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Clinical paper

Extracorporeal cardiopulmonary resuscitation for refractory out-of-hospital cardiac arrest: 10-year experience in a metropolitan cardiac arrest centre in Milan, Italy

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Abstract

Introduction: Growing evidence supports extracorporeal cardiopulmonary resuscitation (ECPR) for refractory out-of-hospital cardiac arrest (OHCA) patients, especially in experienced centres. We present characteristics, treatments, and outcomes of patients treated with ECPR in a high-volume cardiac arrest centre in the metropolitan area of Milan, Italy and determine prognostic factors.

Methods: Refractory OHCA patients treated with ECPR between 2013 and 2022 at IRCCS San Raffaele Scientific Institute in Milan had survival and neurological outcome assessed at hospital discharge.

Results: Out of 307 consecutive OHCA patients treated with ECPR (95% witnessed, 66% shockable, low-flow 70 [IQR 58–81] minutes), 17% survived and 9.4% had favourable neurological outcome. Survival and favourable neurological outcome increased to 51% (OR = 8.7; 95% CI, 4.3–18) and 28% (OR = 6.3; 95% CI, 2.8–14) when initial rhythm was shockable and low-flow (time between CPR initiation and ROSC or ECMO flow) ≤60 minutes and decreased to 9.5% and 6.3% when low-flow exceeded 60 minutes (72% of patients). At multivariable analysis, shockable rhythm (aOR for survival = 2.39; 95% CI, 1.04–5.48), shorter low-flow (aOR = 0.95; 95% CI, 0.94–0.97), intermittent ROSC (aOR = 2.5; 95% CI, 1.2–5.6), and signs of life (aOR = 3.7; 95% CI, 1.5–8.7) were associated with better outcomes. Survival reached 10% after treating 104 patients (p for trend <0.001).

Conclusions: Patients with initial shockable rhythm, intermittent ROSC, signs of life, and low-flow ≤60 minutes had higher success of ECPR for refractory OHCA. Favourable outcomes were possible beyond 60 minutes of low-flow, especially with concomitant favourable prognostic factors. Outcomes improved as the case-volume increased, supporting treatment in high-volume cardiac arrest centres.

Keywords: Out-of-hospital cardiac arrest, Extracorporeal cardiopulmonary resuscitation, Extracorporeal membrane oxygenation, Cardiac arrest center

Introduction

Out-of-hospital cardiac arrest (OHCA) is a major health problem worldwide.[1–3] In Italy, emergency medical services (EMS)-attended OHCA occurs with an estimated incidence of 86 per 100,000 population per year[4]. In the metropolitan area of Milan, Italy, a region of five million people with a population density of 2500 people/km^2, 14 individuals suffers an OHCA each day.[5,6] Early basic life support (BLS) followed by advanced life support (ALS) are integral steps in the chain of survival. However, when conventional cardiopulmonary resuscitation (CPR) manoeuvres fail to achieve return of spontaneous circulation (ROSC) chances of survival rapidly decline.[7,8] Extracorporeal CPR (ECPR), the use of veno-arterial extracorporeal

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membrane oxygenation (ECMO) during ongoing CPR, is a procedure with growing evidence of improved outcomes when used in refractory OHCA.[9–11]

In the Milan metropolitan area, in 2013 a new pre-hospital treatment protocol formally introduced mechanical CPR and a network of ECMO-capable hospitals for treating OHCA patients with ECPR. The results of the first 30 months of this novel protocol suggested increased odds of favourable neurological outcome with the use of a mechanical CPR device, especially in patients needing prolonged resuscitation manoeuvres, and a survival rate of 9.3% in patients with refractory OHCA treated with ECPR.[5] Over the past 10 years, the pre-hospital emergency system was optimized, the equipment of ALS vehicles with mechanical CPR devices was completed, and the protocol was improved, becoming standard of care for OHCA patients.

Evidence suggests that a relationship exists between centre experience with ECPR and outcomes.[12] Our centre, part of the ECPR network in the Milan metropolitan area, had the highest ECPR case-volume with 30 patients each year. The primary aim of this study was to provide a comprehensive description of the characteristics, treatments, and the resulting outcomes of patients with all-rhythms refractory OHCA who were transported and treated with ECPR in our centre between 2013 and 2022. This study also explored predictors of survival and favourable neurological outcomes, with the intention of identifying specific subgroups who may benefit most from ECPR.

Methods

Study design

This observational study was performed at a 1,350-bed university hospital and referral centre for cardiogenic shock and refractory cardiac arrest in Milan, Italy. San Raffaele Hospital is equipped 24/7 with an extracorporeal life support team treating each year on average 100 patients with cardiogenic shock, refractory cardiac arrest or acute severe respiratory failure. The study followed the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) checklist for reporting of observational studies[13] and was approved by the hospital ethics committee (protocol code “TP INN” and following amendments).

Patient population

Using our institutional OHCA registry, we included all refractory OHCA patients aged 18 years or over who were treated with ECPR at San Raffaele Hospital in Milan, Italy between January 2013 and November 2022. Patients suffering a cardiac arrest after arrival in the emergency department and OHCA patients transferred from another hospital were not included.

EMS characteristics, ECPR protocol, and in-hospital care

Patients with OHCA were managed in the pre-hospital setting by a two-tiered EMS system. The EMS dispatcher instructed the caller to perform chest compressions. A basic life support (BLS) ambulance usually arrived on scene first and provided BLS with manual CPR, bag-valve-mask ventilation, and an automated external defibrillator (AED). The advanced life support (ALS) unit equipped with a physician trained in anaesthesia and intensive care medicine or emergency medicine, an emergency nurse, and an emergency medical technician provided ALS including advanced airway management (endotracheal intubation or supraglottic airways), intravenous or intraosseous access placement, mechanical CPR, and drugs as necessary.

The metropolitan area of Milan, Italy is equipped since 2013 with a network of six ECMO-capable hospitals for ECPR and our centre had the highest case-volume during the study period (Supplemental Methods**)**. Every time the EMS dispatch centre received an emergency call for an OHCA potentially eligible for ECPR (e.g., age $\leq$70 years, witnessed, bystander CPR in progress), our cardiac arrest centre was alerted for availability for first if in the catchment area or as an alternative in case of unavailability of another centre. After ALS vehicle arrival, a confirmatory contact with our centre was made to confirm patient eligibility. Patients were considered in refractory cardiac arrest after 15 minutes of conventional CPR and were transported with ongoing CPR to our ECPR centre if the following criteria were met: 1) age 12–70 years, 2) witnessed cardiac arrest, 3) no-flow time <12 minutes (no-flow time >12 minutes only if the initial rhythm is shockable), 4) estimated time between OHCA and hospital arrival <60 minutes, 5) mechanical CPR during transport, and 6) end-tidal CO_2 after 20 minutes of CPR >10 mm Hg. Per protocol absolute contraindications were terminal diseases, aortic dissection, severe peripheral arterial disease, severe heart disease without indication for heart transplant or VAD placement, and severe aortic insufficiency. Patients accepted for ECPR were transported by EMS directly to the cardiothoracic ICU. The final decision to initiate ECPR was dependent on the senior ICU physician.

At hospital arrival, the ECMO team (typically comprising two cardiothoracic intensivists, a cardiologist, two ICU nurses, and a perfusionist) immediately initiated VA-ECMO cannulation under transoesophageal echocardiography (TOE) guidance and during ongoing mechanical CPR. After excluding major contraindications, venous (usually 29 Fr) and arterial (usually 15–17 Fr) cannulas were placed percutaneously in the common femoral artery and vein. Anterograde reperfusion cannula was performed with a 5–6 Fr reperfusion cannula. Post-resuscitation care was provided following current guidelines. In brief, temperature was controlled between 33 °C and 36 °C for 24 hours and coronary angiography and percutaneous coronary intervention were provided if indicated.

Primary and secondary outcomes

The primary outcome was the rate of survival at hospital discharge. The secondary outcomes were the rate of survival until ICU discharge, 30-day survival, length of stay in the hospital and in the intensive care unit (ICU), and the neurological outcome at hospital discharge. We defined survival with a favourable neurologic outcome as a score of 3 or less on the modified Rankin scale (which ranges from 0 [no symptoms] to 6 [death]).[14] Patients who died before hospital discharge are indicated by a score of 6. Neurological outcome was determined retrospectively by accessing the full hospital record independently by two investigators.

Data collection

We collected baseline characteristics, pre-hospital and in-hospital care, time intervals from cardiac arrest to ECMO flow, cause of death and complications. Utstein recommendations were followed.[15] No-flow was defined as the time between OHCA and CPR initiation by bystanders or professionals, while low-flow time as the time between CPR initiation and ROSC or ECMO flow. Sustained ROSC was defined as 20 minutes with signs of circulation without the need for CPR.[16] On the contrary, intermittent ROSC was defined as a non-

sustained ROSC (recurrent pulselessness or ventricular fibrillation or pulseless ventricular tachycardia) before ECMO. Signs of life were defined as gasping or regaining of normal breathing, pupillary light reaction, increased level of consciousness before or any movements before or during CPR.

Statistical analysis

Descriptive statistics were used to summarize data on characteristics and outcomes. Categorical data were reported as absolute values and percentages, while continuous variables were presented as median and interquartile range (IQR). Variables were compared by the chi-squared test or the Mann-Whitney test as appropriated. Multivariable logistic regression analyses were performed for survival and favourable neurological outcome at hospital discharge to calculate adjusted odds ratios (ORs) and their 95% confidence intervals (95% CI), adjusting for the following pre-ECMO clinically relevant covariates: age, sex, witnessed cardiac arrest, bystander CPR, initial rhythm, no-flow time, low-flow time, intermittent ROSC, and signs of life. Low-flow was plotted against the predicted probability of survival and favourable neurological outcome obtained from the univariate logistic regression model. Then, the optimal cut-off values of low-flow were determined by a receiver operating characteristic (ROC) curve analysis. A p-value of < 0.05 was considered statistically significant. Statistical analysis was performed with Stata Version 16 (College Station, TX: StataCorp LLC.).

Results

Characteristics of patients

From January 2013 through November 2022, 319 patients with refractory OHCA were transported in our centre. Of these, 12 were excluded from the analysis (6 received ECMO but age <18 years and 6 did not received ECMO as due to absolute contraindications) (Supplemental Fig. 1). In the final analysis, we included 307 consecutive adults with refractory OHCA treated with ECPR, corresponding to a median of 30 (IQR 25–33) patients per year (Supplemental Fig. 2).

Patients were predominantly male (83%) with a median age of 55 (IQR 46–62) years. Most OHCAs were witnessed (95%), bystanders initiated CPR in 66% of cases, and the median no-flow was 2.0 (IQR 2.0–5.0) minutes. Only 10% had a no-flow > 10 minutes. Initial rhythm was shockable in 66% of patients. A mechanical CPR device was used in 84% of cases. Median time from OHCA to ECMO flow was 75 (IQR 62–86) minutes. The complete characteristics of patients are presented in Tables 1–2 and in Supplemental Tables 1-2 according to neurological outcome.

Primary and secondary outcomes

Survival rate at ICU discharge and at hospital discharge were 18% and 17%, respectively (Table 2). Kaplan–Meier curve for 30-day survival according to initial rhythm is shown in Supplemental Fig. 3. Favourable neurological outcome at hospital discharge was observed in 9.4%, corresponding to 57% of patients discharged alive from the hospital **(**Table 2**)**. Severe neurologic impairment occurred in 7.2% of patients. The distribution of patients' scores on the modified Rankin scale is shown in Fig. 1**A**.

At multivariable analysis (Table 3), initial shockable rhythm, low-flow time, intermittent ROSC, and presence of signs of life were significantly associated with both survival and favourable neurological outcome at hospital discharge.

Cumulative rate of patients discharged alive and with a favourable neurological outcome increased over the 10-year period from 2013 and 2022 (p for trend <0.001). Cumulative survival rate reached 10% after treating 104 patients over 3.7 years (Fig. 1**B**).

Clinical course, in-hospital interventions, and complications

Veno-arterial ECMO flow was established after a median of 15 (IQR 10–22) minutes from hospital arrival. Most patients were cannulated with a percutaneous technique (98%) in the cardiothoracic ICU (97%) while the remaining patients in the emergency department (1.9%) or in the catheterization laboratory (1.3%). In addition to ECMO, 65% received IABP, 10% Impella, and 18% Cytosorb. Temperature control was initiated in 83% of patients. Patients underwent coronary angiography and revascularisation in 23% and 17% of cases, respectively. Renal replacement therapy was provided to 8.8% of patients. The most frequently identified cause of cardiac arrest was coronary artery disease (36%) (Table 2).

Overall, patients were supported with ECMO in the ICU for 2 days. Patients discharged alive from hospital had a higher duration of ECMO support (4.0 [IQR 3.0–5.0] days vs 1.0 [IQR 1.0–3.0] days; $p < 0.001$), mechanical ventilation (8.0 [IQR 3.0–12] days vs 1.0 [IQR 1.0–3.0] days, $p < 0.001$), ICU stay (13 [IQR 10–22] days vs 1.0 [IQR 1.0–3.0] days; $p < 0.001$), and hospital stay (30 [IQR 17–49] days vs 1.0 [IQR 1.0–3.0] days; $p < 0.001$) compared to non-survivors (Table 2).

Bleeding was the most common complication (53%) followed by acute kidney injury (39%) and ischemic limb (17%). Gastrointestinal bleeding and access site bleeding occurred in 20% and 13% of patients, respectively. Survivors had fewer complications compared to non-survivors (Table 2).

The two most common causes of death were brain death (28%) and multi-organ failure (17%). In 11% of patients, withdrawal of life-sustaining therapy occurred. Organ donation occurred in 22% of patients.

Outcomes according to initial rhythm and low-flow time

Patients with an initial shockable rhythm had higher rate of survival (20% vs 11%; OR = 2.1 [95% CI, 1.02–4.24]; $p = 0.045$) and favourable neurological outcome (12% vs 3.9%; OR = 3.51 [95% CI, 1.2–10]; $p = 0.023$) at hospital discharge compared to patients with an initial non-shockable rhythm. Patients with an initial shockable rhythm had more frequently coronary artery disease as the cause of OHCA (43% vs 20%; $p < 0.001$). There were no differences in term of complications, cause of death, and withdrawal of life-sustaining therapy. A detailed comparison between patients with an initial shockable and non-shockable initial rhythm is provided in Supplemental Tables 3–4.

The median low-flow was 70 (IQR 58–81) minutes, and each minute of increase in low-flow was associated with a 5% lower probability of survival (adjusted OR = 0.95 [95% CI, 0.94–0.97]; $p < 0.001$) and a 5% lower probability favourable neurological outcome (adjusted OR = 0.95 [95% CI, 0.94–0.97]; $p < 0.001$) at hospital discharge (Fig. 2). Low-flow had good predictive ability for survival (area under ROC curve = 0.75, 95% CI, 0.69–0.83, Hosmer–Lemeshow goodness of fit test $\chi^2_{(df\ =\ 8)} = 8.69$, $p = 0.37$) and favourable neurological outcome (area under ROC curve = 0.70, 95% CI, 0.60–0.80, Hosmer–Lemeshow goodness of fit test $\chi^2_{(df\ =\ 8)} = 8.29$, $p = 0.41$). Using the ROC curve (Supplemental Fig. 3), the most dis-

Table 1 – Characteristics of patients with out-of-hospital cardiac arrest treated with extracorporeal cardiopulmonary resuscitation according to survival at hospital discharge.

Characteristic	All patients (*n* = 307)	Survivors (*n* = 51)	Non-survivors (*n* = 256)	*p*-value
Age (years), median (IQR)	55 (46–62)	58 (50–65)	54 (46–62)	0.107
Sex (male), *n* (%)	254 (83%)	45 (88%)	209 (82%)	0.255
Body mass index (kg/m^2), median (IQR)	27 (25–29)	26 (24–28)	27 (25–29)	0.023
Medical history, *n* (%)				
Hypertension	84 (27%)	18 (35%)	66 (26%)	0.164
Smoking	67 (22%)	21 (41%)	46 (18%)	<0.001
Diabetes	34 (11%)	6 (12%)	28 (11%)	0.864
Chronic heart failure	31 (10%)	4 (7.8%)	27 (11%)	0.558
Obesity	30 (9.8%)	5 (9.8%)	25 (9.8%)	0.993
Alcoholism	20 (6.5%)	2 (3.9%)	18 (7.0%)	0.411
Dyslipidemia	23 (7.5%)	10 (20%)	13 (5.1%)	<0.001
Ischemic heart disease	30 (9.8%)	8 (16%)	22 (8.6%)	0.119
Stroke	9 (2.9%)	2 (3.9%)	7 (2.7%)	0.646
COPD	7 (2.3%)	2 (3.9%)	5 (2.0%)	0.390
Implanted ICD	4 (1.3%)	0 (0.0%)	4 (1.6%)	0.369
Cancer	4 (1.3%)	1 (2.0%)	3 (1.2%)	0.650
Chronic kidney disease	2 (0.7%)	0 (0.0%)	2 (0.8%)	0.527
Location of cardiac arrest, *n* (%)				
Home	147 (48%)	23 (45%)	124 (48%)	0.663
Street	57 (19%)	14 (28%)	43 (17%)	0.074
Public building	54 (18%)	9 (18%)	45 (18%)	0.991
Workplace	26 (8.5%)	4 (7.8%)	22 (8.6%)	0.860
Sport	12 (3.9%)	0 (0.0%)	12 (4.7%)	0.115
Public transport	5 (1.6%)	0 (0.0%)	5 (2.0%)	0.314
Ambulance	2 (0.7%)	1 (2.0%)	1 (0.4%)	0.203
Other	4 (1.3%)	0 (0.0%)	4 (1.6%)	0.369
Etiology, *n* (%)				
Medical	300 (98%)	51 (100%)	249 (97%)	0.232
Drowning	4 (1.3%)	0 (0.0%)	4 (1.6%)	0.369
Traumatic	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Drug overdose	1 (0.3%)	0 (0.0%)	1 (0.4%)	0.655
Asphyxial	1 (0.3%)	0 (0.0%)	1 (0.4%)	0.655
Electrocution	1 (0.3%)	0 (0.0%)	1 (0.4%)	0.655
Pre-arrest chest pain, *n* (%)	103 (34%)	19 (37%)	84 (33%)	0.540
Witnessed, *n* (%)	293 (95%)	48 (94%)	245 (96%)	0.620
Bystander CPR, *n* (%)	201 (66%)	33 (65%)	168 (66%)	0.900
Minutes from cardiac arrest to CPR (no-flow), median (IQR)	2.0 (2.0–5.0)	2.0 (2.0–5.0)	2.0 (2.0–5.0)	0.654
Patients with no-flow > 10 minutes, *n* (%)	32 (10%)	4 (7.8%)	28 (11%)	0.509
Bystander AED use, *n* (%)	15 (4.9%)	2 (3.9%)	13 (5.1%)	0.726
Minutes from cardiac arrest to EMS arrival, median (IQR)	10 (7.0–14)	10 (6.0–12)	10 (7.0–14)	0.347
Initial shockable rhythm, *n* (%)	203 (66%)	40 (78%)	163 (64%)	0.042
Endotracheal tube, *n* (%)	282 (92%)	47 (92%)	235 (92%)	0.932
Mechanical CPR, *n* (%)	256 (83%)	44 (86%)	212 (83%)	0.776
Minutes from cardiac arrest to hospital arrival, median (IRQ)	60 (52–71)	51 (44–62)	61 (55–72)	<0.001
Any ROSC before hospital arrival, *n* (%)	65 (21%)	25 (49%)	40 (16%)	<0.001
Intermittent	54 (18%)	18 (35%)	36 (14%)	<0.001
Sustained	18 (5.9%)	11 (22%)	7 (2.7%)	<0.001
Presence of signs of life, *n* (%)	37 (12%)	13 (26%)	24 (9.4%)	0.001
Initial pH, median (IQR)	6.9 (6.8–7.1)	7.1 (6.9–7.3)	6.9 (6.8–7.1)	<0.001
Initial lactate, mmol/L (IQR)	15 (12–19)	11 (7.5–15)	16 (13–19)	<0.001
Minutes from hospital arrival to ECMO flow, median (IQR)	15 (10–22)	15 (10–22)	15 (10–22)	0.818
Minutes from start of CPR to ECMO flow (low-flow), median (IQR)	70 (58–81)	57 (45–68)	73 (61–83)	<0.001
Patients with low-flow >60 minutes, *n* (%)	222 (72%)	21 (41%)	201 (79%)	<0.001
Minutes from cardiac arrest to ECMO flow, median (IQR)	75 (62–86)	60 (49–70)	77 (66–88)	<0.001

Abbreviations: IQR, interquartile range; CPR, cardiopulmonary resuscitation; AED = automated external defibrillator; ROSC, return of spontaneous circulation; EMS, emergency medical services; ALS, advanced life support; ECMO, extracorporeal membrane oxygenation.

Percentages may not total 100 because of rounding.

criminating duration of low-flow for predicting survivors from non-survivors and patients with favourable from unfavourable neurological outcome was respectively 62 minutes (sensitivity: 0.69, specificity: 0.75, area under ROC curve: 0.72) and 64 minutes (sensitivity: 0.69, specificity: 0.67, area under ROC curve: 0.68). Patients with low-flow duration $\leq$ 60 minutes had higher rate of survival (35% vs

Table 2 – Clinical course, in-hospital interventions, and outcomes according to survival at hospital discharge.

Outcome	All patients (*n* = 307)	Survivors (*n* = 51)	Non-survivors (*n* = 256)	*p*-value
Coronary angiography, *n* (%)	71 (23%)	29 (57%)	42 (16%)	<0.001
PCI or CABG, *n* (%)	53 (17%)	25 (49%)	28 (11%)	<0.001
IABP, *n* (%)	200 (65%)	44 (86%)	156 (61%)	0.001
Impella, *n* (%)	32 (10%)	15 (29%)	17 (6.6%)	<0.001
Cytosorb, *n* (%)	54 (18%)	11 (22%)	43 (17%)	0.654
Renal replacement therapy, *n* (%)	27 (8.8%)	5 (9.8%)	22 (8.6%)	0.781
Temperature control, n (%)	256 (83%)	51 (100%)	205 (80%)	<0.001
Duration of ECMO support (days), median (IQR)	2.0 (1.0–4.0)	4.0 (3.0–5.0)	1.0 (1.0–3.0)	<0.001
Length of ICU stay (days), median (IQR)	2.0 (1.0–5.0)	8.0 (3.0–12)	1.0 (1.0–3.0)	<0.001
Length of mechanical ventilation (days), median (IQR)	2.0 (1.0–4.0)	13 (10–22)	1.0 (1.0–3.0)	<0.001
Survival at ICU discharge, *n* (%)	54 (18%)	-	3 (1.2%)	-
Survival at hospital discharge, *n* (%)	51 (17%)	-	-	-
Favourable neurological outcome at hospital discharge, *n* (%)	29 (9.4%)	29 (57%)	-	-
Length of hospital stay (days), median (IQR)	2.0 (1.0–6.0)	30 (17–49)	1.0 (1.0–3.0)	<0.001
Cause of cardiac arrest[a], *n* (%)				<0.001
Coronary artery disease	109 (36%)	40 (78%)	69 (27%)	
Aortic dissection	17 (5.5%)	0 (0.0%)	17 (6.6%)	
Chronic heart failure	5 (1.6%)	0 (0.0%)	5 (2.0%)	
Cardiomyopathy	4 (1.3%)	3 (5.9%)	1 (0.4%)	
Myocarditis	2 (0.7%)	2 (3.9%)	0 (0.0%)	
Drowning	4 (1.3%)	1 (2.0%)	3 (1.2%)	
Pulmonary embolism	1 (0.3%)	1 (2.0%)	0 (0.0%)	
Atrioventricular block	1 (0.3%)	0 (0.0%)	1 (0.4%)	
Papillary muscle rupture	1 (0.3%)	0 (0.0%)	1 (0.4%)	
Respiratory failure	3 (1.0%)	0 (0.0%)	3 (1.2%)	
Asthma	4 (1.3%)	0 (0.0%)	4 (1.6%)	
Stroke	2 (0.7%)	0 (0.0%)	2 (0.8%)	
Electrocution	1 (0.3%)	0 (0.0%)	1 (0.4%)	
Undetermined	153 (50%)	4 (7.8%)	149 (58%)	
Complications, *n* (%)				
Any bleeding	163 (53%)	17 (33%)	146 (57%)	0.002
Access site bleeding	39 (13%)	7 (14%)	32 (13%)	0.810
Gastrointestinal bleeding	60 (20%)	6 (12%)	54 (21%)	0.125
Acute kidney injury	121 (39%)	12 (24%)	109 (43%)	0.011
Ischemic limb	52 (17%)	9 (18%)	43 (17%)	0.882
Cause of death, *n* (%)				
Brain death	87 (28%)	-	87 (34%)	-
Hypoxic-ischemic brain injury	11 (3.6%)	-	11 (4.3%)	-
Multi-organ failure	52 (17%)	-	52 (20%)	-
Insufficient ECMO flow	43 (14%)	-	43 (17%)	-
Cardiogenic shock	34 (11%)	-	34 (13%)	-
Refractory cardiac arrest	22 (7.2%)	-	22 (8.6%)	-
Bleeding	7 (2.3%)	-	7 (2.7%)	-
Withdrawal of life-sustaining therapy, *n* (%)	34 (11%)	-	34 (13%)	-
Organ donation, *n* (%)	68 (22%)	-	68 (27%)	-

Abbreviations: IQR, interquartile range; ROSC, return of spontaneous circulation; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.
Percentages may not total 100 because of rounding.
[a] autopsy findings are included.

9.5%; OR = 5.2 [95% CI, 2.8–9.8]; $p < 0.001$) and favourable neurological outcome (18% vs 6.3%; OR = 3.2 [95% CI, 1.5–6.9]; $p = 0.003$) at hospital discharge compared to patients with low-flow exceeding 60 minutes. However, 72% of patients had a low-flow time higher than 60 minutes: 9.5% survived and 6.3% had a favourable neurological outcome at discharge. Characteristics of patients with low-flow time higher than 60 minutes are detailed in Supplemental Tables 5–6. The longest low-flow time to achieve at least one survivor with favourable neurological outcome was 98 minutes.

When narrowing the analysis to patients who experienced witnessed cardiac arrest, were aged 70 years or younger, and had a no-flow duration of 10 minutes or less and a low-flow duration of 60 minutes or less (77 patients, 25% of the total), the rate of survival and favourable neurological outcome at hospital discharge increased to 36% (OR = 5.1 [95% CI, 2.7–9.7]; $p < 0.001$) and 18% (OR = 3.2 [95% CI, 1.5–7.0]; $p = 0.004$), respectively, from 17% and 9.5% when including patients with low-flow duration up to 120 minutes. When further narrowing the analysis to patients with an initial shockable rhythm, survival and favourable neurological outcome at hospital discharge reached 51% (OR = 8.7 [95% CI, 4.3–18]; $p < 0.001$) and 29% (OR = 6.3 [95% CI, 2.8–14]; $p < 0.001$), respectively (Fig. 3). Unadjusted associations between criteria and outcomes at hospital discharge are shown in Supplemental Table 7.

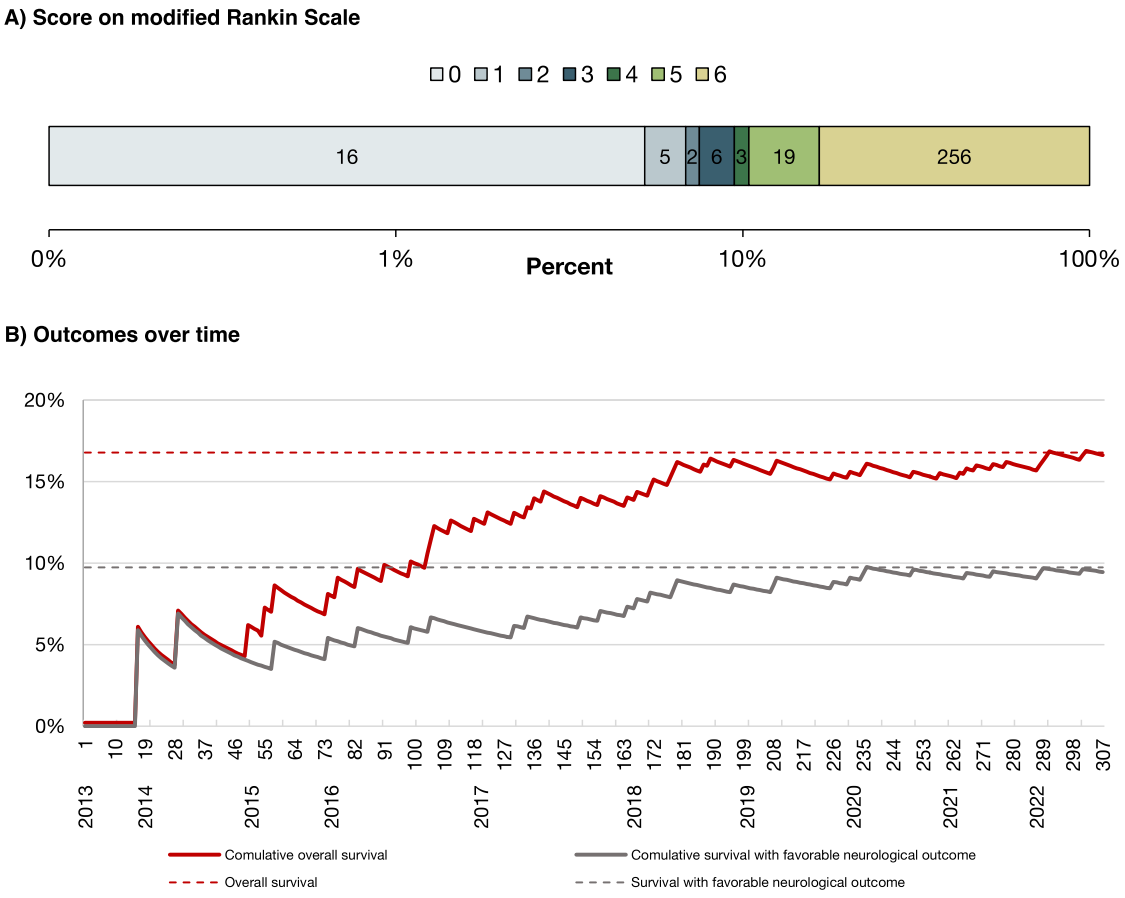

Fig. 1 – Distribution of patients' scores on the modified Rankin scale on a log 10 scale of the percentages of patients (A) and cumulative rate of out-of-hospital cardiac arrest patients treated with extracorporeal cardiopulmonary resuscitation discharged alive and with a favourable neurological outcome (B).

Discussion

Key findings

Over a period of 10 years, 17% of 307 consecutive patients treated with ECPR in a metropolitan, high-volume cardiac arrest centre in Milan, Italy with liberal inclusion criteria was discharged alive from the hospital, more than half of them with a favourable neurological outcome. Outcomes improved as the number of treated patients increased and survival reached 10% after approximately the first 100 patients and four years of experience. An initial shockable rhythm, lower low-flow time, presence of signs of life, and intermittent ROSC were associated with better outcomes. In witnessed OHCA patients $\leq$70 years, with a no-flow time $\leq$10 minutes, a low-flow time $\leq$60 minutes, and an initial shockable rhythm, survival and favourable neurological outcome was achieved in 51% and 29% of patients, respectively. However, 48% of patients discharged alive with a favourable neurological outcome had a low-flow $\geq$60 minutes and the longest low-flow time to achieve at least one survivor with favourable neurological outcome was 98 minutes, challenging how long resuscitation should be extended in OHCA patients.

Relationship to previous studies

In the last decade, several single-centre studies highlighted the potential of ECPR to improve outcomes in refractory OHCA. However, survival rates were highly variable, from 8% to 40%.[17–21] In our cohort, survival was achieved in 17% of patients and 9.4% were discharged with favourable neurological outcome. Variability in patient's selection criteria together with heterogeneity in the strength of the chain of survival, implementation of ECPR, centre experience, and post-resuscitation practice, including withdrawal of life-support therapy[22], can explain differences in outcomes observed among studies and centres. Survival and favourable neurological outcome were 43% in the ARREST trial and 33% and 32%, respectively, in the Prague OHCA study.[9,10] However, most patients had a low-flow $\leq$60 minutes and the ARREST trial excluded patients with non-shockable rhythms. When applying restrictive criteria to our patients, survival and favourable neurological outcome at hospital discharge reached 36% and 18%, respectively, in patients with low-flow $\leq$60 minutes, and 51% and 29% when excluding non-shockable rhythms. Such outcomes are comparable to those reported in the two landmark randomized trials.[9,10]

A shockable rhythm was the initial presentation of 78% of survivors and 86% of patients with a favourable neurological outcome

Table 3 – Unadjusted and adjusted associations with survival and favourable neurological outcome at hospital discharge.

Variables	Survival				Favourable neurological outcome (mRS score ≤3)			
	Univariate analysis		Multivariable analysis[a]		Univariate analysis		Multivariable analysis[a]	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	1.02 (0.99–1.05)	0.143	1.02 (0.99–1.05)	0.327	1.00 (0.97–1.03)	0.994	0.99 (0.96–1.03)	0.655
Male sex	1.69 (0.68–4.20)	0.260	1.48 (0.54–4.06)	0.450	1.90 (0.55–6.53)	0.308	1.72 (0.45–6.61)	0.428
Witnessed cardiac arrest	0.72 (0.19–2.67)	0.622	0.33 (0.06–1.80)	0.201	1.37 (0.17–11)	0.764	0.76 (0.08–7.73)	0.325
Bystander CPR	0.96 (0.51–1.80)	0.900	0.91 (0.42–2.01)	0.821	0.72 (0.33–1.58)	0.416	0.61 (0.23–1.64)	0.325
Initial shockable rhythm	2.07 (1.02–4.24)	**0.045**	2.39 (1.04–5.48)	**0.040**	3.51 (1.19–10)	**0.023**	5.07 (1.45–18)	**0.011**
No-flow time	0.97 (0.90–1.03)	0.296	0.95 (0.86–1.04)	0.244	0.96 (0.88–1.05)	0.406	0.93 (0.82–1.05)	0.223
Low-flow time	0.96 (0.94–0.97)	**<0.001**	0.95 (0.94–0.97)	**<0.001**	0.97 (0.95–0.98)	**<0.001**	0.96 (0.94–0.99)	**0.001**
Intermittent ROSC	3.33 (1.70–6.54)	**<0.001**	2.53 (1.16–5.55)	**0.020**	4.70 (2.10–11)	**<0.001**	3.19 (1.29–7.92)	**0.012**
Signs of life	3.31 (1.55–7.05)	**0.002**	3.66 (1.54–8.69)	**0.003**	4.02 (1.67–9.67)	**0.002**	4.10 (1.51–11)	**0.006**

[a] Logistic regression model adjusting for age, sex, witnessed cardiac arrest, bystander CPR, initial shockable rhythm, no-flow time, low-flow time, intermittent ROSC, and signs of life. Odds ratios (OR) greater than 1 indicates that survival or favourable neurological outcome is more likely to occur.

in our cohort, probably due to a high prevalence of reversible causes, such as acute coronary syndrome.[23]

Low-flow time is another crucial factor[21,24] and guidelines suggest 60 minutes as the ideal therapeutic window for ECPR.[25] We confirmed 64 minutes to be the optimal cut-off for discriminating patients with favourable from unfavourable outcome. However, observational studies frequently report high median low-flow times.[24] In our experience, low-flow was 70 (IQR 58–81) minutes and exceeded 60 minutes in 72% of patients, highlighting the shared challenges of establishing ECMO within this timeframe. Impressively, despite low-flow >60 minutes, 9.5% survived and 6.3% had a favourable neurological outcome.

Implications of study findings

While our findings confirm predictors of good outcome,[26] they also point out that favourable outcomes are possible beyond 60 minutes in carefully selected patients. Of course, reducing pre-hospital delays could allow to further improve outcomes since time from hospital arrival to ECMO flow was already minimized in our centre (15 [IQR 10–22] minutes) and time from cardiac arrest to hospital arrival constituted the longest time interval (60 [IQR 52–71] minutes). Signs of life, when present during CPR, are associated with survival and neurological outcome[27–29] and may exclude an already established brain damage, thus indicating an optimal ECPR candidate. Among our patients, signs of life and intermittent ROSC were the strongest predictors of survival and favourable outcome. In the overall population, 12% of patients had signs of life, a factor significantly associated with survival (aOR = 3.7; 95% CI, 1.5–8.7) and favourable outcome (aOR = 4.1; 95% CI, 1.5–11). Similarly, in a French ECPR cohort, signs of life were associated with favourable neurological outcome (OR = 7.35, 95% CI, 2.71–20).[27] When assessing eligibility for ECPR, it could be advisable to evaluate multiple patient's criteria as one single accurate predictor of poor outcome does not currently exist.

Finally, ECPR is complex and its implementation in other settings might fail to reproduce our results. As a strong relationship exists between ECPR case volume and outcomes,[12] close cooperation between EMS and a high-volume ECMO-capable cardiac arrest centre[30] is important for a powerful ECPR program and better outcomes. In our study, outcomes improved as the number of treated patients increased and survival reached 10% after 104 patients over 3.7 years.

Strengths and limitations of the study

Strengths include the detailed collection and reporting of baseline characteristics, time intervals, clinical course, complications, cause of death, and outcomes in one of the largest cohort of patients treated with ECPR in Europe in a single centre with liberal criteria. We also presented results of multiple subgroup and statistical analyses answering relevant clinical questions. Limitations of the study include the retrospective and single-centre design, the absence of a control group of patients that did not receive ECPR, follow-up of patients censored at hospital discharge, the retrospective determination of neurological outcome, and no investigation of quality of life in survivors.

Future studies and prospects

Future studies should confirm in broader populations and different settings the accuracy and relevance of our findings, especially on patients' selection. Certain upper boundaries for ECPR remains to be determined: patients with extremely long low-flow time may

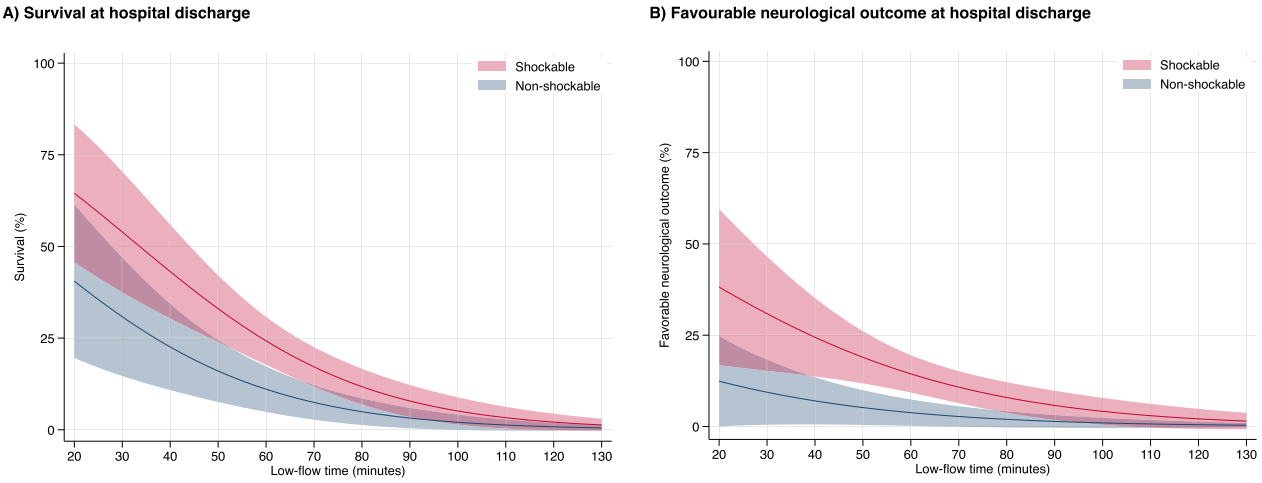

Fig. 2 – Probabilities and 95% confidence intervals of survival at hospital discharge (A) and favourable neurological outcome at hospital discharge (B) at increasing duration of low-flow time according to initial rhythm.

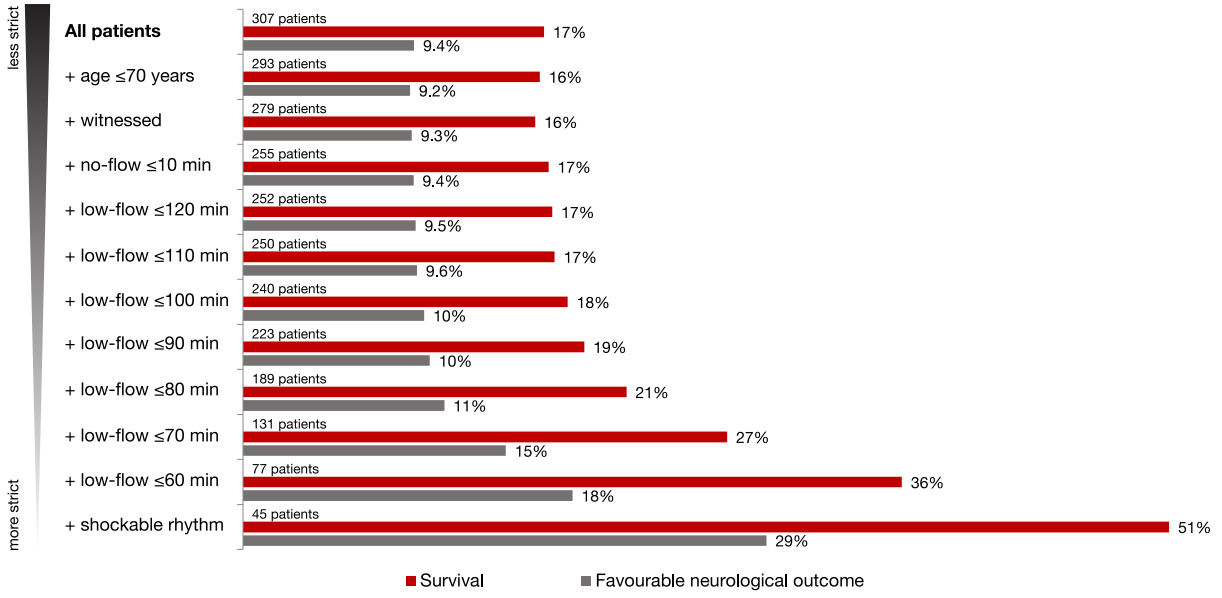

Fig. 3 – Rate of survival and favourable neurological outcome at hospital discharge in different subgroup of patients based on the progressive addition of more restrictive criteria.

have a chance to survive in presence of other strong positive prognostic factors. However, sudden reperfusion after a prolonged OHCA could cause severe additional injury and therapeutic approaches to limit detrimental effects of ischemia–reperfusion injury could further improve ECPR efficacy.[31,32]

Conclusions

In a large metropolitan, high-volume cardiac arrest centre, ECPR was feasible and successfully treated patients with all-rhythms refractory OHCA. Over a period of 10 years, 17% of 307 patients survived to hospital discharge, 57% of them with a favourable neurological outcome. Patients with an initial shockable rhythm, shorter low-flow, signs of life and intermittent ROSC had better outcomes. In patients with a low-flow $\leq$60 minutes and an initial shockable rhythm, survival and favourable neurological outcome was achieved in 51% and 29% of patients and in 9.5% and 6.3% when low-flow exceeded 60 minutes. Outcomes improved as the number of treated patients increased, contributing to the supportive evidence for treating OHCA patients in high-volume and high-expertise cardiac arrest centres.

Declaration of competing interest

TS is the Social Media Editor of Resuscitation Plus. All other authors declare they have no financial interests/personal relationships which may be considered as potential competing interests.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resplu.2023.100521.

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