

# Extra Corporeal Life Support for Cardiac ARrest patients with post-cardiac arrest syndrome: the ECCAR study

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- 1 Extra Corporeal Life Support for Cardiac ARrest patients with post-cardiac arrest syndrome: the
- 2 ECCAR study
- 3
- 4 Running Head: ECLS for Post Cardiac Arrest Syndrome
- 5
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#### 1 ABSTRACT

Purpose: Post-Cardiac Arrest Shock (PCAS) occurring after resuscitated cardiac arrest (CA),
is a main cause of early death. Extra-Corporeal Life Support (ECLS) could be useful pending
recovery of myocardial failure. We aimed to describe our PCAS population, and factors
associated with ECLS initiation.

Materials and Methods: This analysis included 924 patients admitted in two intensive care
units (ICU) between 2005 and 2014 for CA and PCAS, and, of those patients, 43 patients for
whom an ECLS was initiated. Neurological and ECLS-related outcomes were gathered
retrospectively.

Results: The 43 ECLS patients were predominantly young males with evidence of myocardial 10 infarction on coronary angiography (70%). ECLS was initiated in patients suffering from 11 12 severe cardiovascular dysfunction (Left Ventricular Ejection Fraction: 15 [10 - 25] %), with a median delay of 9 [6 - 16] hours following CA. At one year, 8 patients survived (19%) without 13 neurological disability. Blood lactate and coronary etiology were associated with neurological 14 outcomes. Logistic regression conducted using 878 PCAS controls identified age, sex, 15 current smoking, location of CA, blood lactate and creatinine levels as risk factors for 16 initiation of ECLS. 17

18 Conclusions: ECLS, as a salvage therapy for PCAS, could represent an acceptable 19 alternative for highly selected patients.

20

21

#### 1 Introduction

Despite many improvements in Cardiac Arrest (CA) management, survival rate ranges from 2 11 to 17% [1,2]. Among CA patients who survived initial resuscitation, less than 30% 3 survived to hospital discharge [3-5]. Post Cardiac Arrest shock (PCAS), defined as the 4 association of a myocardial dysfunction and vasoplegia occurring after return on 5 6 spontaneous circulation (ROSC) [6], is globally responsible of one-third of deaths [5]. While persistence of myocardial dysfunction at 24h may be associated with early death [7], no 7 8 differences in neurological outcomes have been shown between post-CA patients with PCAS and those without PCAS [5,7]. 9

10 Recently, two studies have described the use of Extracorporeal Life Support (ECLS) in 11 successfully resuscitated CA patients experiencing severe PCAS [8,9]. Although survival 12 benefit was not demonstrated, ECLS-assisted patients had acceptable neurological 13 prognosis. A solid understanding of key governing factors that lead those patients to die are 14 thus requested to better select the patients the most likely to benefit for this strategy.

Our objectives were 1/ to describe a cohort of PCAS patients treated with ECLS and 2/ to identify factors that lead physicians to indicate initiation of ECLS in post-CA patients.

17

#### 18 Material and Methods

#### 19 Population and Data collection:

This retrospective observational study was conducted in two tertiary university centers in Paris. We included consecutive patients admitted to intensive care unit (ICU) for CA and PCAS (defined as the need for continuous norepinephrine or epinephrine infusion to maintain mean arterial pressure above 60 mmHg for more than 6 hours following restoration of ROSC despite adequate fluid loading [5]), and for whom an ECLS was initiated. Patients with

refractory CA and in-hospital CA (except those that occurred in the cath-lab and the
 emergency ward) were not included.

3 ECLS-treated patients' data were collected retrospectively. Prospective database
4 implemented in Cochin Hospital was used to identify control group of patients experiencing
5 PCAS without ECLS [2].

Our local ethics committees approved the data collection and study protocol (CE SRLF N°
12-384).

8 Treatment protocol

9 Patients admitted for CA were treated according to international guidelines, and similar
10 procedures have been described elsewhere [2,10]. ECLS implantation and patient's
11 management during ECLS support, including anticoagulant treatment or weaning procedure
12 followed ELSO guidelines [12] and were previously described [11].

Neurological outcome was daily assessed by ICU physicians, until death or ICU discharge. According to guidelines [13–16], neuroprognostication was performed daily using a multimodal approach, and life-sustaining therapies withdrawal decision was taken during a collegial consultation.

17 Outcomes

The primary outcome was the neurological evolution at one year, assessed by the Cerebral
Performance Category [17] (Favorable Outcome : CPC score = I - II ; Poor Outcome: CPC
score = III - V) [18] at 1 year.

21 Analysis

We performed a description of factors associated with unfavorable neurologic outcomes at one year in the population of PCAS patients treated with ECLS. A logistic regression was performed to assess the association between the selected variables and the neurological

outcome. ECLS group was compared with control group, using two-sided t test, or chi 2 test
 when necessary. Finally, we performed a univariate and multivariate analysis, using a
 stepwise logistic regression, to identify factors associated with the ECLS implantation.

Results are expressed as median (interquartiles 25-75) or number (percentage). The R
project software (The R Foundation for Statistical Computing, Vienna, Austria) was used for
statistical analysis.

7

#### 8 Results

9 From January 2005 to December 2014, 46 PCAS patients treated by ECLS were included. 10 Three patients were non-included because of in-Hospital CA. Among the 3 patients nonincluded, one was admitted for septic shock consecutive to a pulmonary infection, the CA 11 occured 8 days after the admission, and the patient deceased. One patient was a severely 12 13 burned patient with ARDS. He deceased 17 days after his admission while on ECLS for CA 14 consecutive to pulmonary embolism occurring 14 days after his admission. The last non-15 included patient was admitted for intoxication with beta-blockers, the ECLS being inserted 5 days after his admission, for extreme hemodynamic instability, he died while on ECLS. 16

Finally, 43 patients fulfilled the inclusion criteria. We also include a control population composed by 878 PCAS patients. ECLS population was predominantly young males, with a previous history of coronary events (Table 1). Sixty percent of them presented an initial shockable rhythm, with No-Flow of 2 [0-10] min and a Low-Flow of 28 [14-42] min. Hemodynamic parameters are described in table 2.

Nine patients survived (21%) at ICU discharge: myocardial recovery was observed for 7 patients (78%), one benefited from a heart transplantation, and one patient died at one year from end stage cancer. A favorable neurological outcome at one year was observed for 8 (19%) of the ECLS cohort (89% of survivors).

Death rate during the ICU stay (79%) was mainly related to multiple organ failure (MOF) (63%). Forty-five percent of death by MOF occurred in the first three days after ICU admission (Figure 1). ECLS inefficacy, defined as the inability to maintain cardiac output and arterial pressure despite maximal therapeutic investment, was observed in 11 of deceased patients (31%). Life-sustaining therapy withdrawal was initiated for 9 of them (26%), and cerebral brain death was pronounced for 2 patients (6%).

No statistical difference was found between centers except for the percentage of bystander
CPR and Low-Flow duration (Table S1).

9 ECLS-treated patients who survived without severe neurological disability were younger than 10 those with severe neurological impairment (Table 1). CPR characteristics and severity scores 11 were not different between the favorable and the poor neurological outcome group, despite 12 OHCA score showed a trend toward higher values in poor neurological group. By contrast, 13 blood lactate level at ECLS implantation discriminated the two groups (Table 2 and figure 14 S1). Coronary etiology of CA was associated with unfavorable outcome at one year, whereas 15 the arrhythmia was associated with a better prognosis (Table 1).

ECLS-treated patients were younger, with a longer time to ROSC and a higher proportion of
 non-public location of CA and bystanded CPR, as compared to control group (Table 3).
 ECLS-treated patients had higher blood lactate and creatinine levels than the control.

In multivariate analysis (Figure 2), factors independently associated with ECLS implantation were as follows: age < 62 years old, serum creatinine > 109  $\mu$ mol/l, administration of adrenaline < 2 mg, and public location of CA.

When considering the whole PCAS population, non-survivors at ICU discharge were older and experienced higher blood lactate and serum creatinine levels (Table 4). Time to ROSC were longer when comparing non-survivors to survivors. The etiology for CA in survivors was predominantly cardiac, with higher rates of coronary angioplasty. The proportion of ECLStreated patients was not different in survivors versus non-survivors.

1

#### 2 Conclusions Discussion

Emphasizing on functional neurological outcomes, this observational study offers interesting
 findings.

The present retrospective study aimed at reporting the ten-year experience of two Parisian 5 intensive care units in the application of ECLS for PCAS patients. Even though the death rate 6 was high, the survivors of ECLS-treated PCAS population exerted no or minor neurological 7 8 disabilities. Furthermore, the death rate in the ECLS-treated population is of a magnitude of 9 the death rate of the PCAS population, although the severity was higher in the first population as compared to the second. The latter observation might raise the question of the 10 potential benefit of ECLS in such a severe population. It also highlights the need for better 11 identification of patients who could benefit of such investment. Therefore, we have identified 12 blood lactates level at ECLS implantation and reversible cause of OHCA as potential factors 13 associated with better outcomes. 14

15 In the survivors of ECLS-treated PCAS population, the potential for recovery of neurological 16 function was high (89% of surviving patients were alive without severe neurological 17 impairment). These data are consistent with previously published data [5,7], although ECLS 18 wasn't used in those latter studies. Faster time to implantation could be a particular endpoint 19 to achieve, as suggested by available data in the setting of refractory cardiogenic shock [19]. 20 Well-designed studies are lacking to support this hypothesis in the setting of PCAS. On the contrary, selecting patients the most likely to benefit for such a therapy could improve 21 22 functional outcomes. Indeed, despite we observed that the mortality was not significantly 23 different in the ECLS-treated population as compared to the control, blood lactate level, as well as the etiology of CA, was associated with neurological outcomes. Initiating ECLS on 24 25 patients with low blood lactate level, and suffering for PCAS consecutive to reversible cause, could improve survival rates. Indeed, even though Bougouin et al. [9] showed no association 26 27 between ECLS implantation and survival, our study suggests that the coronary etiology could

be a potential confounding factor. Reversible causes of myocardial dysfunction could then have a better prognosis in terms of myocardial recovery [20]. By contrast, in case of constituted myocardial infarct, the potential for recovery could be altered [21–23]. In fact, mortality observed in patients treated with ECLS for PCAS secondary to acute coronary syndrome, was higher than mortality observed in patients treated with ECLS for reversible causes. The mortality rates observed in our study remained high, but were comparable to those reported in the two previously published studies, respectively 72 [8] and 73% [9].

8 Complications occurred frequently, but were close to those reported in a meta-analysis of 20 9 studies evaluating ECLS usage [24]. The most frequent complication in our study was acute 10 kidney injury requesting renal replacement therapy (50%), being probably more a marker of the severity of the shock rather than a specific complication of ECLS. On the contrary, the 11 12 high rates of specific complications of ECLS observed in our cohort, as the rate of lower limb ischemia (28% versus 17% in Cheng's study [24]), could worsened the prognosis of some 13 14 patients. However, ECLS implantation was performed by physicians trained to percutaneous cannulation with previously published good results [11]. 15

The retrospective design of the study limits the strength of the findings. We focused on a specific subpopulation of PCAS patients, and we retrieved data from 10 years' experience of two tertiary care centers. No randomized study could have been achievable in a reasonable time-frame. A matched analysis designed to identify the variables associated with survival would have been useful, but the low sample size of the ECLS cohort, as well as the particular severity of these patients have prevented us to conduct such a matching. Moreover, we were unable to collect information regarding severity at admission in the control population.

We limited the inclusion to the patients admitted for OHCA on purpose, even though the outcomes of the 3 patients non-included could have influenced the overall results of this study. Indeed, OHCA is a sudden and life-threatening pathology for whom the delay for initiation of the treatments is a key aspect of the prognosis. In-Hospital CA is a more

heterogeneous entity, where pre-existing life-threatening pathology leads to CA. The prognosis of the CA should be the combination of the pre-existing condition and the CA by itself. It would have been difficult to conclude on the ECLS intervention, because of this heterogeneity.

5

#### 6 Conclusion

Despite high rate of death in the ECLS-treated population, the neurological outcomes of the 7 8 survivors suggest a potential beneficial effect of ECLS on neurological recovery and justify its 9 implantation for extremely severe population, as a salvage therapy. While ECLS initiation, reported in this present work, does not impact mortality, neurologic outcomes of survivors 10 suggest a potential beneficial effect on neurological recovery. The neurological evolution 11 could be more likely related to the initial brain injury, rather than the PCAS by itself. 12 13 Furthermore, Reversible etiologies of cardiac arrest were associated with better outcomes, emphasizing on selection of patients who could benefit of such a therapy. Considering the 14 15 assistance only for patients for whom the myocardial depression has the potential to recover 16 could be an interesting option to improve outcomes. Then, considering ECLS for a carefully 17 selected population of PCAS patients could be promising.

18

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22

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- 26 27

## 1 **TABLES**

2 Table 1. General characteristics of the ECLS population according to outcome. Results

- 3 are expressed as median [IQR] or n (%).
- 4

	All N = 43	Favorable Outcome N = 8	Poor Outcome N = 35	P Value
Age (yo)	54 [46 - 59]	43 [35 - 54]	55 [49 - 61]	0.029
Male <i>n</i> (%)	32 (74)	5 (62)	27 (77)	0.409
Body Mass Index	26 [25 - 28]	27 [25 - 31]	26 [25 - 28]	0.736
		Previous Medical I	Diseases	
Coronaropathy n (%)	9 (21)	1 (12)	8 (23)	0.535
Diabetes mellitus <i>n (%)</i>	7 (16)	0 (0)	7 (20)	0.18
Hypertension <i>n (%)</i>	15 (35)	1 (12)	14 (40)	0.151
Dyslipidemia <i>n (%)</i>	6 (14)	1 (12)	5 (14)	0.917
Active smoker n (%)	4 (9)	0 (0)	4 (11)	0.336
	S	Severity scores on a	admission	
IGS II	73 [67 - 81]	70 [66 - 79]	73 [68 - 82]	0.468
SOFA score	12 [11 - 15]	12 [10 - 12]	13 [12 - 15]	0.227
SOFA cardio-vascular	4 [4 - 4]	4 [4 - 4]	4 [4 - 4]	-
OHCA score	39 [31 - 51]	32 [26 - 36]	42 [33 - 52]	0.078
	L	Biological Data on a	admission	
рН	7.19 [7.05 - 7.26]	7.15 [7.11 - 7.23]	7.19 [6.97 - 7.26]	0.521
Troponin (µmol/l)	5.5 [1.32 - 63.2]	7.2 [1.86 - 20.98]	4 [1.35 - 63.7]	0.984
Blood lactate (mmol/l)	10 [6 - 13]	6 [4 - 8]	11 [7 - 14]	0.029
Serum creatinine (µmol/l)	148 [138 - 188]	150 [134 - 164]	148 [138 - 198]	0.708
Serum potassium (mmol/l)	3.7 [3.2 - 4.2]	3.3 [2.9 - 4]	3.8 [3.4 - 4.4]	0.147
	c	ardiac Arrest Char	acteristics	
No Flow (min)	2 [0 - 10]	1 [0 - 9]	3 [0 - 10]	0.734
Low Flow (min)	28 [14 - 42]	25 [11 - 30]	28 [18 - 48]	0.28
Adrenaline bolus (mg)	3 [1 - 9]	1 [0 - 3]	4 [1 - 9]	0.168
Non public location <i>n (%)</i>	16 (37)	2 (25)	14 (40)	0.445
Bystander CPR n (%)	32 (74)	5 (62)	27 (77)	0.414
Shockable rhythm n (%)	26 (60)	4 (50)	22 (63)	0.519
Coronary Angiogram n (%)	38 (88)	7 (88)	31 (89)	0.37
Coronary Angioplasty n (%)	15 (35)	2 (25)	13 (37)	0.414
Hypothermia n (%)	33 (77)	6 (75)	27 (77)	0.207

	Cardiac Arrest Diagnoses			
Atrioventricular block n (%)	3 (7)	1 (12)	2 (6)	0.5
Coma <i>n (%)</i>	1 (2)	0 (0)	1 (3)	0.688
Hyperkalemia <i>n (%)</i>	2 (5)	0 (0)	2 (6)	0.534
Asphyxia <i>n</i> (%)	3 (7)	1 (12)	2 (6)	0.5
ACS n (%)	26 (60)	2 (25)	24 (69)	0.009
Tamponnade <i>n (%)</i>	1 (2)	0 (0)	1 (3)	0.688
Arrhythmia n (%)	6 (14)	3 (38)	3 (9)	0.03
Drowning n (%)	1 (2)	0 (0)	1 (3)	0.688
		Assistance	es	
Impella <i>n (%)</i>	7 (16)	1 (12)	6 (17)	0.77
IACPB <i>n (%)</i>	8 (19)	3 (38)	5 (14)	0.139

1 BMI: Body Mass Index ; CA : Cardiac Arrest ; CPR : Cardio-Pulmonary Resuscitation; IACPB : Intra-

2 Aortic Counter-Pulsation Balloon; OHCA : Out-Of-Hospital Cardiac Arrest ; SOFA : Sequential Organ

3 Failure Assessment ; ACS : Acute Coronary Syndrome

4

5

### 1 Table 2. Hemodynamic parameters and ECLS complications in the ECLS population

2 according to outcome. Results are expressed as median [IQR] or n (%).

	All N = 43	Favorable Outcome N = 8	Poor Outcome N = 35	P Value
		ECLS Implanta	tion Data	
CA to ECLS delay (hours)	9 [6 - 16]	8 [7 - 18]	10 [6 - 15]	0.967
Hemodynamic				
MAP (mmHg)	58 [44 - 72]	60 [55 - 74]	57 [42 - 68]	0.553
Cardiac Index (L/min/m <sup>2</sup> )	1,37 [0,9 - 1,81]	1.73 [1.08 - 2.05]	1.36 [0.94 - 1.39]	0.786
Cardiac Power (Watt)	0,27 [0,14 - 0,44]	0.38 [0.25 - 0.49]	0.18 [0.14 - 0.35]	1
LVEF (%)	15 [10 - 25]	15 [12 - 21]	20 [10 - 25]	0.597
Inotropic Equivalent	220 [137 - 410]	160 [118 - 193]	230 [140 - 410]	0.247
		ECLS Effic	cacy	
ECLS Withdrawal n (%)	8 (19)	7 (88)	1 (3)	< 0.001
Inefficacy n (%)	11 (26)	0 (0)	11 (31)	0.092
CPC ≤ 2 at D90 <i>n (%)</i>	8 (19)	7 (88)	1 (3)	< 0.001
Death at 1 year n (%)	35 (81)	0 (0)	35 (100)	< 0.001
	Po	otential complication	ns ECLS-related	
Complications	36 (84)	6 (75)	30 (86)	0.554
Total per patient (n = 71)	2 [1 - 3]	1 [1 - 2]	2 [1 - 2]	0.743
Hemorrhage n (%)	10 (23)	0 (0)	10 (29)	-
Lower Limb Ischemia n (%)	12 (28)	3 (38)	9 (26)	-
Coagulopathy n (%)	12 (28)	0 (0)	12 (34)	-
Hemolysis <i>n</i> (%)	1 (0)	0 (0)	1 (3)	-
ARDS <i>n</i> (%)	1 (0)	0 (0)	1 (3)	-
Femoral site infection <i>n</i> (%)	2 (0)	2 (25)	0 (0)	-
Renal Replacement Therapy <i>n (%)</i>	21 (50)	5 (63)	16 (46)	-
(%) VAP n (%)	4 (1)	0 (0)	4 (11)	-
GastroIntestinal Bleeding <i>n</i>				
(%)	1 (0)	0 (0)	1 (3)	-
Mesenteric Ischemia n (%)	7 (16)	1 (13)	6 (17)	-

3 CA: Cardiac Arrest; LVEF: Left Ventricle Ejection Fraction; CPC : Cerebral Performance Category

4 Score ; ARDS : Acute Respiratory Distress Syndrome ; VAP : Ventilator Associated Pneumonia

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# 1 Table 3. Comparison between ECLS treated PCAS patients (ECLS group) and non

2 ECLS treated PCAS patients group (Control group). Results are expressed as median

3 [IQR] or n (%).

	Overall n =921	ECLS group n = 43	Control Group n = 878	P Value
Age (yo)	62 [52 - 74]	54 [46 - 59]	63 [52 - 74]	<0.001
Male <i>n</i> (%)	633 (69)	32 (74)	601 (68)	0.50
Body Mass Index	25 [23 - 28]	26 [25 - 28]	25 [23 - 28]	0.19
	Previous N	ledical History		
Coronaropathy n (%)	205 (24)	9 (21)	196 (25)	0.72
Diabete mellitus <i>n (%)</i>	184 (22)	7 (16)	177 (23)	0.45
Arterial Hypertension n (%)	374 (45)	15 (35)	359 (46)	0.21
Dyslipidemia <i>n (%)</i>	210 (26)	6 (14)	204 (26)	0.08
Active smoker n (%)	295 (40)	4 (9)	291 (42)	<0.001
	Biological paran	neters on admission		
Blood Lactate (mmol/l)	5 [3 - 10]	10 [6 - 13]	5 [3 - 10]	0.002
Serum Creatinine (µmol/l)	109 [84 - 146]	148 [138 - 188]	108 [83 - 144]	<0.001
Potassium (mmol/l)	3.9 [3.3 - 4.5]	3.7 [3.2 - 4.2]	3.9 [3.3 - 4.5]	0.66
	Characteristics	s of Cardiac Arrest		
No Flow (min)	3 [0 - 8]	2 [0 - 10]	3 [0 - 8]	0.33
Low Flow <i>(min)</i>	16 [10 - 25]	28 [14 - 42]	16 [10 - 25]	0.001
Adrenaline bolus <i>(mg)</i>	2 [0 - 5]	3 [1 - 9]	2 [0 - 5]	0.41
Non public location <i>n (%)</i>	617 (67)	16 (37)	601 (69)	<0.001
Bystander CPR n (%)	482 (52)	32 (74)	450 (51)	0.007
Shockable initial rythm <i>n (%)</i>	439 (48)	26 (60)	413 (47)	0.09
Coronary Angiogram n (%)	622 (68)	38 (90)	584 (67)	0.001
Coronary Angioplasty n (%)	238 (27)	15 (35)	223 (25)	0.14
Hypothermia <i>n (%)</i>	755 (80)	33 (77)	722 (82)	0.83

4 CPR : Cardio-Pulmonary Resuscitation;

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# 1 Table 4. Factors associated with survival at ICU discharge in the whole PCAS

**population (n=921).** Results are expressed as median [IQR] or n (%)

	Survivors n = 237	Death n = 684	P Valu
Age (yo)	61 [49 - 71]	63 [53 - 75]	0.01
Male <i>n</i> (%)	165 (70)	468 (68)	0.73
Body Mass Index	26 [22 - 28]	25 [23 - 30]	0.22
	Previous Medical Diseas	es	
Coronaropathy n (%)	13 (6)	27 (4)	0.35
Diabetes mellitus n (%)	28 (13)	156 (26)	<0.00
Hypertension n (%)	91 (41)	283 (47)	0.18
Dyslipidemia n (%)	66 (30)	144 (24)	0.11
Active smoker n (%)	84 (40)	211 (40)	0.91
	Biological Data at admiss	ion	
Blood lactate (mmol/l)	3 [2 - 5]	9 [5 - 13]	<0.00
Serum creatinine (µmol/l)	98 [76 - 124]	129 [97 - 169]	<0.00
Serum potassium (mmol/l)	3.6 [3.1 - 4.2]	4 [3.4 - 4.8]	<0.00
c	ardiac Arrest Characteris	stics	
No Flow <i>(min)</i>	2 [0 - 5]	5 [0 - 10]	<0.00
Low Flow <i>(min)</i>	13 [7 - 20]	20 [13 - 30]	<0.00
Adrenaline <i>(mg)</i>	0 [0 - 3]	3 [2 - 6]	<0.00
Non public location <i>n (%)</i>	110 (47)	188 (28)	<0.00
Bystander CPR <i>n (%)</i>	140 (61)	342 (51)	0.008
Shockable rhythm <i>n (%)</i>	163 (69)	276 (40)	<0.00
Coronary Angiogram n (%)	187 (79)	435 (64)	<0.00
Coronary Angioplasty n (%)	85 (39)	153 (24)	<0.00
Hypothermia n (%)	216 (92)	539 (79)	<0.00
	Assistances		
ECMO n (%)	9 (4)	34 (5)	0.59

1	FIGURE LEGENDS
2	
3	Figure 1: Mode and timing of death during ICU length of stay in the ECLS treated
4	population.
5	
6	Figure 2: Multivariate analysis of factors associated with ECLS initiation in the PCAS
7	population
8	
9	Figure S1: Serum Lactate levels according to neurological outcomes
10	
11	
12	