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## **A time-dependent propensity score matching approach to assess epinephrine use on patients survival within out-of-hospital cardiac arrest care**

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### **Declarations of competing Interest**

None.

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1 **A time-dependent propensity score matching approach to assess epinephrine use on**  
2 **patients survival within out-of-hospital cardiac arrest care**

3 **Abstract**

4 **Background:** Epinephrine effectiveness and safety are still questioned. It is well-known  
5 **that the effect of epinephrine varies depending of patients' rhythm and of time to**  
6 **injection.**

7 **Objectives:** We aimed to assess the association between epinephrine use during out-of-  
8 **hospital cardiac arrest (OHCA) care and patient D30 survival.**

9 **Methods:** Between 2011 and 2017, 27,008 OHCA patients were included from the French  
10 **OHCA registry. We adjusted populations using a time-dependent propensity score**  
11 **matching. Analyses were stratified according to patient's first rhythm. After matching,**  
12 **2,837 pairs of patients with a shockable rhythm were created and 20,950 with a**  
13 **nonshockable rhythm.**

14 **Results:** Whatever the patients' rhythm (shockable or nonshockable), epinephrine use  
15 **was associated with less D30 survival (respectively: OR=0.508 [0.440; 0.586] and**  
16 **OR=0.645 [0.549;0.759]). In shockable rhythms, on all outcomes, epinephrine use was**  
17 **deleterious. In nonshockable rhythms, no difference was observed regarding ROSC and**  
18 **survival at the hospital admission. However, epinephrine use was associated with worse**  
19 **neurological prognosis (OR=0.646 [0.549;0.759]).**

20 **Conclusions:** In shockable and nonshockable rhythms populations, epinephrine does not  
21 **seem to have any benefit on D30 survival. These results underscore the need to perform**  
22 **further studies to define the optimal conditions for using epinephrine in patients with**  
23 **OHCA.**

24 **Keywords**

25 **Out-of-hospital Cardiac Arrest, epinephrine, resuscitation, time-dependent propensity score**

26

27

## 28 INTRODUCTION

29 Out-of-hospital cardiac arrest (OHCA) is a major public health issue. In France, 46,000 cardiac  
30 arrests occur each year (1,2). Furthermore, survival rates are dramatically low. Only 5% of  
31 victims survive 30 days after the onset of cardiac arrest, and of them, 85% survive with few or  
32 no neurological sequelae (3).

33 To improve care practices and survival rates, the International Liaison Committee On  
34 Resuscitation (ILCOR) generates guidelines and defines drug strategies for OHCA care (4). These  
35 strategies include the epinephrine use for patients who suffer an OHCA. The most recent  
36 guidelines update (2015) advises a standard dose of 1 mg every 3 to 5 minutes of resuscitation  
37 (5). The advice to use epinephrine was never withdrawn, even if evidence of its effectiveness is  
38 not yet conclusive in the literature, as highlighted by the ILCOR (6). Several non-adjusted studies  
39 assessing epinephrine effectiveness exist (7-9). These studies have biases that could be avoided  
40 by performing prospective randomized controlled trials, but these designs are difficult to  
41 implement. As an example, the study by Jacobs *et al.* (10) experienced methodological problems,  
42 as they excluded 67.11% of patients after randomization. In addition, Olasveengen *et al.* (11)  
43 compared patients who benefited from intravenous cannulation (including epinephrine and  
44 other drugs) with patients who did not benefit from such cannulation, so that study did not focus  
45 on the use of epinephrine. Finally, we can only rely on a recent reliable randomized study  
46 (PARAMEDIC2) (12). Other recent studies used propensity score matching to be as close as  
47 possible to a randomized controlled trial, but their results are conflicting (13-15).

48 We assume that the effectiveness of the use of epinephrine in OHCA is not constant and may  
49 vary according to the initial rhythm (13) and to the injection time (16,17). On the French  
50 national Cardiac Arrest Registry (RéAC) (3), the aim of our study was to assess the associations  
51 between the use of epinephrine and patient survival and neurological outcomes in patients with  
52 OHCA in the real-world setting (according to their first recorded rhythm, shockable or  
53 nonshockable) using a time-dependent propensity score matching.

## 54 MATERIAL AND METHODS

### 55 *Ethics approval and consent to participate*

56 This study was approved by the French Advisory Committee on Information Processing in  
57 Material Research in the Field of Health (“Comité Consultatif sur le Traitement de l’Information  
58 en Matière de Recherche dans le Domaine de la Santé”: CCTIRS) and by the French National Data  
59 Protection Commission (“Commission Nationale de l’Informatique et des Libertés”: CNIL;  
60 authorization number 910946).

61

### 62 *Study design*

63 In France, the prehospital emergency medical system is a two-tiered system with a fire  
64 department ambulance available for providing a first response and basic life support (BLS) and a  
65 mobile emergency and resuscitation service (MERS) including a mobile medical team (MMT) for  
66 advanced cardiac life support (ACLS) (18). Medical dispatch centers are responsible for out-of-  
67 hospital emergency coordination. All MERSs use a specific RéAC recording form during OHCA  
68 interventions to enter patient data, times, care, and immediate survival status. The RéAC form  
69 meets the requirements of the French Emergency Medical System (EMS) organizations and is  
70 structured according to the universal Utstein style (3,19). Data are reported in the RéAC secure  
71 database ([www.registreac.org](http://www.registreac.org)). A 30-day follow-up data collection after the onset of the OHCA  
72 or at the time of hospital discharge is performed and entered into the database.

### 73 *Study population and data*

74 Our comparative, multicenter study used data from the RéAC. Data were collected between July  
75 1, 2011, and December 31, 2017.

### 76 *Inclusion criteria*

- 77 - medical OHCA according to the Utstein template (19)
- 78 - patients aged 18 or older



79 - patients in whom ACLS was attempted.

#### 80 *Exclusion criteria*

81 - physical indications of death (*rigor mortis*)

82 - files lacking data for mandatory criteria (Utstein core data)

83 - for patients who had epinephrine during their care: files lacking data for the time  
84 between OHCA and the epinephrine injection (if the RéAC investigator did not recorded  
85 the time of the first epinephrine injection during the intervention)

86 - files lacking data for the time between T0 (first call) and the time of death

87 - time between call (T0) and MMT arrival longer than 60 minutes

88 - patients with a return of spontaneous circulation (ROSC) before MMT arrival

89 - patients with a known Do Not Attempt Resuscitation (DNAR) order.

90 The data collected included baseline clinical characteristics, times, history, bystander BLS, first  
91 aid provider BLS, first rhythm recorded by the MMT, ACLS, prehospital treatment, patient  
92 transport, and admission parameters. Thirty-day follow-up data included patient vital status and  
93 neurological outcome.

#### 94 *Endpoints*

95 The primary endpoint was patient survival D30, it corresponded to the patient follow up 30 days  
96 after the OHCA, at the patient death or at hospital discharge. The secondary endpoints were the  
97 ROSC, the survival at hospital admission (D0) and the neurological outcome at 30 days post-  
98 OHCA or hospital discharge assessed by the Cerebral Performance Category score (CPC) for alive  
99 patients (20).

#### 100 *Statistical analysis*

101 First, we described and compared two cohorts of patients. Patients who received epinephrine  
102 were compared with patients who did not. We stratified the results according to the first patient  
103 rhythm recorded by the MMT (shockable or nonshockable).

104 Second, we compared the populations' survival rates according to the primary and secondary  
105 endpoints after matching both populations (epinephrine vs. no epinephrine). As the risk of  
106 receiving epinephrine varies over time, we considered that a patient receiving epinephrine at a  
107 time  $t$  cannot be part of the same group as a patient receiving epinephrine at time  $t+k$  minutes.  
108 Hence, we performed a time-dependent propensity score matching per stratified group (21–23).

#### 109 *Description and comparison of cohorts*

110 The quantitative variables are described as medians and first and third quartiles [Q1; Q3]. The  
111 qualitative variables are described as frequencies. Bivariate analysis were assessed using the  
112 Pearson Chi-Square test for categorical variables and the non-parametric Wilcoxon rank test for  
113 continuous variables. The level of significance was set at a p-value  $<0.05$ .

114

#### 115 *Estimation of the time-dependent propensity score*

116 We estimated the effect of time to injection based on a Cox proportional hazard regression  
117 model. We considered as censored; the deceased patients who did not receive epinephrine and  
118 patients arriving alive at the hospital. For alive patients at the hospital, the censor time was the  
119 arrival time when available or the ROSC. We included 13 covariates in the model: year of OHCA,  
120 patients' age, patients' sex, bystander presence, type of bystander, OHCA cause, immediate CPR,  
121 during BLS: chest compressions, ventilation, shock by AED; defibrillator shock by MMT,  
122 intubation and time between T0 (first call) and MMT arrival. A quadratic effect was used on the  
123 age. We tested proportional hazards assumption for each covariate using a chi-squared test on  
124 the Schoenfeld's residuals (24). We observed that the ratio of the hazards were not constant  
125 over time for type of bystander ( $p=0.0009$ ) and time from T0 to MMT arrival ( $p<0.0001$ ) in the  
126 group of shockable rhythm, and for type of bystander ( $p=0.0001$ ), immediate CPR ( $p=0.0195$ )  
127 and time from T0 to MMT arrival ( $p<0.0001$ ) in the group of nonshockable rhythm. These  
128 covariates were considered as time dependent with a step function (25) about 5-minute time

129 intervals. The covariates that verified the assumption of proportional risk hazards were selected  
130 in the models as time constant. After time stratification, the global test on Schoenfeld's residuals  
131 was not significant for the shockable rhythm ( $p=0.9914$ ) and the nonshockable rhythm  
132 ( $p=0.8380$ ). Finally, we estimated the time dependent propensity score as the linear predictor  
133 for each patient at  $t$  time down to the minute.

134

### 135 *Matching method*

136 Sequential matching of patients was performed between 0 and 65 minutes. The 65-minute  
137 threshold corresponded to the quantile at 98% of the time before injection of epinephrine in the  
138 overall population. The matching distance used was the nearest neighbor with replacement,  
139 within a caliper of 10% of the standard deviation.

140 In the shockable population, 2,837 patients receiving epinephrine at time  $t$  were matched to  
141 2,837 control patients corresponding to 1,055 patients that did not received epinephrine and  
142 1,782 patients receiving epinephrine later. Of those 1,782 patients, 1,262 received epinephrine  
143 within 10 minutes after the case and 520 at least 10 minutes later and up to 119 minutes later.  
144 Among the control group, 2,131 patients were matched several times with 9 duplicate cases  
145 maximum for 9 control patients.

146 In the nonshockable population, 20,950 patients receiving epinephrine at time  $t$  were matched  
147 to 20,950 control patients corresponding to 5,509 patients that did not received epinephrine  
148 and 15,441 patients receiving epinephrine later. Of those 15,441 patients, 10,918 received  
149 epinephrine within 10 minutes after and 4,522 at least 10 minutes later and up to 619 minutes  
150 later. Among the control group, 16,055 patients were matched several times with 13 duplicate  
151 cases maximum for 39 control patients.

152

153 *Quality of matching*

154 We measured the matching quality with the weighted standardized mean difference  
155 (Supplementary figure 1 and 2). The time between T0 and the MMT arrival was unbalanced after  
156 pairing. In the group of shockable rhythm, the difference was greater than the 10% threshold. In  
157 practice, the matching was considered satisfying as the average delay was 22.55 minutes for  
158 cases vs 21.16 minutes for control and the standardized difference about 12.6%.

159

160 *Conditional weighted logistic regression*

161 We performed a logistic regression for non-adjusted Odds Ratios (OR) and a conditional  
162 weighted logistic regression (26) based on matching pairs for adjusted OR. We supplied 95%  
163 confidence interval in both cases.

164

165 Statistical analysis were performed using R 3.5.1 software, with the “survival” package (27) for  
166 developing time dependent propensity score algorithms and fitting a conditional logistic  
167 regression. The “MatchIt” package (28) for sequential matching. The “tableone” package (29) to  
168 compute the standardized differences before and after matching.

169

170 **RESULTS**

171 *Unadjusted population*

172 *Study participants*

173

174 Between July 1, 2011, and December 31, 2017, we identified 81,780 patients with OHCAs during  
175 the study period (Fig. 1), of whom 27,008 met the inclusion criteria of the study. An epinephrine

176 injection was administered to 90.0% of the patients. A shockable rhythm was found in 3,448  
177 patients and a nonshockable rhythm in 23,560 patients.

#### 178 *Description of the studied population*

179 Our studied population was mainly male (68.9%), and the median age was 68. A bystander was  
180 present at the onset of the OHCA in 73.1% of cases. The first recorded rhythm by MMT was  
181 nonshockable in 87.2% of patients. A ROSC occurred in 28.5% of patients, and 22.7% of patients  
182 were admitted to the hospital alive. Thirty days after the OHCA, 5.1% of the patients were alive,  
183 and among them, 72.9% had a good neurological outcome. The detailed results are presented in  
184 Table 1.

#### 185 *Comparison between the epinephrine and no epinephrine groups in the studied population*

186 We observed significant differences for almost every descriptive criterion between our two  
187 groups, except the presence of a bystander and a shock delivered during BLS (Table 1).  
188 At 30 days, a lower survival rate was observed when epinephrine was used (3.5% vs. 19.3%,  $P <$   
189  $0.001$ ). The ROSC rate was not different between our two groups (28.5% vs. 28.3%,  $P = 0.898$ ),  
190 whereas the survival rate at the time of hospital admission was higher in the no epinephrine  
191 group than in the epinephrine group (22.2% vs. 27.2%,  $P < 0.001$ ). At 30 days, we recorded a  
192 worse neurological outcome in the epinephrine group than in the no epinephrine group (65.3%  
193 vs. 85.3%,  $P < 0.001$ ) (Table 1).

#### 194 *Comparison between epinephrine and no epinephrine groups in patients with shockable rhythms*

195 Epinephrine was used in 83.5% of patients who had a shockable rhythm at the time of MMT  
196 arrival (VF/pulseless VT). When epinephrine was injected, the population was significantly,  
197 older, more likely to be male, with less bystander presence, the bystander was more a family  
198 member. During ACLS, in the epinephrine population we observed significantly more shock and  
199 the time from call (T0) to ROSC or death was longer. Regarding survival at 30 days, lower rate

200 was observed in the epinephrine group (15.1 vs. 69.1,  $P < .001$ ). All other survival rates (ROSC  
201 and hospital admission) and good neurological outcome rates were significantly lower in the  
202 epinephrine group (Table 2).

203 *Comparison between epinephrine and no epinephrine groups in patients with nonshockable*  
204 *rhythms*

205 Among patients in whom the initial rhythm on MMT arrival was not shockable, in the  
206 epinephrine group the population was older and more often male, with more bystander  
207 presence and OHCA etiology was more cardiac. The time from the call to ROSC or death was  
208 longer in the epinephrine group than in the no epinephrine group. The MMT delivered a shock  
209 four times more often in the epinephrine group than in the no epinephrine group.

210 The D30 survival was lower in the epinephrine group (2.0 vs. 6.2,  $P < .001$ ). Rates of ROSC and  
211 survival at hospital admission were higher in the epinephrine group than in the no epinephrine  
212 group. However, the rate of good neurological outcome was significantly lower in the  
213 epinephrine group (Table 2).

214

215 *Adjusted population*

216 *Comparison when the initial rhythm was shockable*

217 On D30 survival we observed significantly less survival in the epinephrine group compared to  
218 the no epinephrine group on unadjusted results (OR = 0.080 [0.065;0.098]). Less D30 survival  
219 was also observed in the epinephrine group compared to controls in the matched populations  
220 (OR = 0.508 [0.440;0.586]). On all other secondary outcomes, regardless whether of populations  
221 were matched, epinephrine was always associated with less survival and worse neurological  
222 outcome (Fig. 2).

223 *Comparison when the initial rhythm was nonshockable*

224 Regardless of whether the population was adjusted, epinephrine use was associated with a  
225 lower survival rate at 30 days compared to the no epinephrine group for unadjusted results and  
226 to controls for adjusted results (OR (unadjusted)=0.307 [0.251;0.375] and OR (adjusted)=0.645  
227 [0.549;0.759]). On non-adjusted results, epinephrine was associated with more ROSC and D0  
228 survival. By comparing the epinephrine group with controls on adjusted results, no difference  
229 was observed on ROSC and D0 survival (respectively: OR = 1.048 [0.997;1.101] and OR = 1.037  
230 [0.980;1.098]). Regarding good neurological outcome at D30, in non-adjusted and adjusted  
231 results, epinephrine was significantly associated with lower rates (respectively: OR = 2.163  
232 [1.908;2.452] and OR = 1.048 [0.997; 1.101]) (Fig. 3).

233 **DISCUSSION**

234 Our study was performed with a large cohort of OHCA patients and based on a time-dependent  
235 propensity score-matched analysis. This methodology enabled us to assess the link between  
236 epinephrine use and survival in the real-world setting by limiting the inherent bias of the impact  
237 of time to injection on patient survival. Regarding survival, in both groups with nonshockable  
238 rhythms or with shockable rhythms, we observed that the epinephrine use was associated with  
239 a decrease in 30-day survival compared to controls. Some other studies have also highlighted  
240 negative impacts of epinephrine on 30-day survival (9,15,30), while others did not (7,12,13).  
241 However, previous findings did not support robust conclusions regarding the efficacy of  
242 epinephrine due to methodological issues (10,11) or conflicting results (13–15).  
243 In our adjusted analysis, epinephrine use was never associated with a better outcome. We  
244 always observed deleterious effects of epinephrine 30 days after OHCA. The results regarding  
245 D30 survival are in agreement with those of the studies by Hagihara *et al.* (15) and Olasveengen  
246 *et al.* (11). Those studies also found deleterious effects of epinephrine 30 days after the OHCA. In  
247 the Olasveengen *et al.* study, they reported a 48% lower change of survival when epinephrine  
248 was injected than when epinephrine was not injected (11). However, some recent studies noted

249 results that conflicted with ours. The Perkins *et al.*(12), Holmberg *et al* (31) and Finn *et al.* (32)  
250 studies observed a better 30-day survival among patients who received epinephrine than among  
251 those who did not receive epinephrine. However, they did not notice any difference in  
252 neurological outcomes.

253 If we focus on shockable rhythms, in our study, a deleterious effect of epinephrine use is evident  
254 for all endpoints (ROSC, D0 survival, 30-day survival, and neurological outcome) in the adjusted  
255 population. In general, other studies' results conflicted with ours (7,8,13). For example,  
256 Nakahara *et al* .who also used a time-dependent propensity score matching found a positive  
257 impact of epinephrine on 30-day survival but no significant difference with regard to the  
258 neurological outcome (13). In the recent randomized Perkins *et al.* study, in shockable rhythms,  
259 they observed a better rate of ROSC and survival at the hospital admission in the epinephrine  
260 group. However, they did not highlighted any significant difference regarding survival and  
261 neurological outcome 30 days after the OHCA when epinephrine was injected (33).

262 However, regarding patients with nonshockable rhythms, we observe more survival on  
263 unadjusted results regarding ROSC and D0 survival. However, on adjusted population, this  
264 beneficial effect became non-significant. Nevertheless, there was a negative association between  
265 epinephrine use and 30-day outcomes. In studies that investigated the subpopulation of patients  
266 with nonshockable rhythms, better short-term survival was largely observed among those who  
267 received epinephrine than among those who did not (7,14,33). However, Goto *et al.* and Perkins  
268 *et al.* noticed an absence of significance regarding the difference in neurological outcomes  
269 between the two groups (7,33). Tomio *et al.* observed a better neurological outcome in their  
270 asystole group and no significant difference in their PEA group (14).

271 Our results may be explained by the pharmacology of epinephrine. The  $\alpha_1$  and  $\beta$  stimulation  
272 increases myocardial perfusion pressure. Hence, the higher rate of immediate survival in  
273 patients with nonshockable rhythms in unadjusted populations can at least partially be  
274 explained by these effects (34). However, the action of epinephrine has deleterious effects on  
275 mid-term survival and neurological outcomes (35,36) (myocardial dysfunction (37,38),



276 development of new arrhythmias (37,38), cerebral microcirculation impairment) (30,34,39).  
277 Our results related to mid-term survival can also be partially explained by these effects.  
278 Our study was based on reliable French national registry-based data. The RéAC registry  
279 provided an overview of real-life professional practices and conditions regarding OHCA (2). We  
280 used a validated time-dependent propensity-score matching method to reduce bias. Our study  
281 provided consistent results that bolstered the limited literature regarding the issue of  
282 epinephrine efficacy. In addition, we stratified our results according to the initial patient rhythm  
283 on MMT arrival. Guidelines regarding epinephrine use differ based on if the initial patient  
284 rhythm is shockable or not (20). Furthermore, some studies have suggested that the impact of  
285 epinephrine differs according to the initial rhythm identified (7,16). Hence, our results were not  
286 influenced by the time to epinephrine injection and the patient's rhythm.

#### 287 *Limitations*

288 Our study has some limitations. The first is linked to the use of the French National Cardiac  
289 Arrest Registry (RéAC), which is based on the voluntary participation of the MMT; the list of  
290 participating MMTs was not exhaustive during the study period. However, the participating  
291 MERS are spread over the entire French territory and provide an overview of guideline  
292 implementation. A further limitation concerns the epinephrine use; it was not randomly  
293 administered. To mimic as much as possible a randomized controlled study, we used time-  
294 dependent propensity score matching. The retrospective nature of this study is another  
295 limitation. However, the data were collected through the use of a standardized form. The last  
296 limitation is that we did not take into account differences in postresuscitation care that could  
297 influence D30 survival and neurological outcomes. However, other studies did not consider  
298 these in-hospital parameters either.

299 Our study was based on data from a national registry. The French emergency system is based on  
300 the “stay and play” model. Hence, our results are not fully generalizable to countries applying  
301 the “scoop and run” model (40). Additionally, the study population was predominantly

302 Caucasian and had specific characteristics that prevent us from generalizing our results to the  
303 whole world.

304

305 **CONCLUSIONS**

306 The currently recommended use of epinephrine does not seem to have any benefit on mid-term  
307 outcomes, regardless of the patients' initial rhythm and after adjustment for time imbalances.

308 Questions such as the optimal epinephrine dose or the association with other drugs still have to  
309 be investigated within the context of a global therapeutic strategy surrounding the use of  
310 epinephrine.

311

312

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- 437
- 438



439 ARTICLE SUMMARY

440 1. Why is this topic important?

441 Epinephrine is used for Out-of-Hospital cardiac arrest care since 1960's, nevertheless, its  
442 effectiveness is still questioned. Identify for which patients and how epinephrine is effective  
443 seems to be a priority.

444 2. What does this study attempt to show?

445 The objective of this study was to determine if epinephrine was effective for all patients  
446 (according to patients' cardiac rhythm) by taking into account the time of the injection.

447 3. What are the key findings?

448 We observed that epinephrine does not seem to improve patients' survival 30 days after their  
449 cardiac arrest. Further studies need to be carried out in order to find the optimal use of  
450 epinephrine.

451 4. How is patient care impacted?

452 Patients should be cared separately according to their cardiac rhythm. The optimal use of  
453 epinephrine should improve survival rates and limit neurological outcome.

454

455

456 **Legends to figures**

457 **Fig. 1** Flow chart

458 *OHCA: out-of-hospital cardiac arrest, DNAR: do not attempt resuscitation, MMT: mobile*  
459 *medical team, ROSC: return of spontaneous circulation, MERS: mobile emergency and*  
460 *resuscitation service*

461

462 **Fig. 2** Comparison of endpoints in shockable group

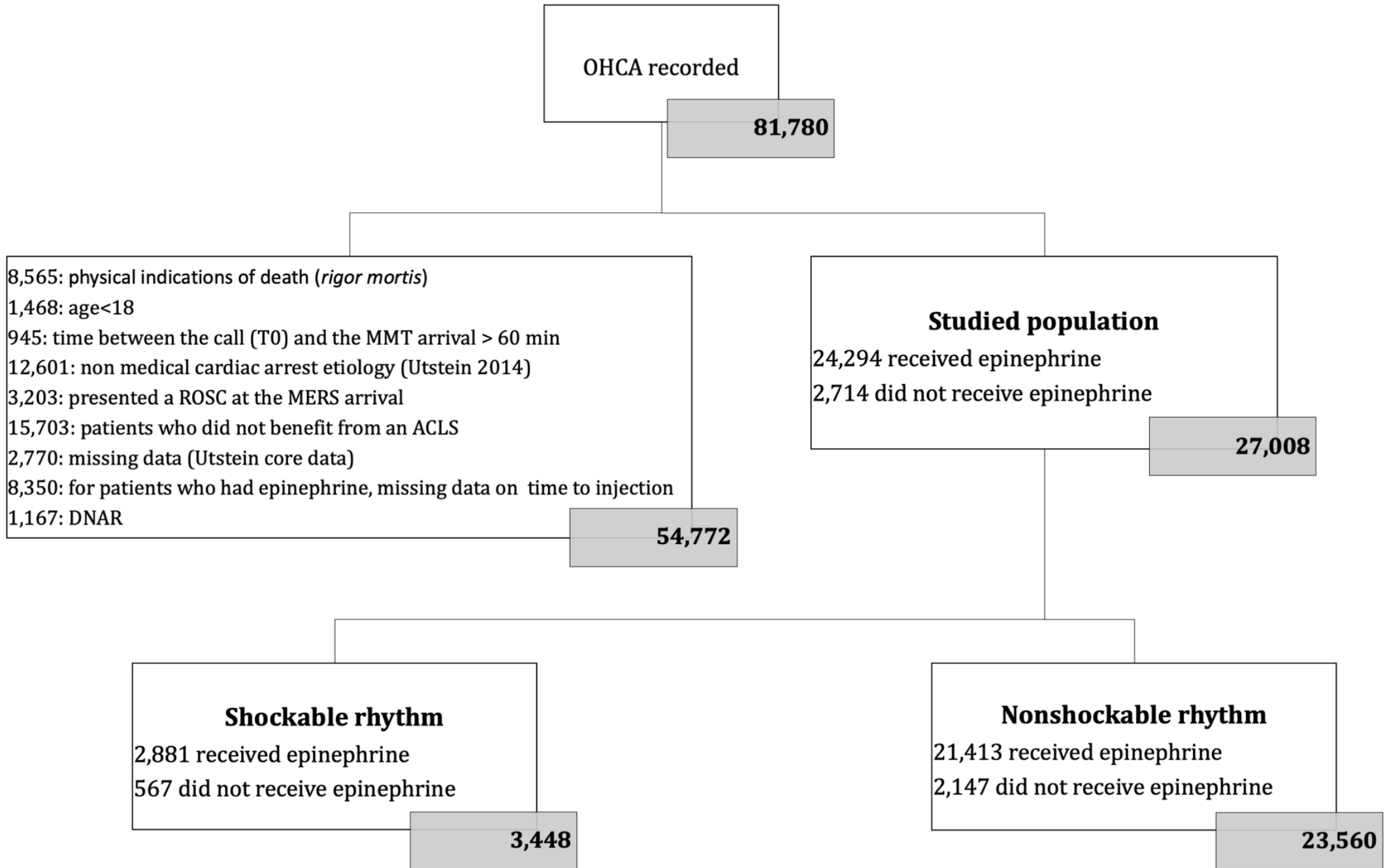
463 *ROSC: return of spontaneous circulation; D30: 30 days*

464

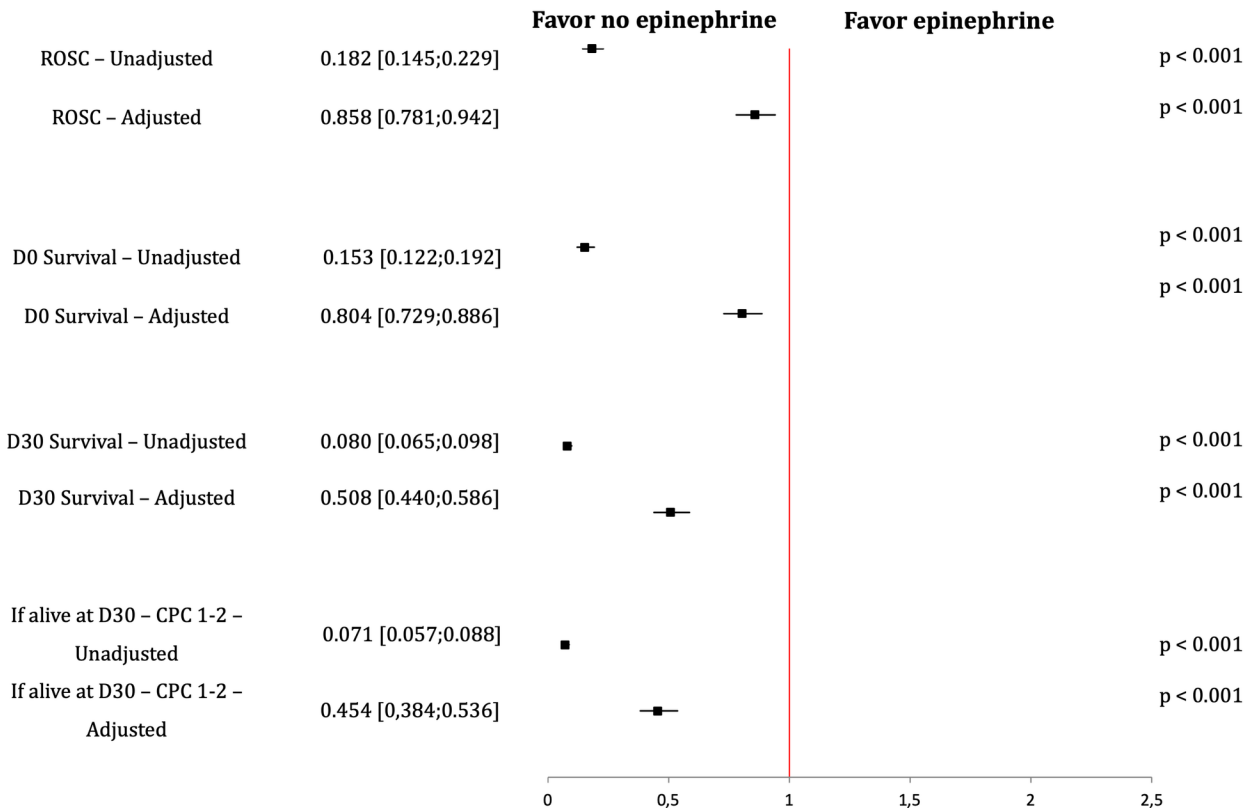
465 **Fig. 3** Comparison of endpoints in nonshockable group

466 *ROSC: return of spontaneous circulation; D30: 30 days*

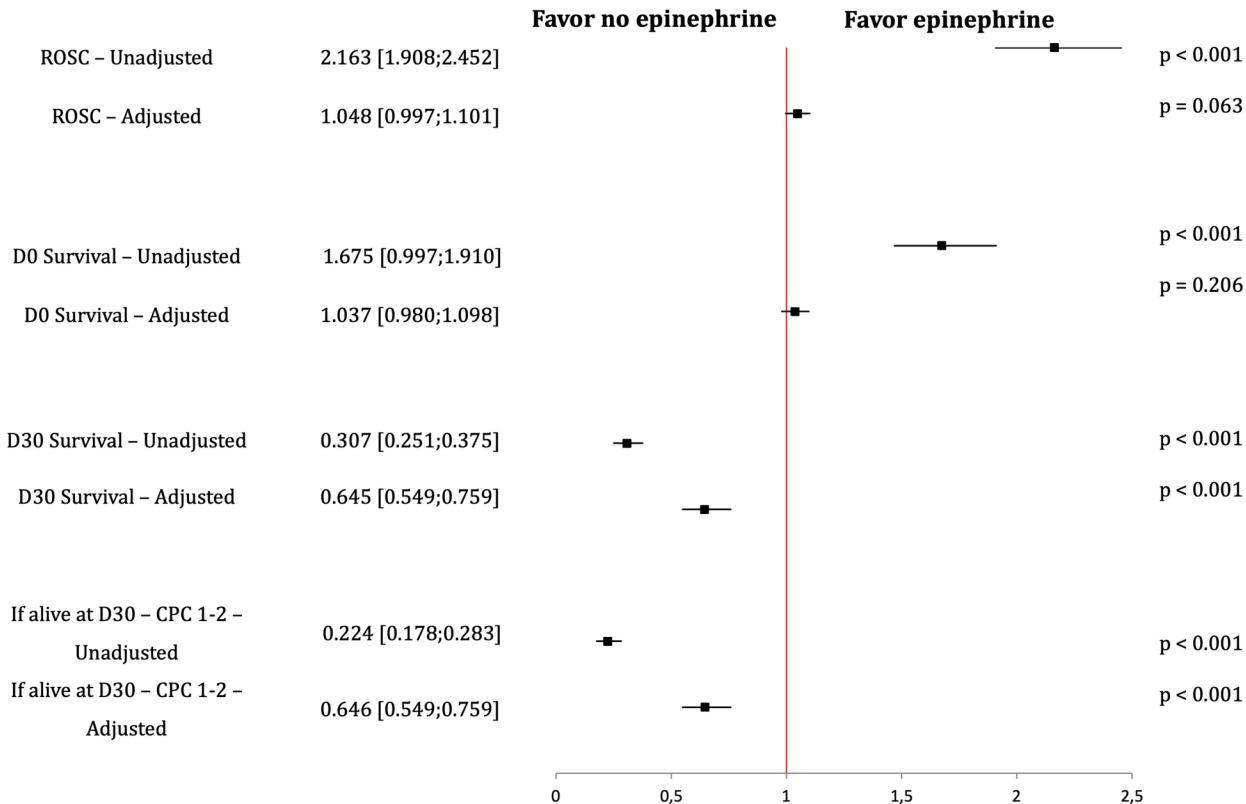
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Shockable rhythm – OR (95% CI)



Nonshockable rhythm – OR (95% CI)



**Table 1.** Population characteristics and global analysis<sup>a</sup>

Characteristics	Description Studied Population 27,008	Comparison		
		Epinephrine 24,294	No Epinephrine 2,714	<i>P</i>
Cases per year				
- 2011	349 (1.3)	326 (1.3)	23 (0.9)	<0.001
- 2012	2699 (10.0)	2421 (10.0)	278 (10.2)	
- 2013	5120 (19.0)	4585 (18.9)	535 (19.7)	
- 2014	5216 (19.3)	4655 (19.2)	561 (20.7)	
- 2015	5339 (19.8)	4896 (20.2)	443 (16.3)	
- 2016	4374 (16.2)	3965 (16.3)	409 (15.1)	
- 2017	3911 (14.5)	3446 (14.2)	465 (17.1)	
Age (years)	68 (57;78)	67 (56;78)	74 (60;84)	< 0.001
Gender (male)	18,613 (68.9)	16,931 (69.7)	1,682 (62.0)	< 0.001
Bystander presence	19,735 (73.1)	17,743 (73.0)	1,992 (73.4)	0.703
Type of bystander (% family)	16,863 (62.4)	15,287 (62.9)	1,576 (58.1)	< 0.001
OHCA etiology (% cardiac)	19,688 (72.9)	17,760 (73.1)	1,928 (71.0)	0.023
<b>BLS</b>				
- Immediate CPR	10,534 (39.0)	9,421 (38.8)	1,113 (41.0)	0.025
- Chest compressions	25,473 (94.3)	22,940 (94.4)	2,533 (93.3)	0.022
- Ventilation	23,112 (85.6)	20,839 (85.8)	2,273 (83.8)	0.005
- AED shock	5,190 (19.2)	4,682 (19.3)	508 (18.7)	0.503
<b>Times</b>				
- call (T0) to MMT arrival	19 (14;26)	19 (14;27)	19 (13;26)	0.032
- call (T0) to ROSC or death	47 (35;60)	48 (37;60)	35 (25;48)	< 0.001
<b>ACLS</b>				
Initial cardiac rhythm:				<0.001
- Asystole/PEA (shockable)	3,448 (12.8)	2,881 (11.9)	567 (20.9)	
- VF/pulseless VT (non-shockable)	23,560 (87.2)	21,413 (88.1)	2,147 (79.1)	
Defibrillator shock by MMT	6,749 (25.0)	6,206 (25.55)	543 (20.01)	< 0.001
Intubation	25,058 (92.8)	22,923 (94.36)	2,135 (78.67)	< 0.001
Insertion of an injection route	26,687 (98.8)	24,294 (100.00)	2,393 (88.17)	< 0.001
<b>Survival</b>				
- ROSC	7,686 (28.5)	6,917 (28.5)	769 (28.3)	0.898
- Vital status at hospital admission (alive)	6,138 (22.7)	5,399 (22.2)	739 (27.2)	< 0.001
- Vital status at D30 (alive)	1,382 (5.1)	858 (3.5)	524 (19.3)	< 0.001
- If alive, CPC 1-2 at 30 days <sup>b</sup>	1,007 (72.9)	560 (65.3)	447 (85.3)	< 0.001

OHCA: out-of-hospital cardiac arrest, BLS: basic life support, CPR: cardiopulmonary resuscitation, AED: automated external defibrillator, ACLS: advanced cardiac life support, MMT: mobile medical team, ROSC: return of spontaneous circulation, PEA: pulseless electrical activity, VF/pulseless VT: ventricular fibrillation/pulseless ventricular tachycardia, D30: day 30, CPC: cerebral performance categories.

<sup>a</sup>Data are expressed as frequencies. (%) for qualitative variables or median (Q1;Q3) for quantitative variables

<sup>b</sup>140 missing values

**Table 2** Comparison between epinephrine and no epinephrine according to cardiac rhythms<sup>a</sup>

	Shockable rhythm			Non-shockable rhythm		
	Epinephrine N = 2,881	No epinephrine N = 567	P	Epinephrine N = 21,413	No epinephrine N = 2,147	P
Cases per year						
2011	41 (1.4)	3 (0.5)		285 (1.3)	20 (0.9)	
2012	323 (11.2)	59 (10.4)		2,098 (9.8)	219 (10.2)	
2013	600 (20.8)	92 (16.2)		3,985 (18.6)	443 (20.6)	
2014	771 (19.8)	112 (19.8)	0.659	4,084 (19.1)	449 (20.9)	<0.001
2015	740 (18.7)	102 (18.0)		4,356 (20.3)	341 (15.9)	
2016	426 (14.8)	99 (17.5)		3,539 (16.5)	310 (14.4)	
2017	380 (13.2)	100 (17.6)		3,066 (14.3)	365 (17.0)	
Age (years)	63 (54;74)	61 (50;74)	0.041	68 (57;78)	77 (65;85)	<0.001
Gender (male)	2,280 (79.1)	414 (73.0)	0.002	14,651 (68.4)	1,268 (59.1)	< 0.001
Bystander presence	2,510 (87.1)	529 (93.3)	<0.001	15,233 (71.1)	1,463 (68.1)	0.004
Type of bystander (% family)	1,675 (58.1)	208 (36.7)	< 0.001	13,612 (63.6)	1,368 (63.7)	0.911
OHCA etiology (% cardiac)	2,460 (85.4)	499 (88.0)	0.117	15,300 (71.5)	1,429 (66.6)	< 0.001
BLS						
- Immediate CPR	1,507 (52.3)	396 (69.8)	<0.001	7,914 (37.0)	717 (33.4)	0.001
- Chest Compression	2,749 (95.4)	534 (94.2)	0.248	20,191 (94.3)	1,999 (93.1)	0.028
- Ventilation	2,411 (83.7)	456 (80.4)	0.066	18,428 (86.1)	1,817 (84.6)	0.074
- AED shock	1,793 (62.2)	314 (55.4)	0.003	2,889 (13.5)	194 (9.0)	<0.001
Times						
- call (T0) to MMT arrival	17 (12;23)	16 (11;23)	0.083	20 (14;27)	19 (13;27)	0.763
- call (T0) to ROSC or death	49 (34;62)	25 (17;43)	<0.001	48 (37;60)	37 (28;49)	<0.001
ACLS						
- Defibrillator shock by MMT	2,536 (88.0)	442 (77.95)	<0.001	3,670 (17.1)	101 (4.7)	<0.001
- Intubation	2,778 (96.4)	423 (74.60)	<0.001	20,145 (94.1)	1,712 (79.7)	<0.001
- Insertion of an injection route	2,881 (100.0)	549 (96.83)	<0.001	21,413 (100.0)	1,844 (85.9)	<0.001
Survival						
- ROSC	1,334 (46.3)	468 (82.5)	<0.001	5,583 (26.1)	301 (14.0)	<0.001
- Vital status at hospital admission (alive)	1,185 (41.1)	465 (82.0)	<0.001	4,214 (19.7)	274 (12.8)	<0.001
- Vital status at D30 (alive)	436 (15.1)	392 (69.1)	<0.001	422 (2.0)	132 (6.2)	<0.001
- If alive, CPC at 30 days	312 (71.56)	341 (86.99)	<0.001	248 (58.8)	106 (80.3)	<0.001

OHCA: out-of-hospital cardiac arrest, BLS: basic life support, CPR: cardiopulmonary resuscitation, CC: chest compression, AED: automated external defibrillator, ACLS: advanced cardiac life support, MMT: mobile medicalteam, ROSC: return of spontaneous circulation, D30: day 30, CPC: cerebral performance categories.

<sup>a</sup>Data are expressed as frequencies (%) for qualitative variables or median (Q1;Q3) for quantitative variables