

# Venoarterial extracorporeal membrane oxygenation to rescue sepsis-induced cardiogenic shock: a retrospective, multicentre, international cohort study

Nicolas Bréchot, David Hajage, Antoine Kimmoun, Julien Demiselle, Cara Agerstrand, Santiago Montero, Matthieu Schmidt, Charles-Edouard Luyt, Guillaume Lebreton, Guillaume Hékimian, et al.

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# 1 Venoarterial extracorporeal membrane oxygenation to rescue sepsis-

# 2 induced cardiogenic shock

3

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39	
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41	
42	Abbreviations
43	ASD, absolute standardized difference
44	ECMO, extracorporeal membrane oxygenation
45	ICU, intensive care unit
46	LVEF, left ventricular ejection fraction
47	SOFA, Sequential Organ Failure Assessment
48	SAPS-II, simplify acute physiology score-II
49	VA-ECMO, veno-arterial membrane oxygenation
50	

- 51 Key words: extracorporeal membrane oxygenation; veno-arterial; ECMO; extracorporeal life
- 52 support; sepsis; septic shock; cardiogenic shock

#### 53 ABSTRACT (281 words)

54

#### 55 Background

56 Patients with sepsis-induced cardiomyopathy with cardiogenic shock have a very high mortality.

57 This study evaluated VA-ECMO support for sepsis-induced cardiogenic shock refractory to

58 conventional treatments.

#### 59 Methods

60 This multi-centre, international, retrospective study compared the outcomes of 82 septic shock

61 patients who received VA-ECMO at 5 academic ECMO centres, to 130 controls (not receiving

62 ECMO) obtained from 3 large septic shock databases. All patients had severe myocardial

63 dysfunction (cardiac index  $\leq 3L/min/m^2$  or left ventricular ejection fraction (LVEF)  $\leq 35\%$ ) and

64 severe hemodynamic compromise (inotrope score  $\geq$ 75 µg/kg/min or lactatemia  $\geq$ 4 mmol/L) at the

time of inclusion. The primary endpoint was survival at 90 days. A propensity score-weighted

66 analysis was performed to control for confounders.

#### 67 Findings

68 At baseline, VA-ECMO patients had more severe myocardial dysfunction than controls (mean

69 cardiac index 1.5 vs. 2.2 L/min/m<sup>2</sup>, LVEF 17 vs. 27%), more severe hemodynamic impairment

(inotrope score 279 vs. 145  $\mu$ g/kg/min, lactatemia 8.9 vs. 6.5 mmol/L), and more severe organ

failure (SOFA score 17 vs. 13), with p < 0.0001 for each comparison. Survival at 90 days for VA-

72 ECMO patients was significantly higher than controls (60% vs. 25%, RR for mortality 0.54, 95%CI

73 [0.40-0.70], p<0.0001). After propensity score weighting, ECMO remained associated with a better

74 survival (51% vs. 14%, adjusted RR for mortality 0.57, 95%CI [0.35-0.93], p=0.0029). Lactate and

catecholamine clearance was also significantly enhanced in ECMO patients. Among the 49 ECMO

real survivors, 32 who had been treated at the largest centre reported satisfactory SF-36 evaluated health-

77 related quality of life at one-year follow-up.

#### 78 Interpretation

- 79 Patients with severe sepsis-induced cardiogenic shock treated with VA-ECMO had a large and
- 80 significant improvement in survival compared to controls not receiving ECMO. However, despite the
- 81 careful propensity-weighted analysis, we cannot rule out unmeasured confounders.

#### 82 Introduction

83 Sepsis remains a major issue worldwide. In the United States alone, it is responsible for 1.7 million 84 hospitalizations annually, and has a mortality ranging from 35 to 50% when septic shock is present.<sup>1,2</sup> Transient reversible myocardial dysfunction is a common feature during septic shock, 85 affecting 20 to 65% of patients.<sup>3,4</sup> While mild decreases in left ventricular ejection fraction (LVEF) 86 87 combined with left ventricular dilation and a preserved cardiac index appears to be associated with a 88 good survival,<sup>3,4</sup> the mortality of patients with severe myocardial dysfunction and decreased cardiac index may exceed 80%.<sup>3,5,6</sup> The incidence of this condition in adults is uncertain, but may be up to 89 24% of septic shock patients requiring >24 hours of vasopressors,<sup>5</sup> translating into >25,000 episodes 90 91 annually in the US.<sup>1</sup>

92 The use of venoarterial extracorporeal membrane oxygenation (VA-ECMO) during septic 93 shock refractory to conventional treatment remains controversial. Encouraging results in children 94 with survival rates ranging from 50 to 75%,<sup>7,8</sup> led to the inclusion of this therapeutic option in recent 95 septic shock pediatric guidelines,<sup>8</sup> whereas data in adults have been more equivocal.<sup>9–14</sup> In this study, 96 we evaluated the use of VA-ECMO in adults with sepsis-induced cardiogenic shock refractory to 97 conventional treatments.

98

#### 99 Methods

#### 100 Trial design

101 This retrospective, international, multi-centre study compared the outcomes of patients who received 102 VA-ECMO for refractory sepsis-induced cardiogenic shock, to non-ECMO patients obtained from 3 103 large septic shock databases. Patients were included in our study if septic shock was the main reason 104 for cardiovascular dysfunction. However, patients with pre-existing myocardial dysfunction were not 105 excluded (Appendix). The study complied with STROBE criteria. Institutional review board 106 approval from French centres and Columbia University were obtained, as required (Appendix). 107

#### 108 ECMO patients

109 Data from septic shock patients receiving VA-ECMO were collected from January 2008 to March 110 2018 at five university hospital ECMO centres (La Pitié-Salpêtrière, Amiens, Nancy, Rennes – all in 111 France - and Columbia University Medical Centre/New York-Presbyterian Hospital, New-York, 112 NY, USA). Data from 14 patients, previously reported in a proof-of-concept study of VA-ECMO for septic shock, were included in this study.<sup>13</sup> Septic shock patients were considered for ECMO at these 113 114 expert ECMO centres if they developed severe myocardial dysfunction and signs of end-organ 115 malperfusion, despite optimized fluid resuscitation and high-dose inotropes and vasopressors. For the 116 purpose of this study, we used the following criteria for severe cardiovascular dysfunction leading to 117 VA-ECMO initiation (i) left ventricular ejection fraction (LVEF)  $\leq 35\%$  or cardiac index  $\leq 3$ 118 L/min/m<sup>2</sup>, (ii) lactatemia  $\geq$ 4 mmol/L, and (iii) inotrope score  $\geq$ 75 µg/kg/min (with inotrope score 119 calculated as dobutamine dose  $[\mu g/kg/min] + (epinephrine dose [\mu g/kg/min] + norepinephrine dose$ [µg/kg/min]) x 100).<sup>13</sup> ECMO patients underwent advanced hemodynamic monitoring of cardiac 120 121 output with Doppler-echocardiography, a pulmonary artery catheter or the PICCO system before 122 ECMO and only with Doppler-echocardiography after ECMO, since thermodilution-based 123 techniques do not provide accurate measurements during ECMO. LVEF was assessed with 124 echocardiography in all patients. Patients <18 years old were excluded. 125 Management of VA-ECMO was performed as described previously.<sup>13</sup> Briefly, cannulas were 126 surgically or percutaneously inserted and VA-ECMO instituted, locally or by mobile ECMO 127 retrieval teams. Pump speed was set to achieve a blood flow of 3.5-5 L/min. Anticoagulation was 128 achieved with unfractionated heparin (target activated partial thromboplastin time 1.5 to 2 times the 129 control), and stopped for severe bleeding or coagulation disorders. If severe respiratory failure 130 persisted during VA-ECMO weaning, veno-venous ECMO was initiated.

#### **132** Non-ECMO patients

133 Data from severe septic shock patients who did not receive ECMO were collected from three 134 databases which provided daily monitoring of patient's hemodynamic status: 1) SEPSISPAM, a 135 multi-centre, randomized controlled trial comparing two targets of mean arterial pressure for the treatment of septic shock;<sup>2</sup> 2) a retrospective cohort study conducted at the Brabois intensive care 136 Unit (ICU) (Nancy, France) of septic shock patients receiving high doses of vasopressors;<sup>15</sup> 3) the 137 138 BDD database of septic shock patients from Angers university hospital's intensive care unit (ICU) 139 (Angers, France). Additional information on these databases and on hemodynamic monitoring of 140 non-ECMO patients is presented in the Appendix. Patients were included the first time they met the 141 following criteria: severe cardiac dysfunction (LVEF  $\leq 35\%$  or cardiac index  $\leq 3 \text{ L/min/m}^2$ ); and 142 serum lactate  $\geq 4$  mmol/L or inotrope score  $\geq 75 \,\mu$ g/kg/min. Since all ECMO-group patients received 143 mechanical assistance less than 5 days after the onset of septic shock and to minimize potential 144 biases linked to the duration of septic shock before inclusion, we restricted the selection of control 145 patients to those meeting these severity criteria within the first 4 days after the occurrence of sepsis.

146

#### 147 **Outcomes**

The primary outcome was survival at 90 days. Secondary outcomes included rate of decrease in inotrope score and the rate of lactate clearance in the 5 days after inclusion of both ECMO and non-ECMO patients; and hospital and one-year outcomes of ECMO-treated patients. Health-related quality-of-life, anxiety, depression and post-traumatic stress disorder were prospectively evaluated by phone interviews at one year after hospital discharge for patients from La Pitié-Salpêtrière (n=32; Appendix).<sup>13</sup>

154

#### 155 Statistical analysis

156 Day-90 survival was estimated by the Kaplan-Meier method for ECMO (exposed) and non-ECMO 157 (unexposed) patients, and compared with a log rank test. A propensity score-weighted analysis was 158 performed for treatment effect estimation. This method which weights each subject according to 159 his/her propensity score value, includes all subjects in the analysis. First, we performed multivariable 160 logistic regression to predict the conditional probability of ECMO (i.e., the estimated propensity 161 score), controlling for pre-specified covariates: 1) co-variables associated with the level of 162 myocardial dysfunction (cardiac index), 2) co-variables associated with survival during septic shock 163 (inotrope score, lactatemia, Sequential Organ Failure Assessment (SOFA) score, age, immunocompromised status, and cumulative fluid therapy before inclusion) $^{15-18}$  and 3) delay 164 165 between shock onset and inclusion.<sup>11</sup> Briefly, each subject was weighted using the overlap weights approach, which down-weights individuals on the basis of propensity score values.<sup>19</sup> Covariate 166 167 balance between the two groups was assessed after weighting, and we considered an absolute 168 standardized difference (ASD) <0.1 as evidence of balance. Then, the effect of ECMO on survival at 169 90 days was estimated within the weighted pseudo-population. Adjusted Kaplan-Meier estimator and log-rank test (taking into account the weighting scheme) were used.<sup>20</sup> Standard error of the estimated 170 171 relative risk of death was calculated using a bootstrap procedure. Multiple imputations were used to replace missing values when appropriate. Ten copies of the dataset were created with the missing 172 173 values replaced by imputed values, based on observed data including outcomes and baseline 174 characteristics of participants. Each dataset was then analyzed using standard statistical methods, and 175 the results from each dataset were pooled into a final result using Rubin's rule <sup>21</sup> (details in the 176 supplementary Appendix). A number of sensitivity analyses were performed: impact of (1) early vs. 177 late mortality on ECMO effect, after excluding patients who died in the first 24 hours; (2) early vs. 178 late inclusion after the onset of shock; (3) year of inclusion; (4) site of infection; (5) time-dependent 179 (early vs. late) ECMO effect on mortality on the whole cohort. The same procedure was also

180	performed excluding patients with missing data and the effect of ECMO on 90-day mortality was
181	estimated using the prognostic score framework <sup>22</sup> (see Appendix for details).
182	Rate of decrease in inotrope score and lactatemia between ECMO and non-ECMO patients
183	were compared using a linear mixed effect model. Other secondary outcomes were compared
184	between survivors and non-surviving ECMO patients using Student's t test or Wilcoxon rank sum
185	test for continuous variables, and chi-square tests of Fisher exact tests for categorical variables, as
186	appropriate. Detailed statistical procedures are provided in the supplementary Appendix.
187	
188	Role of the funding source
189	There was no funding source for this study. The corresponding author had full access to all the data
190	and had final responsibility for the decision to submit for publication.
191	
192	Results
193	ECMO patients
194	Characteristics of the 82 patients who received VA-ECMO for sepsis-induced cardiogenic shock are
195	given in table 1. Community-acquired pneumonia accounted for the largest portion of infections.
196	
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205 patients (one axillary artery and one central cannulation). Twelve (15%) patients first received veno-

206 venous ECMO and were rapidly switched to VA-ECMO, while eight (10%) received veno-arterio-

207 venous ECMO. Fifty-seven (70%) patients were cannulated by a mobile ECMO retrieval team. At

the time of ECMO implantation 61 (74%) patients were receiving corticosteroids.

209

#### 210 Non-ECMO patients

211 Among the 990 patients from the three control databases, 468 had received advanced hemodynamic 212 monitoring and 130 were selected as non-ECMO controls the first day they met criteria for ECMO 213 implantation (figure 1). Non-ECMO patients were older, had a lower occurrence of pneumonia as the 214 source of sepsis, less severe hemodynamic impairment and less organ failures at inclusion than 215 ECMO patients (table 1). Urinary tract and abdominal infections accounted for 8% and 26% of 216 infectious episodes, respectively (p=0.0856 and p=0.0002 vs. ECMO group). Stress dose 217 corticosteroids were administered to 80 (88%) of the 91 control patients for whom the data was 218 available (i.e. all but BDD database) (vs. 61 (74%) of the ECMO patients; p=0.0303).

219

#### 220 **Primary outcome**

221 Survival at 90 days was markedly higher in ECMO patients compared to controls, (60% vs. 25%, RR

for mortality 0.54, 95%CI [0.40-0.70], p<0.0001 between groups) (figure 2). The difference in

survival persisted after propensity score weighting of the patients according to their baseline severity

224 and potential confounders (51% vs. 14%, RR for mortality 0.57, 95%CI [0.35-0.93], p=0.0029,

table 1 and figure 2). The relative risk for 90-day mortality was 0.47 [95% CI 0.34-0.65; p < 0.0001]

for ECMO vs. non-ECMO patients based on the prognostic score (see Appendix for details).

- 227 Limiting the analysis to patients included during the first 24 hours of sepsis or excluding patients
- dying very early in the 24 hours after inclusion led to comparable results, as well as adjusting for the

site of infection, year of inclusion, time of inclusion after the onset of sepsis (see Appendix fordetails, sensitivity analyses).

231

#### 232 Secondary outcomes

233 ECMO patients had significantly more rapid lactate clearance and decrease in inotrope score than 234 controls (figure 3). Myocardial function recovery occurred rapidly in ECMO patients and was 235 normalized in survivors (Appendix figure 6). Peak troponin was  $15 \cdot 26 \pm 44 \cdot 3 \mu g/L$  for troponin I (38 236 patients), and  $518.0 \pm 953.7$  ng/ml for troponin T (46 patients). Nine patients had coronary 237 angiography, showing no significant lesions. Of the 33 patients who died, 18 (54%) died of 238 refractory multiple organ failure and two (6%) of extensive bowel ischemia shortly after ECMO 239 initiation. Baseline characteristics were comparable between survivors and non-survivors, except for 240 older age and less frequent acute kidney injury in non-survivors (table S4, Appendix). Of the 61 241 (74%) patients weaned from VA-ECMO, 30 received immediate veno-venous-ECMO for persistent 242 respiratory failure for a mean of  $13.4 \pm 16.6$  days but none experienced subsequent myocardial 243 dysfunction. Among successfully explanted patients, 12 (20%) subsequently died, two (4%) after 244 being discharged from the ICU. Despite short times on VA-ECMO support, survivors had prolonged 245 ICU and hospital stays, and a high level of healthcare resource consumption (table 2). Ten (12%) 246 patients had a limb amputation due to lesions of purpura fulminans, which existed at the time of 247 ECMO initiation; two patients had all four limbs partially amputated. A major complication of 248 ECMO occurred in 35 (43%) patients with infection, and hemorrhage at the cannula insertion site 249 being the most frequent (table 2).

250

#### 251 Long-term outcomes

Among the 49 survivors at 90 days, 24 experienced persistent complications at the insertion site: 13
infections, six crural nerve sensory-motor deficits, three late wound healing and two arterial

aneurysms. Eleven local complications necessitated subsequent surgical treatment. Of the 64 patients
included at La Pitié-Salpêtrière hospital, 35 (55%) survived and one-year health-related quality of
life was obtained for 32 of these patients. They reported mild impairment in physical activities, and
highly preserved mental and social conditions. Their SF-36 component scores were comparable or
better than those reported for patients on chronic dialysis or after myocardial infarction (Appendix
figure 7) at one year. Anxiety, depression and post-traumatic stress disorder symptoms were reported
by eight (25%), five (16%), and two (6%) of the patients, respectively.

261

#### 262 **Discussion**

263 Our major finding is that the 90-day survival of our VA-ECMO patients was dramatically improved 264 compared to propensity-weighted patients with similar characteristics who were treated with medical 265 management alone. VA-ECMO permitted a rapid decrease in vasopressor dose, and restored 266 adequate perfusion of vital organs, as indicated by relatively rapid decreases in serum lactate. 267 Improvement of cardiac function was also relatively quick and permitted weaning of ECMO support 268 after a mean of only 6 days in survivors, a shorter time than reported in patients who receive ECMO 269 for primary cardiogenic shock. Lastly, although survivors had prolonged ICU and hospital stays and 270 suffered severe sepsis- and ECMO-related complications, long-term quality of life was deemed 271 satisfactory in a cohort of survivors followed for one year.

Our study has a number of strengths including the fact that it was conducted in high-volume, multi-national and experienced academic ECMO centres. However, our study also has clear limitations. The major limitation is that the study was not randomized, and thus is open to potential biases. While conducting a randomized trial would have been ideal, it would be logistically very difficult if not impossible to conduct. There would be a very narrow window for enrolling these medically complex, desperately ill patients. In addition, the lack of clinical equipoise at experienced ECMO centres (the ones who would conduct such a trial) would be anticipated to result in a very 279 high rate of crossover to ECMO for patients randomized to the control arm, biasing the results to the 280 null. To address this weakness we performed a rigorous statistical analysis using propensity score weighting to control for known confounders, as well as performing a number of sensitivity analyses. 281 282 Despite this propensity weighting, differences persisted between groups for some important baseline 283 characteristics. For example, the ECMO group had worse LV dysfunction, and more lung infections 284 as the cause of their sepsis than controls. However septic shock related to lung infections carries a comparable prognosis as compared with infections at most other sites.<sup>23,24</sup> Accordingly the site of 285 286 infection did not affect 90-day mortality in this study. Moreover, these differences largely produced a 287 control group that was less sick at baseline than the ECMO-treated group. Of course, there may have 288 been residual unknown confounders in the selection of ECMO and non-ECMO patients, which could 289 not be taken into account in our propensity analyses. As an example, indication for ECMO or referral 290 for ECMO biases, differences between ECMO and non-ECMO centres in the management of severe 291 septic shock patients, as well as variations over time in the management of sepsis may have existed. 292 Reversible myocardial dysfunction is a common feature during septic shock, affecting 20 to 65% of patients.<sup>3,4</sup> Many mechanisms are thought to be responsible for this dysfunction including 293 294 mitochondrial dysfunction, capillary leak, excessive release of inflammatory cytokines, nitric oxide, free radicals,<sup>4,25</sup> and catecholamine-induced cardiomyopathy.<sup>26,27</sup> Adult patients developing severe 295 myocardial dysfunction in the context of sepsis have a dismal prognosis.<sup>3,5,6,28</sup> In 1989, Parker *et al.* 296 297 described that 11 of 21 non-survivors during sepsis died with a cardiogenic shock-like profile.<sup>3</sup> In 25 298 patients receiving vasopressors for more than 48 hours, Poelaert *et al.* reported a survival rate of only 17% for patients with LVEF <40%.<sup>5</sup> Irrespective of myocardial function, the level of administered 299 300 catecholamines strongly correlated with mortality in previous sepsis studies, with mortality rates >90% in patients with inotrope scores >100  $\mu$ g/kg/min.<sup>29,30</sup> We found that 13% (130/990) of the 301 302 patients in recent cohorts of septic shock who met our criteria for sepsis-induced severe cardiogenic shock had a survival of only 25%.<sup>2,15</sup> In this context, VA-ECMO may halt the vicious cycle leading 303

304 to irreversible multiple organ failure by restoring perfusion to vital organs and by allowing a rapid 305 decrease in the dose of catecholamines. Indeed, "salvage" therapy with VA-ECMO in septic children was associated with survival rates ranging from 50 to 75%,<sup>7,8</sup> leading to this therapy being 306 recommended in pediatric guidelines.<sup>8</sup> Interestingly, very recent data also suggest that VA-ECMO 307 308 may be able to reverse the dismal course of cardiogenic shock in acute myocardial infarction patients,<sup>31–34</sup> a situation that shares many pathophysiological features with sepsis-induced 309 310 cardiogenic shock. Three large randomized controlled trials comparing venoarterial ECMO to 311 medical treatment are currently underway in this setting (NCT03813134, NCT03637205,

312 NCT04184635).

313 There is a paucity of data on outcomes of adults with septic shock who received VA-ECMO.<sup>9-14</sup> In one series of 52 patients, only 15% survived to hospital discharge.<sup>9</sup> Most of these 314 patients had preserved myocardial function (median LVEF 56%).<sup>9</sup> Other recent cohorts also reported 315 316 very low survival rates (7-25%) for VA-ECMO patients with unselected hemodynamic profiles (i.e. mostly circulatory failure due to refractory vasoplegia with low systemic vascular resistance)<sup>11,12</sup> or 317 ECMO implanted under CPR.<sup>10</sup> In contrast, the Pitié-Salpêtrière group published data on a cohort of 318 319 14 patients with sepsis-induced cardiogenic shock and high systemic vascular resistances treated 320 with VA-ECMO. Ten (71%) survived after rapid and complete recovery of the sepsis-induced 321 myocardial dysfunction, and reported a good quality of life several months after being discharged home.<sup>13</sup> Similarly, encouraging results were recently published in a small series of 12 patients who 322 323 received veno-arteriovenous ECMO for severe myocardial dysfunction.<sup>14</sup>

In conclusion, this multi-centre, multi-national study suggests that in patients with sepsisinduced refractory cardiogenic shock, VA-ECMO may be associated with an improvement in survival compared with controls not receiving ECMO. The results need to be interpreted carefully because unmeasured confounders and referral biases of the highly selected group may have persisted despite propensity score weighting. However, the early identification of this very specific group of

329	patients, which may represent up to 10% of all septic shock patients, and the earlier application of
330	VA-ECMO support, may be critical to improve their outcomes.

331

332 333	Author contributions:					
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336	NB, DH, MS, CEL, GH, EF, EZ, AS, DB, BL, PA, AC were involved in analysis of the data.					
337	NB, AS, DB and AC wrote the manuscript.					
338	All authors contributed to the revision of the manuscript and read and approved its final version.					
339	NB takes responsibility for the integrity of the work as a whole, from inception to published article.					
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- 439

# Table 1: Characteristics at ECMO implantation (ECMO patients) or at the first time meeting criteria for ECMO implantation\* (non-ECMO patients), in baseline population and propensity-weighted patients†.

	Baseline population Propensity-weighted					
	patients			ients		
	ECMO	Non ECMO		ECMO	Non ECMO	
	( <b>n=82</b> )	( <b>n=130</b> )	p-value	( <b>n=82</b> )	( <b>n=130</b> )	ASD
Demographic data						
Age	48 (15)	66 (16)	<0.0001	56 (15)	56 (20)	0.00
Male sex	36 (44)	93 (71)	0.0001	39%	57%	0.04
Charlson score	1.1 (1.3)	1.6 (1.2)	0.0013	1.4 (1.3)	$1 \cdot 2 (1 \cdot 1)$	0.14
Immunodeficiency	13 (16)	34 (26)	0.0787	16%	16%	0.00
Community-acquired infection	71 (88)	90 (70)	0.0022	77%	76%	0.04
Source of infection: lung	64 (78)	50 (38)	<0.0001	87%	22%	1.66
Post-operative	7 (8)	20 (15)	0.1452	21%	14%	0.15
Delay after shock onset, days‡	1.1 (0.9)	0.7 (1.0)	<0.0001	1.1 (0.9)	$1 \cdot 1 (1 \cdot 4)$	0.00
Hemodynamic condition						
Mean arterial pressure, mmHg	70 (15)	72 (14)	0.1204	68 (16)	68 (15)	0.04
Heart rate	123 (24)	114 (27)	0.0011	119 (28)	111 (25)	0.32
Arterial pH	7.13 (0.15)	7.23 (0.16)	<0.0001	7.14 (0.14)	7.22 (0.16)	0.51
Serum lactate level, mmol/L	8.9 (4.4)	6.5 (4.5)	0.0001	7.9 (4.0)	7.9 (5.1)	0.00
Inotrope score, µg/kg/min	279 (247)	145 (128)	<0.0001	169 (157)	169 (148)	0.00
Cardiac index, L/min/m <sup>2</sup>	1.54 (0.54)	2.21 (0.59)	<0.0001	1.77 (0.56)	1.77 (0.67)	0.00
LVEF, %	17.1 (7.3)	27.5 (6.2)§	<0.0001	15.3 (6.3)	26.7 (7.8)	1.63
Fluid therapy before inclusion, mL	4925 (2886)	1654 (1952)	<0.0001	2764 (2113)	2764 (2779)	0.00
General clinical status						
Mechanical ventilation	82 (100)	124 (95)	0.0840	100%	100%	0.09
PaO <sub>2</sub> :FiO <sub>2</sub>	105 (77)	177 (106)	<0.0001	97 (60)	161 (92)	0.08
Acute kidney injury‡‡	66 (81)	90 (71)	0.0810	75%	80%	0.11

SOFA score	16.6 (2.9)	12.7 (3.5)	<0.0001	15.0 (3.1)	15.0 (3.7)	0.00
SAPS-II score	78.3 (16.1)	68-4 (18-8)	0.0001	76.8 (20.7)	75.6 (19.5)	0.06

Data are n (%) or mean (SD). ECMO, extracorporeal membrane oxygenation; ASD, absolute standardized difference; Na, not applicable. LVEF, left ventricular ejection fraction; PaO<sub>2</sub>:FiO<sub>2</sub> the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen; SAPS-II, Simplified acute physiology score-II; SOFA, sepsis-related organ failure assessment score. \* Criteria for ECMO implantation: (cardiac index  $\leq$ 3 L/min/m<sup>2</sup> or LVEF  $\leq$ 35%) + (inotrope score  $\geq$ 75 µg/kg/min or serum lactate  $\geq$ 4 mmol/L); with inotrope score (µg/kg/min) = dobutamine dose (µg/kg/min) + (epinephrine dose [µg/kg/min] + norepinephrine dose [µg/kg/min]) x 100; no other inotrope or vasopressor were used in both ECMO and non-ECMO patients.<sup>13</sup> † Propensity score included 1) co-variables associated with the level of myocardial dysfunction (cardiac index), 2) co-variables associated with survival during septic shock (inotrope score, lactatemia, Sequential Organ Failure Assessment (SOFA) score, age, immunocompromised status, cumulative fluid therapy before inclusion) and 3) delay between shock onset and inclusion. ‡ Onset of septic shock was defined as the time vasopressors were started for treating hypotension. § Parameter available for 12 patients. ‡‡ Defined as renal SOFA score  $\geq$ 2 (plasma creatinine level >1.9 mg/dl [168 µmol/L] or urinary output <500 ml/day).

# Table 2: Outcomes of ECMO-assisted patients

All (n=82)	Survivors (n=49)	Non survivors (n=33)	р
61 (74)	49 (100)	12 (36)	<0.0001
5.8 (5.6)	6.2 (6.1)	5.2 (4.7)	0.3874
16.9 (2.7)	16.4 (2.8)	18.0 (2.3)	0.0276
14.1 (4.1)	13.2 (3.7)	16.6 (4.3)	0.0033
8.5 (4.9)	7.5 (4.4)	13.7 (4.4)	0.0010
26.1 (22.6)	34.1 (23.6)	14.2 (14.7)	<0.0001
71 (86)	42 (86)	29 (88)	$1 \cdot 0000$
16.4 (16.2)	20.7 (17.7)	10.3 (11.5)	0.0034
72 (88)	44 (90)	28 (85)	0.8706
39 (47)	26 (53)	13 (39)	0.2641
8.6 (9.4)	8.4 (7.8)	8.8 (11.6)	0.5115
12 (15)	11 (22)	1 (3)	0.0118
35 (43)	22 (45)	13 (39)	0.6554
17 (21)	12 (24)	5 (15)	0.4055
17 (21)	11 (22)	6 (18)	0.7833
10 (12)	6 (12)	4 (12)	$1 \cdot 0000$
4 (5)	3 (6)	1 (3)	0.6450
2 (2)	2 (4)	0	0.5131
7 (8)	4 (8)	3 (9)	$1 \cdot 0000$
1 (1)	0	1 (3)	0.4024
49 (60)	47 (96)	2 (6)	<0.0001
30.4 (25.0)	41.3 (24.8)	14.5 (14.7)	<0.0001
44.8 (34.7)	67.7 (27.5)	15.0 (14.5)	<0.0001
	All (n=82) $61 (74)$ $5 \cdot 8 (5 \cdot 6)$ $16 \cdot 9 (2 \cdot 7)$ $14 \cdot 1 (4 \cdot 1)$ $8 \cdot 5 (4 \cdot 9)$ $26 \cdot 1 (22 \cdot 6)$ $71 (86)$ $16 \cdot 4 (16 \cdot 2)$ $72 (88)$ $39 (47)$ $8 \cdot 6 (9 \cdot 4)$ $12 (15)$ $35 (43)$ $17 (21)$ $17 (21)$ $10 (12)$ $4 (5)$ $2 (2)$ $7 (8)$ $1 (1)$ $49 (60)$ $30 \cdot 4 (25 \cdot 0)$ $44 \cdot 8 (34 \cdot 7)$	All (n=82)Survivors (n=49)61 (74)49 (100)5.8 (5.6)6.2 (6.1)16.9 (2.7)16.4 (2.8)14.1 (4.1)13.2 (3.7)8.5 (4.9)7.5 (4.4)26.1 (22.6)34.1 (23.6)71 (86)42 (86)16.4 (16.2)20.7 (17.7)72 (88)44 (90)39 (47)26 (53)8.6 (9.4)8.4 (7.8)12 (15)11 (22)35 (43)22 (45)17 (21)12 (24)17 (21)11 (22)10 (12)6 (12)4 (5)3 (6)2 (2)2 (4)7 (8)4 (8)1 (1)049 (60)47 (96)30.4 (25.0)41.3 (24.8)44.8 (34.7)67.7 (27.5)	All (n=82)Survivors (n=49)Non survivors 

Data are n (%) or mean (SD). ECMO = extracorporeal membrane oxygenation; ICU, intensive care unit; MV, mechanical ventilation; RRT, renal replacement therapy; SOFA, sepsis-related organ failure assessment score. \*Bleeding episode requiring transfusion of more than 2 packed red blood cells. †Asymmetric and/or associated with arterial thrombosis on the side of ECMO implantation.

#### **FIGURE LEGENDS**

#### **Figure 1: Flow-chart of the study**

\*Cardiac index  $\leq 3$  L/min/m<sup>2</sup> or LVEF  $\leq 35\%$ . † Severe myocardial dysfunction (cardiac index  $\leq 3$  L/min/m<sup>2</sup> or LVEF  $\leq 35\%$ ) + severe hemodynamic compromise (inotrope score  $\geq 75 \ \mu g/kg/min$  or lactatemia  $\geq 4$  mmoles/L), with inotrope score ( $\mu g/kg/min$ ) = dobutamine dose ( $\mu g/kg/min$ ) + (epinephrine dose [ $\mu g/kg/min$ ] + norepinephrine dose [ $\mu g/kg/min$ ]) x100.<sup>13</sup> ECMO = extracorporeal membrane oxygenation; LVEF= left ventricular ejection fraction; VA-ECMO = veno-arterial ECMO.

# Figure 2: Kaplan-Meier survival estimates of ECMO and non-ECMO patients, unadjusted and propensity-weighted for 1) co-variables associated with the level of myocardial dysfunction (cardiac index), 2) co-variables associated with survival during septic shock (inotrope score, lactatemia, Sequential Organ Failure Assessment (SOFA) score, age, immunocompromised status, and cumulative fluid therapy before inclusion) and 3) delay between shock onset and inclusion. ECMO = extracorporeal membrane oxygenation.

Figure 3: Evolution of (A) inotrope score and (B) lactatemia between ECMO and non-ECMO patients propensity-weighted for 1) co-variables associated with the level of myocardial dysfunction (cardiac index), 2) co-variables associated with survival during septic shock (inotrope score, lactatemia, Sequential Organ Failure Assessment (SOFA) score, age, immunocompromised status, and cumulative fluid therapy before inclusion) and 3) delay between shock onset and inclusion. Mean± 95% CI is shown for each time point. Inotrope score ( $\mu g/kg/min$ ) = dobutamine dose ( $\mu g/kg/min$ ) + (epinephrine dose [ $\mu g/kg/min$ ] + norepinephrine dose [ $\mu g/kg/min$ ]) x 100.<sup>13</sup> ECMO = extracorporeal membrane oxygenation.





Time (days)

