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1 **Title Page**

2 **Prognostic value of signs of life throughout cardiopulmonary resuscitation for**
3 **refractory out-of-hospital cardiac arrest.**

4 **Short Title**

5 **Signs of life: prognostic value for refractory cardiac arrest**

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40 **ABSTRACT**

41 **Purpose:** Prognostication of refractory out-of-hospital cardiac arrest (OHCA) is
42 essential for selecting the population that may benefit from extracorporeal
43 cardiopulmonary resuscitation (ECPR).

44 We aimed to examine the prognostic value of signs of life before or throughout
45 conventional CPR for individuals undergoing ECPR for refractory OHCA.

46 **Methods:** Pooling the original data from three cohort studies, we estimated the
47 prevalence of signs of life, for individuals with refractory OHCA resuscitated with
48 ECPR. We performed multivariable logistic regression to examine the independent
49 associations between the occurrence of signs of life and 30-day survival with a CPC
50 score ≤ 2 .

51 **Results:** The analytical sample consisted of 434 ECPR recipients. The prevalence of
52 any sign of life was 61%, including pupillary light reaction (48%), gasping (32%), or
53 increased level of consciousness (13%). Thirty-day survival with favorable
54 neurological outcome was 15% (63/434). In multivariable analysis, the adjusted odds
55 ratios of 30-day survival with favorable neurological outcome were 7.35 (95%
56 confidence interval [CI], 2.71–19.97), 5.86 (95% CI, 2.28–15.06), 4.79 (95% CI,
57 2.16–10.63), and 1.75 (95% CI, 0.95–3.21) for any sign of life, pupillary light
58 reaction, increased level of consciousness, and gasping, respectively.

59 **Conclusion:** The assessment of signs of life before or throughout CPR substantially
60 improves the accuracy of a multivariable prognostic model in predicting 30-day
61 survival with favorable neurological outcome. The lack of any sign of life might
62 obviate the provision of ECPR for patients without shockable cardiac rhythm.

63

64 Keywords: cardiac arrest; heart arrest; extracorporeal cardiopulmonary resuscitation;

65 Extracorporeal membrane oxygenation; Advanced cardiac life support;

66 cardiopulmonary resuscitation.

67 **TEXT**

68 INTRODUCTION

69 Despite considerable advances in cardiopulmonary resuscitation (CPR) during the
70 past decade, survival with functional recovery to hospital discharge has remained
71 disappointingly low for OHCA, ranging from 5% to 10% [1, 2]. When appropriate
72 CPR is provided for more than 20–30 min without return of spontaneous circulation,
73 the cardiac arrest is considered refractory, with the survival rate being as low as 1%
74 [3, 4].

75 Providing venous arterial extracorporeal membrane oxygenation assistance in
76 addition to CPR for refractory OHCA improves hemodynamic and oxygenation until
77 treatment of the underlying cause for cardiac arrest and cardiac recovery [5, 6]. The
78 use of extracorporeal CPR (ECPR) for refractory OHCA has been rapidly adopted at
79 many centers [7-11].

80 Current guidelines recommend considering ECPR in select cardiac arrest
81 patients, in settings where it can be rapidly implemented [12]. However, formal
82 criteria defining the OHCA population that may benefit from ECPR remains to be
83 determined [5, 13]. Prognostic factors for successful ECPR include shockable initial
84 cardiac rhythm, bystander CPR attempt, shorter low-flow duration, and higher pH and
85 lower lactate values on hospital admission [14].

86 Other baseline clinical features might help identify refractory OHCA
87 individuals that are potential candidates for ECPR, including gasping, pupillary light
88 reaction, and increased level of consciousness. Gasping during conventional CPR for
89 OHCA occurs frequently and is associated with increased long-term survival and
90 functional recovery [15, 16]. Earlier studies have already reported on the prognostic
91 significance of pupillary light reaction during CPR [17, 18]. Although infrequently

92 reported in the literature [19, 20], most healthcare professionals have had experience
93 of CPR-induced consciousness encompassing spontaneous eye opening, increased jaw
94 tone, speech, and body movement [21], which might be associated with improved
95 survival to hospital discharge [22]. Yet, evidence on the prognostic significance of
96 these clinical features is anecdotal or limited to a few case reports [23].

97 This study aimed to examine the prognostic value of gasping, pupillary light
98 reaction, and increased level of consciousness before or throughout conventional CPR
99 for individuals undergoing ECPR for refractory OHCA.

100

101 METHODS

102 *Study design*

103 We analyzed de-identified individual participant data from three primary cohort
104 studies of refractory OHCA individuals treated with ECPR. The rationale, data
105 collection methods, verification procedures, and primary outcomes have been
106 reported in detail elsewhere [14, 24, 25]. Briefly, the database for the three
107 observational studies consisted of consecutive, prospectively enrolled refractory
108 OHCA patients. The studies were conducted in France in the 2010s (Appendix 1).
109 The participating centers were reference centers for the management of refractory
110 OHCA. All diagnostic testing, procedures, and medication ordering were performed
111 at the discretion of attending physicians.

112 This analysis was carried out on data from primary studies for which Institutional
113 Review Board approval had been obtained by the investigators.

114 *Subject selection*

115 Individuals were recruited prospectively 24 h a day, 7 days a week by emergency
116 physicians involved in the initial management of OHCA. Adult patients (≥ 18 years of
117 age) were eligible if they had had refractory OHCA treated with ECPR. The present
118 analysis focused on cardiac and noncardiac OHCA. Exclusion criteria were ECPR for
119 cardiac arrest caused by trauma or severe hypothermia ($< 32^{\circ}\text{C}$), cardiogenic shock
120 after return of spontaneous circulation, and pregnancy.

121 The decision to initiate ECPR was multidisciplinary based on recommended
122 selection criteria and ECPR availability. At each study site, compliance with French
123 guidelines for ECPR for refractory OHCA was advocated [26]. OHCA was
124 considered refractory if return of spontaneous circulation was not achieved after 20–
125 30 min of conventional CPR. The selection criteria for ECPR included age under 55
126 years (although patients aged 55 years or more were eligible if they had no significant
127 comorbidity), OHCA witnessed, bystander basic life support provided, initial
128 shockable rhythm with predicted low flow < 100 min, initial nonshockable rhythm
129 with predicted low flow < 40 min, end tidal $\text{CO}_2 > 10$ mmHg at 15 min of CPR [26].

130

131 *Resuscitation procedures*

132 Basic and advanced life support (ALS) were provided according to international
133 guidelines [27]. A mobile intensive care unit staffed with an emergency physician and
134 a nurse was dispatched to provide ALS in addition to the first rescuer response.

135 Individuals with refractory cardiac arrest were transported to the hospital with
136 the use of an automated CPR device or manual CPR if an automated CPR device was
137 unavailable. Patients were directly admitted to the catheter laboratory or the
138 emergency room according to the suspected etiology. A percutaneous coronary
139 angiography was performed for OHCA with suspected cardiac etiology. Then the

140 patient was transferred to a specialized intensive care unit as long as he/she was under
141 ECPR.

142 In Paris, ECPR could be implemented in the prehospital setting in order to
143 reduce low flow time [25]. For this purpose, a mobile dedicated team staffed with a
144 trained emergency physician or an intensivist, an anesthetist nurse, and a paramedic
145 could be dispatched on site.

146

147 *Data Collection*

148 As part of primary cohort studies, attending physicians routinely abstracted
149 prospective information according to the Utstein guidelines [28], including location of
150 cardiac arrest, bystander CPR, no-flow duration (defined as time from collapse to first
151 CPR), low-flow duration (defined as time from conventional to ECPR), initial
152 recorded cardiac rhythm, cardiac arrest etiology, delivery of defibrillation shock, and
153 drug administration.

154 Information on 30-day mortality, cerebral performance category (CPC) status,
155 and length of hospital stay was obtained from receiving units.

156 Using a retrospective structured chart review, clinical research assistants
157 collected detailed information on patient comorbid conditions, early signs of life, first
158 recorded arterial pH and lactate levels on hospital admission, and procedures within
159 24h of admission.

160

161 *Signs of life before or throughout CPR*

162 We defined any sign of life as a composite of gasping, pupillary light reaction, or
163 increased level of consciousness before or throughout conventional CPR. Consistent
164 with previous studies [15, 29], the incidence of gasping was determined based on the

165 documentation by prehospital care providers of any abnormal breathing pattern before
166 or throughout the performance of CPR [16, 30].

167 Pupillary light reaction was defined as the presence or recovery of any pupillary
168 response assessed visually by pen light examination by a physician, other than
169 bilateral nonreactive dilated pupils [18, 31]. Consistent with previous studies [15, 22],
170 increased level of consciousness was defined as the documentation by prehospital
171 care providers of spontaneous eye opening, increased jaw tone, swallowing, speech,
172 or other body movement.

173

174 *Outcome measures*

175 The primary endpoint was 30-day survival with favorable neurological outcome,
176 defined as Cerebral Performance Category (CPC) score of 1 or 2.

177

178 *Statistical analysis*

179 Baseline characteristics were reported as numbers and percentages for categorical
180 variables and means and standard deviations, or median and interquartile range (i.e.,
181 25–75th percentiles) where appropriate, for continuous variables. The univariable
182 associations between the primary endpoint and baseline characteristics were assessed
183 using unadjusted odds ratio (OR) point estimates along with 95% confidence interval
184 (CI). Using multivariable logistic regression, we assessed the independent
185 associations between the primary endpoint and the occurrence of any sign of life, after
186 adjusting for baseline characteristics. The covariates entered into the multivariable
187 model included age, gender, study site, presence of one or more comorbid conditions,
188 bystander CPR attempt, no flow duration, low flow duration, shockable initial cardiac
189 rhythm, and first recorded arterial pH and end tidal CO₂ on admission.

190 To assess the robustness of our findings, we repeated the multivariable
191 analysis while substituting arterial pH with lactate levels on hospital admission and
192 after further adjusting for coronary angiography. We checked for consistency in
193 adjusted OR estimates across primary components of any sign of life by performing
194 separate multivariable logistic regression analysis for gasping, pupillary light reaction,
195 and increased level of consciousness.

196 To quantify the prognostic value of any sign of life, we examined whether the
197 addition of this variable improved the accuracy of a multivariable logistic regression
198 model in predicting short-term survival with favorable neurological outcome, using
199 the concordance (*c*) statistic [32]. The *c*-statistic is identical to the area under the
200 receiver operating characteristic curve and can be interpreted as the chance that a
201 patient with the outcome of interest is assigned a higher probability of the outcome by
202 the multivariable logistic regression model than a randomly chosen patient without
203 the outcome [33]. We compared *c*-statistic for the multivariable logistic regression
204 model with and without signs of life. The significance probability was adjusted for
205 multiple comparisons using the Bonferroni method. We also computed sensitivity,
206 specificity, likelihood ratio, and predictive value estimates for signs of life in
207 predicting short-term survival with favorable neurological outcome.

208 Assuming that data were missing at random, missing values for independent
209 covariates were replaced by multiple imputations (Appendix 2). Fifty imputed data
210 sets were created with a total run length of 50,000 iterations and imputations made
211 every 1000 iterations.

212 Two-sided *P*-values of <0.05 were considered statistically significant. All
213 analyses were performed using Stata Special Edition version 14.0 (Stata Corporation,
214 College Station, TX, USA).

215

216 RESULTS

217 *Study sample*

218 Of 20,630 individuals experiencing OHCA during the study period. Of these, 434
219 were treated with ECPR following refractory OHCA. Overall, 61% of individuals
220 with documented values yielded signs of life before or throughout conventional CPR,
221 including pupillary light reaction (48%), gasping (32%), or increased level of
222 consciousness (13%) (Table 1).

223

224 *Primary endpoint*

225 The thirty-day survival rate was 16% (69/434). Sixty-three (15%) individuals
226 survived with favorable neurological outcome by 30 days of OHCA. In univariable
227 analysis, 30-day survivors with favorable neurological outcome were more likely to
228 yield any sign of life, to have initial shockable cardiac rhythm, and to receive
229 amiodarone. They also received lower epinephrine dosage, had higher median arterial
230 pH value on hospital admission, and were more likely to undergo coronary
231 angiography (Table 1). The estimated proportions of 30-day survival with favorable
232 neurological outcome were 0.22 and 0.04 for patients with and without signs of life
233 (Table 2). Noticeably, 30-day survival with favorable neurological outcome was 0%
234 (95% CI, 0–7) for 53 individuals with asystole or pulseless electrical activity on initial
235 recorded cardiac rhythm and no sign of life (Fig. 1).

236

237 *Independent associations of signs of life with the primary endpoint*

238 In multivariable analysis, the occurrence of any sign of life was associated with an
239 increased adjusted odds ratio (7.35, 95% CI, 2.71–19.97) of 30-day survival with
240 favorable neurological outcome (Table 3, model 1).

241 Consistently, pupillary light reaction (adjusted OR, 5.86, 95% CI, 2.28–15.06)
242 and increased level of consciousness (adjusted OR, 4.79, 95% CI, 2.16–10.63) were
243 independently associated with higher OR of 30-day survival with favorable
244 neurological outcome (Table 3, models 3–4). Gasping was also associated with an
245 increased, although not significant, adjusted OR (1.75, 95% CI, 0.95–3.21) of primary
246 endpoint (Table 3, model 2). The adjusted OR estimates were rather unchanged while
247 substituting arterial pH with arterial lactate level on hospital admission (Appendix 3).
248 Further adjusting for coronary angiography did not modify our conclusions
249 (Appendix 4). Compared with individuals without any sign of life, the adjusted OR of
250 30-day survival with favorable neurological outcome were 5.13 (95% CI, 1.57–
251 16.77), 8.61 (95% CI, 2.95–25.14), and 12.58 (95% CI, 3.46–47.74) for individuals
252 with one, two, and three signs of life (P for trend $<.001$).

253

254 *Prognostic value of any sign of life*

255 The occurrence of any sign of life yielded 89% sensitivity and 96% negative
256 predictive value estimates for predicting survival with favorable neurological outcome
257 (Appendix 5). Accordingly, the c -statistic increased from 0.75 to 0.83 when entering
258 any sign of life as an independent covariate in the multivariable logistic regression
259 model ($P = .002$). Comparable changes in c -statistic were observed with pupillary light
260 reaction or increased level of consciousness while entering gasping as covariate did
261 not improve model accuracy in predicting survival with favorable neurological
262 outcome (Appendix 6).

263

264 DISCUSSION

265 Prognostication of refractory OHCA in the prehospital setting is essential for early
266 identification of ideal candidates for ECPR. Yet, currently available prognostic
267 criteria have unsatisfactorily resolved the issue of selecting the OHCA population that
268 may benefit from ECPR [5]. Using the original data from three primary cohort
269 studies, we documented the prognostic value of signs of life before or throughout
270 conventional CPR in predicting 30-day survival with favorable neurological outcomes
271 for refractory OHCA patients.

272 The main finding of this study was that the addition of any sign of life before or
273 throughout conventional CPR substantially improved the accuracy of a multivariable
274 prognostic model in discriminating individuals with favorable neurological outcome,
275 as reflected by the increase in the *c*-statistic value from 0.75 to 0.83. This observation
276 extends evidence from previous reports showing that the occurrence of any sign of
277 life relates to survival with favorable neurological outcome for patients with OHCA.

278 With a 48% prevalence among patients with a documented value, pupillary
279 light reaction was the most frequently reported sign of life in the present study. This
280 estimate lies within the wide range of published percentages of intact light reflexes
281 (14–83%) before or throughout CPR [17, 18]. Despite a strong independent
282 association with 30-day survival and functional recovery (adjusted odds ratio, 5.86;
283 95% CI, 2.28–15.06), pupillary light reaction alone yielded limited accuracy for the
284 prognostication of refractory OHCA in this study. Although pupillary light reaction
285 during CPR indicates potential cerebral recovery, it was reported in 44% of non-
286 survivors to ECPR. In contrast, pupillary areflexia, which reflects severe depression
287 of midbrain function, was observed in 17% of patients successfully resuscitated with

288 ECPR. These findings might relate to the inaccuracy of visual assessment by
289 conventional pen light application [31]. However, previous studies based on objective
290 measurement of the pupillary light reaction with a portable infrared light pupillometer
291 reported similar results [17].

292 Although previously reported in less than 1% of OHCA cases [22], an
293 increased level of consciousness during CPR was found in 13% of individuals
294 included in our study. Increased level of consciousness was an independent predictor
295 of survival with favorable neurological outcome in the present multivariable analysis,
296 corroborating the findings from previous research. The mechanism behind an
297 increased level of consciousness during CPR remains speculative, although this
298 phenomenon may relate to a high mean arterial pressure (over 50 mmHg), which
299 conveys sustained high levels of cerebral blood flow and oxygenation [19]. Hence
300 consciousness is considered a surrogate for high-quality CPR.

301 Surprisingly, gasping was not independently associated with favorable
302 neurological outcome in our multivariable analysis. This observation is inconsistent
303 with previous research highlighting the association of gasping with increased long-
304 term survival and functional recovery of OHCA [15, 16]. Yet previous evidence on
305 the prognostic value of gasping for refractory OHCA patients undergoing ECPR was
306 limited [23, 34].

307 The three different signs of life analyzed in this study reflect different levels of
308 brain activity, grading from the brain stem for the gasping reflex, the brain stem
309 associated with cortical pathway for the pupillary reflex [35] and cortical pathways
310 for increased level of consciousness, their presence may persist differently over time
311 with the anoxic brain injury. It may also explain the difference on the odds of
312 favorable outcome.

313 Overall, this study demonstrated a significant trend towards higher rates of
314 favorable outcomes for increasing numbers of signs of life throughout CPR. This
315 observation suggests that signs of life provide indirect evidence of cerebral perfusion
316 for refractory OHCA, with multiple manifestations reflecting higher levels of cerebral
317 reperfusion. Indeed, CPR-induced signs of life might be indicative of high levels of
318 regional cerebral oxygen saturation [22], which in turn is associated with
319 neurologically favorable survival at hospital discharge [36].

320 Routine assessment of signs of life before or throughout conventional CPR
321 might help overcome the potential limitations of previously published prognostic
322 factors. Indeed, most of these factors are primarily of statistical value and do not
323 allow individual prognostication in the prehospital setting [31]. They include
324 bystander CPR attempt, low-flow duration, first recorded cardiac rhythm, and pH and
325 lactate values on hospital admission [14].

326 These findings have potential clinical implications. First, the presence of any
327 sign of life before or throughout conventional CPR indicates that the patient is not
328 brain dead and can benefit from ECPR. Second, the absence of any sign of life cannot
329 be used as the sole indicator to stop resuscitation for refractory OHCA since it does
330 not preclude neurological recovery. In this study, 4% of patients with no sign of life
331 survived with favorable neurological outcome at 30 days of refractory OHCA
332 resuscitated with ECPR. However, the absence of any sign of life ruled out survival
333 with favorable neurological outcome for individuals with non-shockable rhythm,
334 suggesting that resuscitation effort might be withdrawn and the provision of ECPR
335 might be futile for these patients.

336 The potential limitations of this study deserve consideration. First, it was
337 observational in design and we cannot exclude that unmeasured baseline

338 characteristics may have confounded the associations observed between the
339 occurrence of signs of life and survival with favorable neurological outcome. Second,
340 the lack of statistical significance between gasping and survival with favorable
341 neurologic outcome might be explained by misclassification due to retrospective data
342 collection. Indeed data abstractors were dependent on the completeness and accuracy
343 of the documentation for signs of life in medical charts and physician notes.

344 Third, ECPR was implemented in the prehospital setting for 60% of
345 individuals enrolled at one study site. Reassuringly, we did not find evidence of a
346 significant first-order interaction involving the occurrence of signs of life and study
347 site for the prediction of 30-day survival with favorable neurological outcome.

348 Fourth, the percentages of individuals with missing sign of life values ranged
349 from 1% for gasping to 26% for pupillary light reaction. Although we used multiple
350 imputation for handling missing data, we cannot exclude bias in recording so that
351 individuals with missing values were more likely to have negative values for sign of
352 life. Fifth, this study was carried out in three university-affiliated hospitals in France
353 with probably some variability in data collection, critical care management and
354 neurologic prognostication.

355
356

357 **CONCLUSION**

358

359 The assessment of signs of life occurring before or throughout conventional CPR
360 substantially improves the accuracy of a multivariable prognostic model in predicting
361 30-day survival with favorable neurological outcome for individuals with refractory
362 OHCA. The lack of any sign of life throughout resuscitation might obviate the
363 provision of ECPR for patients without shockable cardiac rhythm. Yet, prospective
364 evaluation is warranted to determine the effectiveness and safety of incorporating the

365 occurrence of early signs of life in clinical prognostic models intended to guide the
366 selection of candidates for ECPR.

367

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373

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380 responsibility for the decision to submit for publication.

381

382 **CONFLICT OF INTEREST**

383 The authors declare that they have no conflict of interest relevant to this study.

384

385

386

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512

513 **TABLES AND FIGURE**

514 Table 1. Univariable Comparison of Baseline Characteristics and Procedures
515 According to 30-Day Survival with Favorable Neurological Outcome for
516 Extracorporeal Cardiopulmonary Resuscitation Recipients Following Out-of-Hospital
517 Refractory Cardiac Arrest.

518

519 Table 2: Estimated Proportion of 30-Day Survival with Favorable Neurological
520 Outcome for Extracorporeal Cardiopulmonary Resuscitation Recipients Following
521 Out-of-Hospital Refractory Cardiac Arrest.

522

523 Table 3: Independent Association of Signs of Life with 30-Day Survival with
524 Favorable Neurological Outcome for Extracorporeal Cardiopulmonary Resuscitation
525 Recipients Following Out-of-Hospital Refractory Cardiac Arrest.*

526

527 Figure 1: Percentages of 30-day survivors with CPC ≤ 2 stratified by the occurrence of
528 signs of life before or throughout cardiopulmonary resuscitation and initial recorded
529 cardiac rhythm (P for interaction = 0.31).

530 The analytical sample consisted of 372 individuals after excluding 62 individuals with
531 missing values for initial recorded cardiac rhythm ($n = 10$) and any sign of life before
532 or throughout cardiopulmonary resuscitation ($n = 54$).

533 Abbreviations: CI, confidence interval; CPC, cerebral performance category, PEA,
534 pulseless electrical activity; VF, ventricular fibrillation, VT, ventricular tachycardia

535

PEA / Asystole

VF/VT

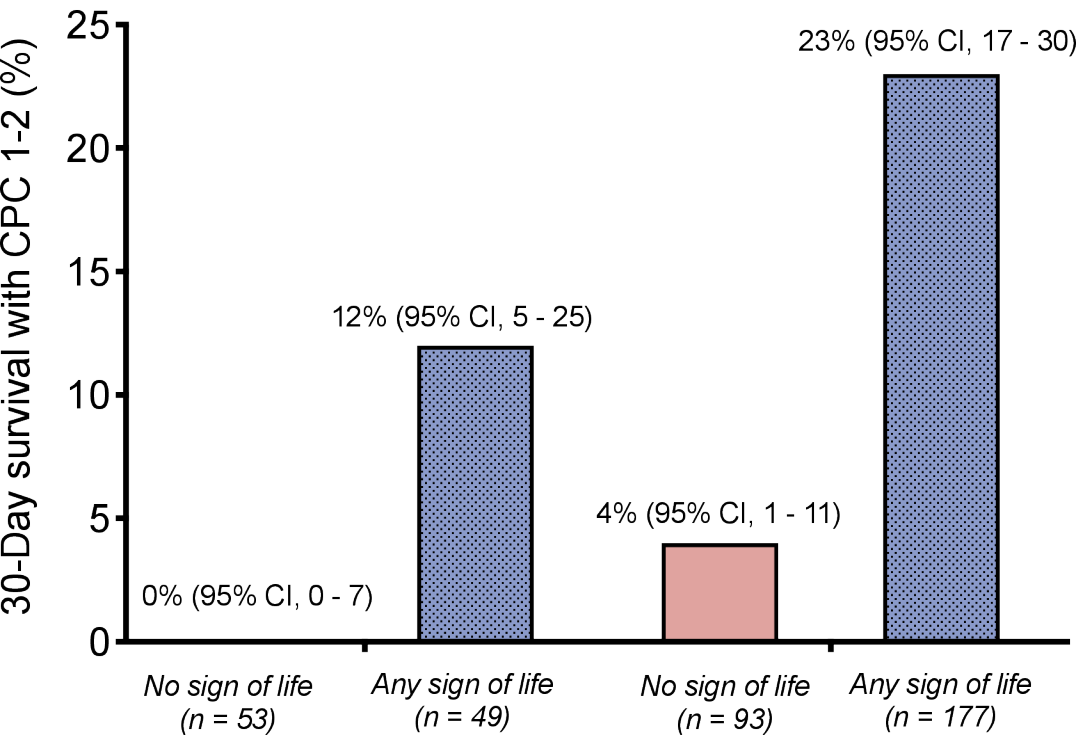


Table 1. Univariable Comparison of Baseline Characteristics and Procedures According to 30-Day Survival With Favorable Neurological Outcome for Extracorporeal Cardiopulmonary Resuscitation Recipients Following Out-of-Hospital Refractory Cardiac Arrest.

Characteristics*	All (n=434)	30-day survival with CPC ≤ 2				Unadjusted OR (95% CI)		
		No (n=371)		Yes (n=63)				
Male gender, <i>n</i> (%)	351/433	(81)	301/370	(81)	50/63	(79)	0.88	(0.45–1.71)
Age, mean (SD), <i>y</i> †	49	(13)	49	(13)	49	(13)	0.98	(0.79–1.21)
≥ 1 comorbid condition, <i>n</i> (%)	207/423	(49)	177/360	(49)	30/63	(48)	0.94	(0.55–1.61)
Cardiac disease	88/423	(21)	75/360	(21)	13/63	(21)	0.99	(0.51–1.91)
Peripheral vascular disease	36/423	(8.5)	33/360	(9.2)	3/63	(7.8)	0.50	(0.15–1.67)
Hypertension	71/425	(17)	63/362	(17)	8/63	(13)	0.69	(0.31–1.52)
Diabetes mellitus	28/425	(6.6)	27/362	(7.5)	1/63	(1.6)	0.20	(0.03–1.50)
Obesity	52/429	(12)	41/366	(11)	11/63	(17)	1.68	(0.81–3.47)
Sleep apnea syndrome	8/425	(1.9)	8/362	(2.2)	0/63	(...)	...	(...)
Chronic kidney disease	8/425	(1.9)	6/362	(1.7)	2/63	(3.2)	1.95	(0.38–9.86)
Cancer	10/425	(2.4)	9/362	(2.5)	1/63	(1.6)	0.63	(0.08–5.08)
COPD	13/425	(3.1)	8/362	(2.2)	5/63	(7.9)	3.81	(1.21–12.06)
Liver disease	1/427	(0.2)	1/364	(0.3)	0/63	(...)	...	(...)
Cardiovascular risk factor, <i>n</i> (%)								
Family history of cardiac disease	24/424	(5.7)	18/361	(5.0)	6/63	(9.5)	2.01	(0.76–5.27)
Dyslipidemia	45/425	(11)	34/362	(9.4)	11/63	(17)	2.04	(0.97–4.28)

(Continued)

Table 1. (Continued)

Characteristics*	All		30-day survival with CPC ≤ 2				Unadjusted OR (95% CI)	
	(n=434)		No (n=371)		Yes (n=63)			
Smoking	116/424	(27)	96/361	(27)	20/63	(32)	1.28	(0.72–2.29)
Cardiac etiology, <i>n</i> (%)	331/383	(86)	274/322	(85)	57/61	(93)	2.50	(0.87–7.19)
Presence of witnesses, <i>n</i> (%) [†]	163/175	(93)	142/154	(92)	21/21	(100)	...	(...)
Bystander CPR attempt, <i>n</i> (%)	303/352	(86)	250/295	(85)	53/57	(93)	2.39	(0.82–6.92)
Initial shockable cardiac rhythm, <i>n</i> (%)	300/424	(71)	249/363	(69)	51/61	(84)	2.33	(1.14–4.76)
No-flow duration, median (IQR), <i>min</i> [‡]	0	(0–5)	0	(0–5)	0	(0–3)	0.88	(0.79–0.97)
Low-flow duration, median (IQR), <i>min</i> [‡]	86	(69–105)	88	(70–106)	77	(63–97)	0.91	(0.82–0.99)
Any sign of life before or throughout CPR, <i>n</i> (%)	230/380	(61)	182/328	(55)	48/52	(92)	9.63	(3.39–27.31)
Gasping	136/431	(32)	106/369	(29)	30/62	(48)	2.33	(1.35–4.01)
Pupillary light reaction	155/323	(48)	126/288	(44)	29/35	(83)	6.21	(2.50–15.42)
Increased level of consciousness	49/376	(13)	30/326	(9.2)	19/50	(38)	6.05	(3.05–11.98)
Prehospital procedures								
Extracorporeal CPR, <i>n</i> (%)	156/429	(36)	131/366	(36)	25/63	(40)	1.18	(0.68–2.04)
Epinephrine dosage, median (IQR), <i>mg</i>	7	(5–10)	7	(5–10)	5	(3–8)	0.87	(0.80–0.94)
Amiodarone use, <i>n</i> (%)	213/382	(56)	168/323	(52)	45/59	(76)	2.97	(1.57–5.61)
Laboratory findings on hospital admission								
End tidal CO ₂ , median (IQR), <i>mmHg</i> [‡]	22	(14–30)	21	(13–30)	24	(18–32)	1.01	(0.98–1.03)

(Continued)

Table 1. (Continued)

Characteristics*	All (n=434)	30-day survival with CPC ≤ 2				Unadjusted OR (95% CI)
		No (n=371)		Yes (n=63)		
Arterial pH, median (IQR) ‡	7.10 (6.92–7.24)	7.08 (6.91–7.22)	7.18 (7.03–7.33)	1.20 (1.06–1.37)		
Arterial lactates, median (IQR), mmol/L ‡	13 (9–16)	13 (10–16)	10 (7–15)	0.90 (0.84–0.96)		
Arterial bicarbonates, median (IQR), mmol/L ‡	13 (9–17)	12 (9–17)	16 (10–19)	1.02 (0.99–1.06)		
Coronary angiography	282/413 (68)	225/351 (64)	57/62 (92)	6.38 (2.49–16.34)		

Abbreviations: CI = confidence interval; CPC = cerebral performance category, COPD = chronic obstructive pulmonary disease, CPR = cardiopulmonary resuscitation, IQR = interquartile range (i.e., 25–75th percentiles), OR = odds ratio; SD = standard deviation,

* The analytical sample consisted of 434 individuals. Values were missing for gender (n=1); comorbid conditions (n=11); cardiovascular risk factors (n=10); etiology of cardiac arrest (n=51); presence of witnesses (n=259), bystander CPR (n=82); initial recorded cardiac arrest rhythm (n=10); no-flow duration (n=11); low-flow duration (n=24); any signs of life (n=54), gasping (n=3), pupillary light reaction (n=111), and increased level of consciousness (n=58) before or throughout conventional CPR; prehospital extracorporeal CPR (n=5), epinephrine dosage (n=38), and amiodarone use (n=52); end tidal CO₂ (n=158), arterial pH (n=78), arterial lactates (n=88), and arterial bicarbonates (n=97) on hospital admission; and coronary angiography (n=21).

† The presence of witnesses was not recorded at one study site.

‡ Unadjusted odds ratios of 30-day survival with CPC ≤ 2 were expressed for 10-year increase in age, 1-minute increase in no-flow duration, 10-minute increase in low-flow duration, 1-mg increase in prehospital epinephrine dosage, 1-mmHg increase in end tidal CO₂, 0.10-point increase in arterial pH on hospital admission, 1-mmol/L increase in arterial lactates level on hospital admission, 1-mmol/L increase in bicarbonates level on hospital admission.

Table 2. Estimated Proportion of 30-Day Survival With Favorable Neurological Outcome for Extracorporeal Cardiopulmonary Resuscitation Recipients Following Out-of-Hospital Refractory Cardiac Arrest.*

Sign of life before or throughout CPR	Proportion (95% CI) of 30-day survival with CPC \leq 2	
Gasping		
No	0.11	(0.07–0.15)
Yes	0.22	(0.15–0.29)
Pupillary light reaction		
No	0.06	(0.02–0.09)
Yes	0.23	(0.17–0.29)
Increased level of consciousness		
No	0.11	(0.07–0.14)
Yes	0.40	(0.26–0.53)
Any sign of life		
No	0.04	(0.01–0.07)
Yes	0.22	(0.17–0.27)
No. signs of life		
0	0.04	(0.01–0.07)
1	0.14	(0.07–0.22)
2	0.27	(0.17–0.36)
3	0.37	(0.18–0.56)

Abbreviations: CI = confidence interval, CPC = cerebral performance category, CPR = cardiopulmonary resuscitation.

* The analytical sample consisted of 434 individuals, after multiple imputation of missing values for 341 observations with a missing value for one or more covariates (gender [n=1]; comorbid conditions [n=11]; gasping [n=3], pupillary light reaction [n=111], and increased level of consciousness [n=58] before or throughout CPR; bystander CPR attempt [n=82]; initial recorded cardiac arrest rhythm [n=10]; no-flow duration [n=11]; low-flow duration [n=24]; prehospital epinephrine dosage [n=38] and amiodarone use [n=52]; end tidal CO₂ [n=158], arterial pH [n=78], arterial lactates [n=88], and arterial bicarbonates [n=97] on hospital admission; and coronary angiography [n=21]) (See Methods).

Table 3. Independent Association of Signs of Life With 30-Day Survival With Favorable Neurological Outcome for Extracorporeal Cardiopulmonary Resuscitation Recipients Following Out-of-Hospital Refractory Cardiac Arrest.*

Characteristics	Odds ratio (95% CI) of 30-day survival with CPC ≤ 2							
	Model 1		Model 2		Model 3		Model 4	
Any sign of life before or throughout CPR	7.35	(2.71–19.97)	...	(...)	...	(...)	...	(...)
Gaspings	...	(...)	1.75	(0.95–3.21)	...	(...)	...	(...)
Pupillary light reaction	...	(...)	...	(...)	5.86	(2.28–15.06)	...	(...)
Increased level of consciousness	...	(...)	...	(...)	...	(...)	4.79	(2.16–10.63)
Male gender	0.79	(0.37–1.71)	0.79	(0.38–1.63)	0.73	(0.33–1.59)	0.91	(0.42–1.95)
Age, per 10-year increase	0.83	(0.65–1.06)	0.87	(0.69–1.11)	0.80	(0.62–1.04)	0.84	(0.65–1.07)
≥ 1 comorbid condition	1.14	(0.61–2.13)	1.06	(0.58–1.92)	1.10	(0.58–2.06)	1.13	(0.61–2.09)
Bystander CPR attempt	0.85	(0.21–3.36)	0.85	(0.22–3.25)	0.88	(0.22–3.44)	0.76	(0.20–2.92)
No-flow duration, per 1-minute increase	0.87	(0.75–1.00)	0.86	(0.75–0.99)	0.86	(0.75–1.00)	0.88	(0.77–1.01)
Low-flow duration, per 10-minute increase	0.92	(0.83–1.02)	0.91	(0.83–1.01)	0.92	(0.83–1.02)	0.90	(0.81–1.00)
Initial shockable cardiac rhythm	2.40	(1.07–5.40)	2.53	(1.15–5.55)	2.68	(1.19–6.07)	2.68	(1.23–5.86)
End tidal CO ₂ , per 1-mmHg increase	0.98	(0.95–1.02)	0.98	(0.95–1.02)	0.98	(0.94–1.01)	0.98	(0.94–1.01)
Arterial pH on admission, per 0.10-point increase	1.17	(1.00–1.36)	1.18	(1.02–1.38)	1.17	(1.00–1.37)	1.19	(1.01–1.40)

Abbreviations: CI = confidence interval; CPC = cerebral performance category; CPR = cardiopulmonary resuscitation.

* The analytical sample consisted of 434 individuals, after multiple imputation of missing values for 341 observations with a missing value for one or more covariates (gender [n=1]; comorbid conditions [n=11]; gasping [n=3], pupillary light reaction [n=111], and increased level of consciousness [n=58] before or throughout CPR; bystander CPR attempt [n=82]; initial recorded cardiac arrest rhythm [n=10]; no-flow duration [n=11]; low-flow duration [n=24]; prehospital epinephrine dosage [n=38] and amiodarone use [n=52]; arterial pH [n=78], arterial lactates [n=88], and arterial bicarbonates [n=97] on hospital admission; and coronary angiography [n=21]). (See Methods).

† Odds ratios were adjusted for study site in addition to covariates displayed in Table 3.