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1 **Venoarterial extracorporeal membrane oxygenation to rescue sepsis-** 2 **induced cardiogenic shock**

3
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9
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32

33

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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 ≤ 3 L/min/m² or left ventricular ejection fraction (LVEF) $\leq 35\%$) and

64 severe hemodynamic compromise (inotrope score ≥ 75 μ g/kg/min or lactatemia ≥ 4 mmol/L) at the

65 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/m², LVEF 17 vs. 27%), more severe hemodynamic impairment

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

71 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

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

76 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
85 present.^{1,2} Transient reversible myocardial dysfunction is a common feature during septic shock,
86 affecting 20 to 65% of patients.^{3,4} While mild decreases in left ventricular ejection fraction (LVEF)
87 combined with left ventricular dilation and a preserved cardiac index appears to be associated with a
88 good survival,^{3,4} the mortality of patients with severe myocardial dysfunction and decreased cardiac
89 index may exceed 80%.^{3,5,6} The incidence of this condition in adults is uncertain, but may be up to
90 24% of septic shock patients requiring >24 hours of vasopressors,⁵ translating into >25,000 episodes
91 annually in the US.¹

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%,^{7,8} led to the inclusion of this therapeutic option in recent
95 septic shock pediatric guidelines,⁸ whereas data in adults have been more equivocal.⁹⁻¹⁴ 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
113 septic shock, were included in this study.¹³ Septic shock patients were considered for ECMO at these
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 ≤ 3
118 L/min/m², (ii) lactatemia ≥ 4 mmol/L, and (iii) inotrope score ≥ 75 $\mu\text{g/kg/min}$ (with inotrope score
119 calculated as dobutamine dose [$\mu\text{g/kg/min}$] + (epinephrine dose [$\mu\text{g/kg/min}$] + norepinephrine dose
120 [$\mu\text{g/kg/min}$] x 100).¹³ ECMO patients underwent advanced hemodynamic monitoring of cardiac
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.¹³ 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.

131

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
136 treatment of septic shock;² 2) a retrospective cohort study conducted at the Brabois intensive care
137 Unit (ICU) (Nancy, France) of septic shock patients receiving high doses of vasopressors;¹⁵ 3) the
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 ≤ 3 L/min/m²); and
142 serum lactate ≥ 4 mmol/L or inotrope score ≥ 75 $\mu\text{g/kg/min}$. 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**

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

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,
164 immunocompromised status, and cumulative fluid therapy before inclusion)^{15–18} and 3) delay
165 between shock onset and inclusion.¹¹ Briefly, each subject was weighted using the overlap weights
166 approach, which down-weights individuals on the basis of propensity score values.¹⁹ Covariate
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
170 log-rank test (taking into account the weighting scheme) were used.²⁰ Standard error of the estimated
171 relative risk of death was calculated using a bootstrap procedure. Multiple imputations were used to
172 replace missing values when appropriate. Ten copies of the dataset were created with the missing
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 ²¹ (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 framework²² (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 Forty-four (54%) patients had sustained bacteremia. *Staphylococcus aureus* and *Streptococcus*
197 *pneumonia*, gram-negative bacteria and non-pneumococcal streptococci were responsible for 26
198 (32%), 20 (24%), 24 (29%) and 12 (15%) episodes, respectively.

199 ECMO was deployed very early (1.1 ± 0.9 days) after shock onset (table 1). ECMO patients
200 had profound myocardial dysfunction and severe lactic acidemia despite very high doses of
201 catecholamines and aggressive fluid therapy. Most patients had developed severe multiple organ
202 failure as indicated by high simplified acute physiology scores (SAPS-II) (78 ± 16 , 91% predicted
203 mortality) and SOFA (17 ± 3) scores. Eleven (13%) patients had cardiac arrest before implantation.
204 All VA-ECMO were implanted at the bedside using femoro-femoral cannulation, except for two

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
208 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
222 for mortality 0.54, 95%CI [0.40-0.70], $p<0.0001$ between groups) (figure 2). The difference in
223 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], $p=0.0029$,
225 table 1 and figure 2). The relative risk for 90-day mortality was 0.47 [95% CI 0.34-0.65; $p<0.0001$]
226 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
228 dying very early in the 24 hours after inclusion led to comparable results, as well as adjusting for the

229 site of infection, year of inclusion, time of inclusion after the onset of sepsis (see Appendix for
230 details, 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 15.26 ± 44.3 $\mu\text{g/L}$ for troponin I (38
236 patients), and 518.0 ± 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 ± 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**

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

254 aneurysms. Eleven local complications necessitated subsequent surgical treatment. Of the 64 patients
255 included at La Pitié-Salpêtrière hospital, 35 (55%) survived and one-year health-related quality of
256 life was obtained for 32 of these patients. They reported mild impairment in physical activities, and
257 highly preserved mental and social conditions. Their SF-36 component scores were comparable or
258 better than those reported for patients on chronic dialysis or after myocardial infarction (Appendix
259 figure 7) at one year. Anxiety, depression and post-traumatic stress disorder symptoms were reported
260 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.

272 Our study has a number of strengths including the fact that it was conducted in high-volume,
273 multi-national and experienced academic ECMO centres. However, our study also has clear
274 limitations. The major limitation is that the study was not randomized, and thus is open to potential
275 biases. While conducting a randomized trial would have been ideal, it would be logistically very
276 difficult if not impossible to conduct. There would be a very narrow window for enrolling these
277 medically complex, desperately ill patients. In addition, the lack of clinical equipoise at experienced
278 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
281 weighting to control for known confounders, as well as performing a number of sensitivity analyses.
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
285 comparable prognosis as compared with infections at most other sites.^{23,24} Accordingly the site of
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
293 65% of patients.^{3,4} Many mechanisms are thought to be responsible for this dysfunction including
294 mitochondrial dysfunction, capillary leak, excessive release of inflammatory cytokines, nitric oxide,
295 free radicals,^{4,25} and catecholamine-induced cardiomyopathy.^{26,27} Adult patients developing severe
296 myocardial dysfunction in the context of sepsis have a dismal prognosis.^{3,5,6,28} In 1989, Parker *et al.*
297 described that 11 of 21 non-survivors during sepsis died with a cardiogenic shock-like profile.³ In 25
298 patients receiving vasopressors for more than 48 hours, Poelaert *et al.* reported a survival rate of only
299 17% for patients with LVEF <40%.⁵ Irrespective of myocardial function, the level of administered
300 catecholamines strongly correlated with mortality in previous sepsis studies, with mortality rates
301 >90% in patients with inotrope scores >100 µg/kg/min.^{29,30} We found that 13% (130/990) of the
302 patients in recent cohorts of septic shock who met our criteria for sepsis-induced severe cardiogenic
303 shock had a survival of only 25%.^{2,15} In this context, VA-ECMO may halt the vicious cycle leading

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
306 was associated with survival rates ranging from 50 to 75%,^{7,8} leading to this therapy being
307 recommended in pediatric guidelines.⁸ Interestingly, very recent data also suggest that VA-ECMO
308 may be able to reverse the dismal course of cardiogenic shock in acute myocardial infarction
309 patients,³¹⁻³⁴ a situation that shares many pathophysiological features with sepsis-induced
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-
314 ECMO.⁹⁻¹⁴ In one series of 52 patients, only 15% survived to hospital discharge.⁹ Most of these
315 patients had preserved myocardial function (median LVEF 56%).⁹ Other recent cohorts also reported
316 very low survival rates (7-25%) for VA-ECMO patients with unselected hemodynamic profiles (i.e.
317 mostly circulatory failure due to refractory vasoplegia with low systemic vascular resistance)^{11,12} or
318 ECMO implanted under CPR.¹⁰ In contrast, the Pitié-Salpêtrière group published data on a cohort of
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
322 home.¹³ Similarly, encouraging results were recently published in a small series of 12 patients who
323 received veno-arteriovenous ECMO for severe myocardial dysfunction.¹⁴

324 In conclusion, this multi-centre, multi-national study suggests that in patients with sepsis-
325 induced refractory cardiogenic shock, VA-ECMO may be associated with an improvement in
326 survival compared with controls not receiving ECMO. The results need to be interpreted carefully
327 because unmeasured confounders and referral biases of the highly selected group may have persisted
328 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:**

334

335 NB, AK, JD, CA, SM, MS, GL, GH, EF, EZ, DB, BL, PA, AC were involved in data generation.

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.

340

341 **Disclosures**

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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		p-value	Propensity-weighted patients		ASD
	ECMO (n=82)	Non ECMO (n=130)		ECMO (n=82)	Non ECMO (n=130)	
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)	1.2 (1.1)	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)	1.1 (1.4)	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 ²	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 ₂ :FiO ₂	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; PaO₂:FiO₂ 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 ≤ 3 L/min/m² or LVEF $\leq 35\%$) + (inotrope score ≥ 75 $\mu\text{g/kg/min}$ or serum lactate ≥ 4 mmol/L); with inotrope score ($\mu\text{g/kg/min}$) = dobutamine dose ($\mu\text{g/kg/min}$) + (epinephrine dose [$\mu\text{g/kg/min}$] + norepinephrine dose [$\mu\text{g/kg/min}$]) x 100; no other inotrope or vasopressor were used in both ECMO and non-ECMO patients.¹³ † 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 ≥ 2 (plasma creatinine level > 1.9 mg/dl [168 $\mu\text{mol/L}$] or urinary output < 500 ml/day).

Table 2: Outcomes of ECMO-assisted patients

	All (n=82)	Survivors (n=49)	Non survivors (n=33)	p
ECMO decannulation	61 (74)	49 (100)	12 (36)	<0.0001
ECMO duration, d	5.8 (5.6)	6.2 (6.1)	5.2 (4.7)	0.3874
SOFA score at day 3	16.9 (2.7)	16.4 (2.8)	18.0 (2.3)	0.0276
SOFA score at day 7	14.1 (4.1)	13.2 (3.7)	16.6 (4.3)	0.0033
SOFA score at day 15	8.5 (4.9)	7.5 (4.4)	13.7 (4.4)	0.0010
MV duration, d	26.1 (22.6)	34.1 (23.6)	14.2 (14.7)	<0.0001
RRT	71 (86)	42 (86)	29 (88)	1.0000
RRT duration, d	16.4 (16.2)	20.7 (17.7)	10.3 (11.5)	0.0034
Patients transfused	72 (88)	44 (90)	28 (85)	0.8706
Major bleeding*	39 (47)	26 (53)	13 (39)	0.2641
# of packed red cells	8.6 (9.4)	8.4 (7.8)	8.8 (11.6)	0.5115
Major amputation	12 (15)	11 (22)	1 (3)	0.0118
ECMO-related complication	35 (43)	22 (45)	13 (39)	0.6554
Insertion site hemorrhage	17 (21)	12 (24)	5 (15)	0.4055
Insertion site infection	17 (21)	11 (22)	6 (18)	0.7833
ECMO-related bacteremia	10 (12)	6 (12)	4 (12)	1.0000
Critical limb ischemia	4 (5)	3 (6)	1 (3)	0.6450
Major amputation†	2 (2)	2 (4)	0	0.5131
Hemolysis	7 (8)	4 (8)	3 (9)	1.0000
Pulmonary edema	1 (1)	0	1 (3)	0.4024
ICU survival	49 (60)	47 (96)	2 (6)	<0.0001
ICU stay, d	30.4 (25.0)	41.3 (24.8)	14.5 (14.7)	<0.0001
Hospital stay, d	44.8 (34.7)	67.7 (27.5)	15.0 (14.5)	<0.0001

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

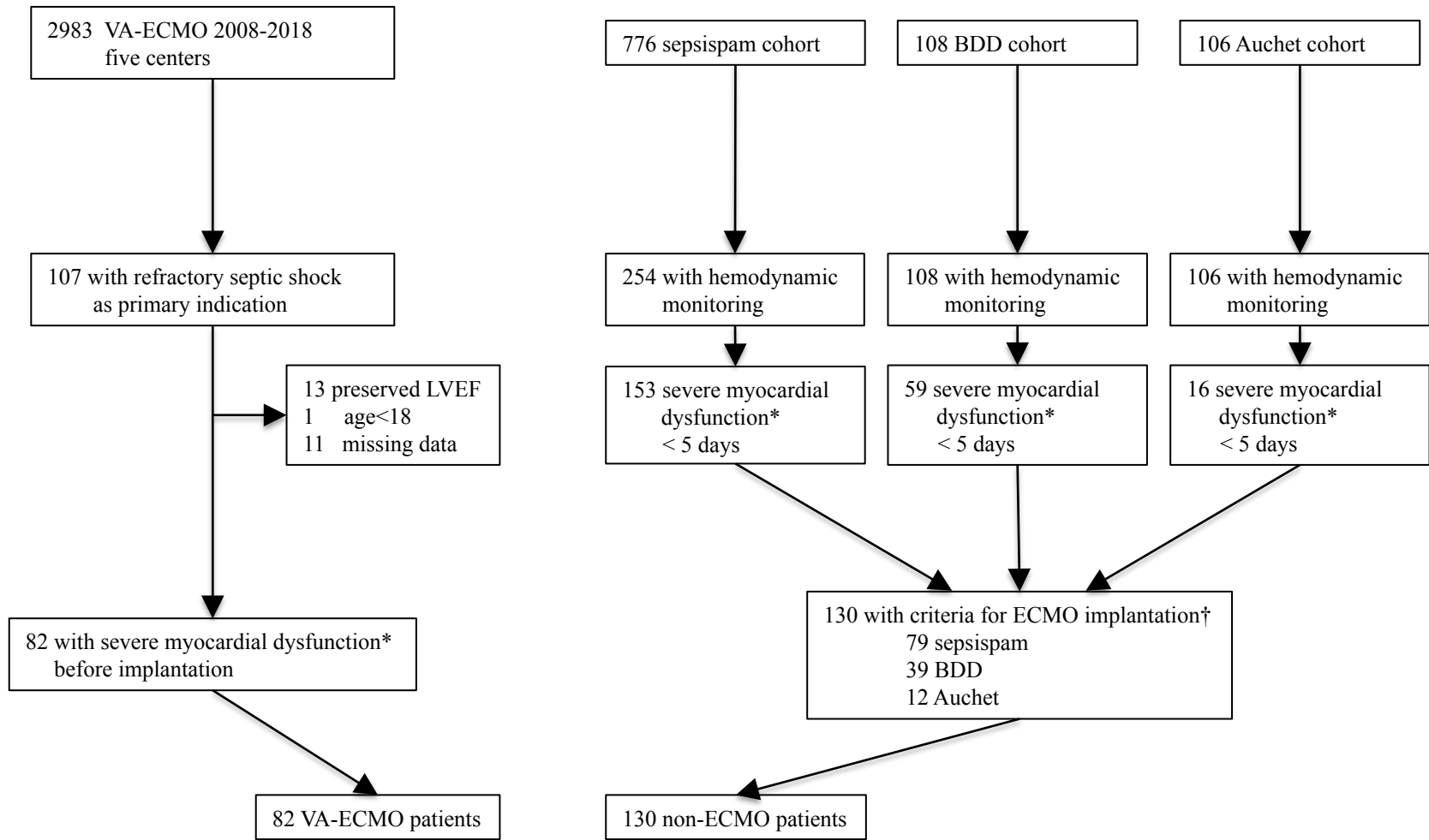
*Cardiac index ≤ 3 L/min/m² or LVEF $\leq 35\%$. † Severe myocardial dysfunction (cardiac index ≤ 3 L/min/m² or LVEF $\leq 35\%$) + severe hemodynamic compromise (inotrope score ≥ 75 $\mu\text{g/kg/min}$ or lactatemia ≥ 4 mmol/L), with inotrope score ($\mu\text{g/kg/min}$) = dobutamine dose ($\mu\text{g/kg/min}$) + (epinephrine dose [$\mu\text{g/kg/min}$] + norepinephrine dose [$\mu\text{g/kg/min}$]) x 100.¹³ ECMO = extracorporeal membrane oxygenation; LVEF= left ventricular ejection fraction; VA-ECMO = veno-arterial ECMO.

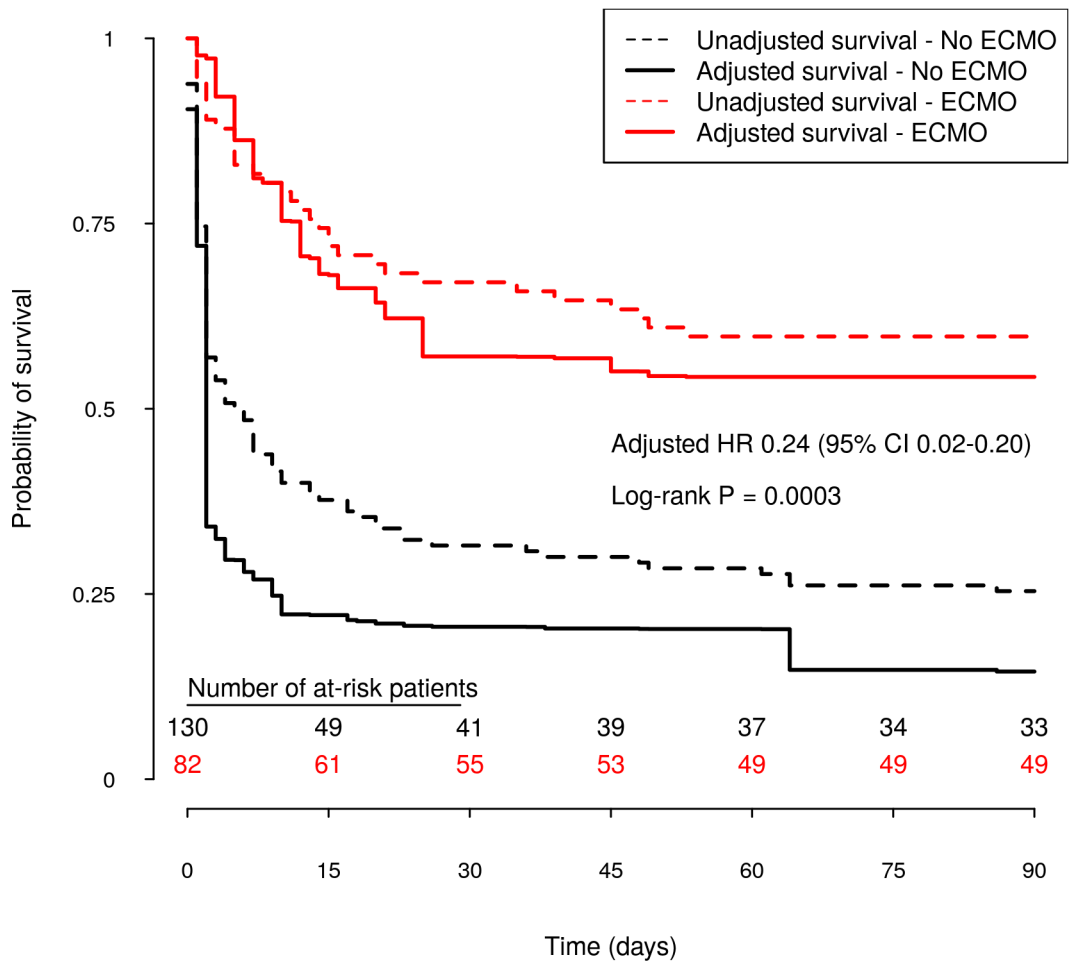
Figure 2: Kaplan-Meier survival estimates of ECMO and non-ECMO patients, unadjusted and propensity-weighted for 1) co-variables associated with the level of myocardial dysfunction

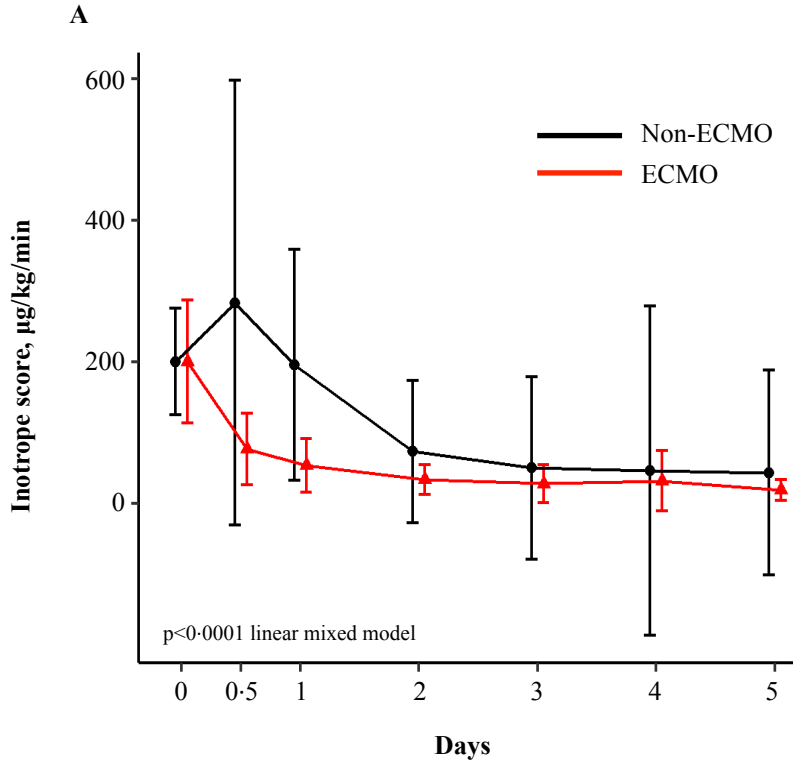
(cardiac index), 2) co-variables associated with survival during septic shock (inotrope score, lactatemia, Sequential Organ Failure Assessment (SOFA) score, age, immunocompromised status, and cumulative fluid therapy before inclusion) and 3) delay between shock onset and inclusion. ECMO = extracorporeal 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 \pm 95% CI is shown for each time point. Inotrope score ($\mu\text{g/kg/min}$) = dobutamine dose ($\mu\text{g/kg/min}$) + (epinephrine dose [$\mu\text{g/kg/min}$] + norepinephrine dose [$\mu\text{g/kg/min}$]) x 100.¹³ ECMO = extracorporeal membrane oxygenation.

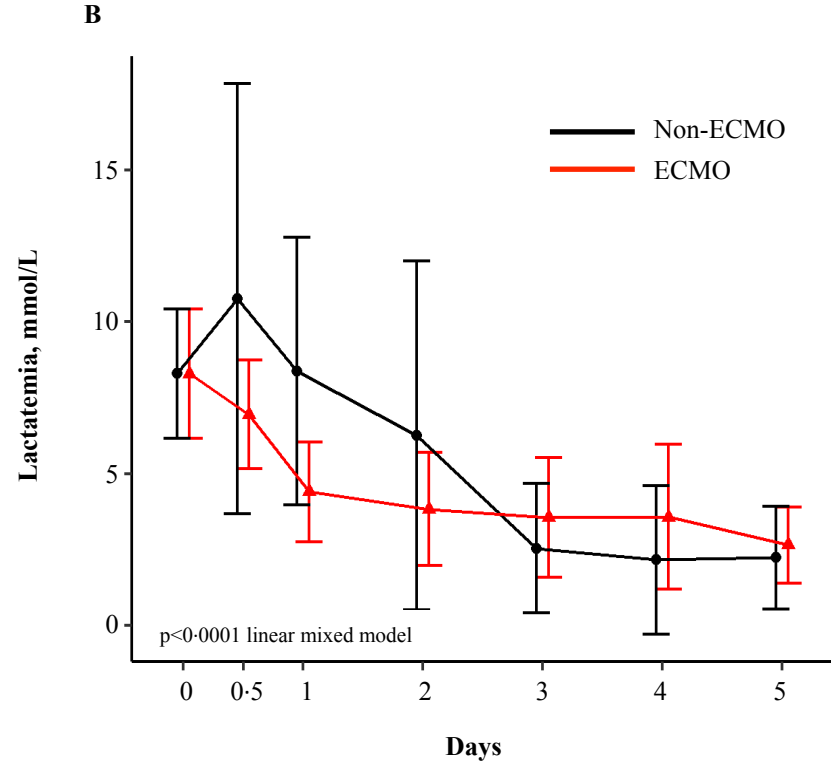






No. at risk

Non-ECMO	130	129	127	94	74	70	65
ECMO	82	81	77	73	72	72	68



No. at risk

Non-ECMO	130	129	127	94	74	70	65
ECMO	82	81	77	73	72	72	68