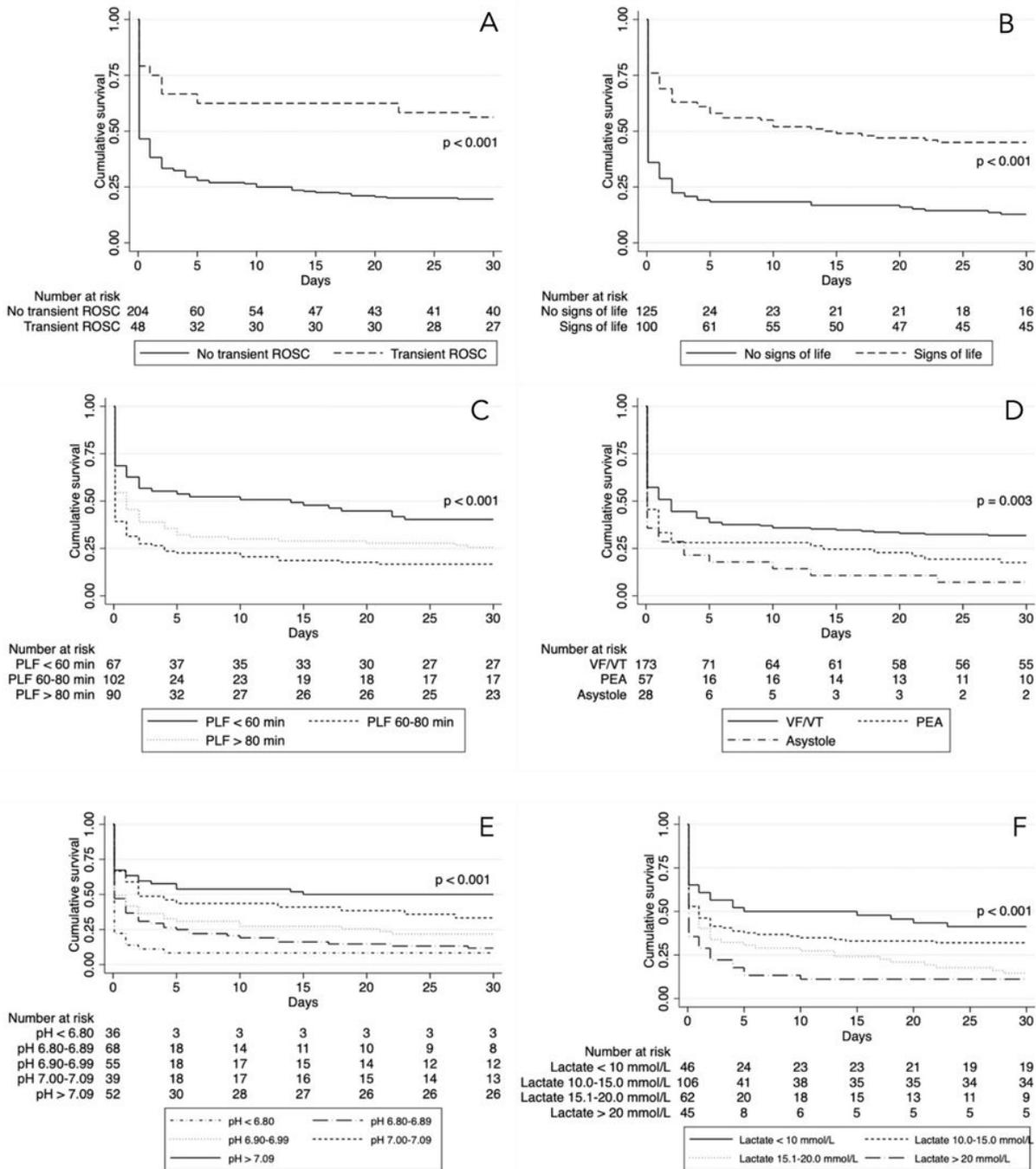


Figure 3

Kaplan-Meier survival curves of patients who had out-of-hospital cardiac arrest and received mechanical circulatory support. Legend: (A) Patients with transient return of spontaneous circulation (ROSC) versus patients with no ROSC prior to mechanical circulatory support. (B) Patients with signs of life during CPR versus no signs of life during CPR prior to mechanical circulatory support. (C) Patients stratified by pre-hospital low-flow time (PLF). (D) Patients stratified by initial presenting rhythm. (E) Patients stratified by

initial pH levels prior to mechanical circulatory support. (D) Patients stratified by initial lactate levels prior to mechanical circulatory support.

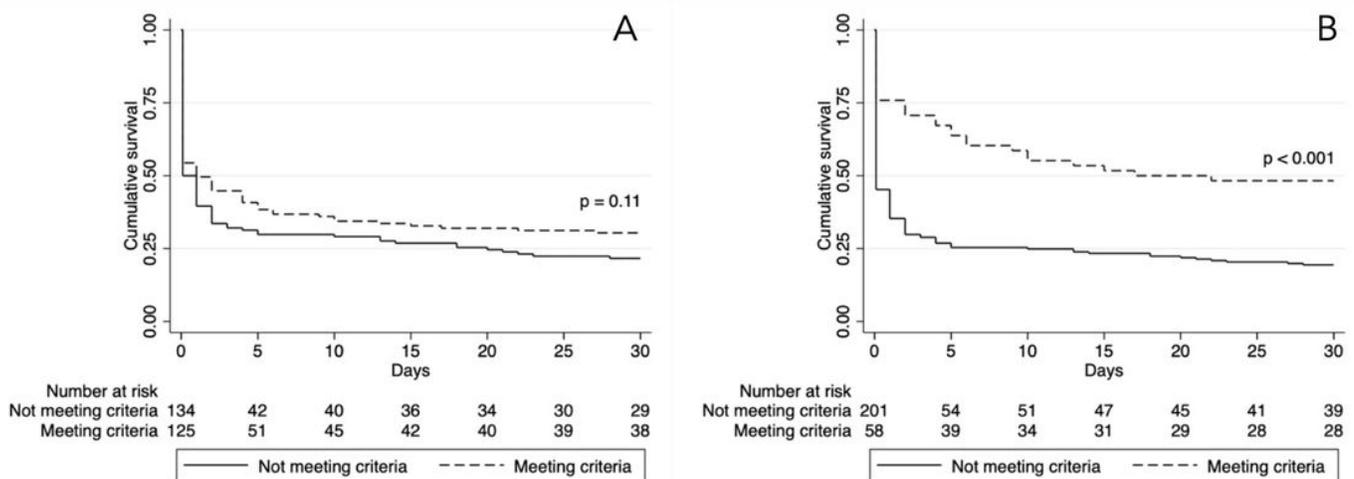


Figure 4

Kaplan-Meier survival curve for patients meeting the selection criteria and patients failing to meet the criteria. (A) Consensus A (National consensus): Survival analysis between patients meeting the Danish national consensus selection criteria in regards to younger age < 65 years, witnessed arrest, bystander CPR, initial shockable rhythm, no-flow < 10 minutes and end-tidal CO₂ < 1.3 kPa, and patients failing to meet one or more criteria. (B) Consensus B (Extended version): Survival analysis based on a more refined assessment of selection criteria. Patients meeting all the selection criteria in the Danish national consensus and additionally one or more of following parameters: signs of life during CPR, pH > 6.8, lactate < 15 mmol/L and a pre-hospital low-flow < 100 minutes.

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