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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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Abstract

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

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

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

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

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

Keywords

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

INTRODUCTION

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

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 The advice to use epinephrine was never withdrawn, even if evidence of its effectiveness is not yet conclusive in the literature, as highlighted by the ILCOR (6).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

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

MATERIAL AND METHODS

Ethics approval and consent to participate

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

Study design

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

Study population and data

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

Inclusion criteria

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

- patients in whom ACLS was attempted.

Exclusion criteria

- physical indications of death (*rigor mortis*)
- files lacking data for mandatory criteria (Utstein core data)
- for patients who had epinephrine during their care: files lacking data for the time between OHCA and the epinephrine injection (if the RéAC investigator did not recorded the time of the first epinephrine injection during the intervention)
- files lacking data for the time between T0 (first call) and the time of death
- time between call (T0) and MMT arrival longer than 60 minutes
- patients with a return of spontaneous circulation (ROSC) before MMT arrival
- patients with a known Do Not Attempt Resuscitation (DNAR) order.

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

Endpoints

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

Statistical analysis

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

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

Description and comparison of cohorts

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

Estimation of the time-dependent propensity score

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

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

Matching method

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

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

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

Quality of matching

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

Conditional weighted logistic regression

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

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

RESULTS

Unadjusted population

Study participants

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

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

Description of the studied population

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

Comparison between the epinephrine and no epinephrine groups in the studied population

We observed significant differences for almost every descriptive criterion between our two groups, except the presence of a bystander and a shock delivered during BLS (Table 1).

At 30 days, a lower survival rate was observed when epinephrine was used (3.5% *vs.* 19.3%, $P < 0.001$). The ROSC rate was not different between our two groups (28.5% *vs.* 28.3%, $P = 0.898$), whereas the survival rate at the time of hospital admission was higher in the no epinephrine group than in the epinephrine group (22.2% *vs.* 27.2%, $P < 0.001$). At 30 days, we recorded a worse neurological outcome in the epinephrine group than in the no epinephrine group (65.3% *vs.* 85.3%, $P < 0.001$) (Table 1).

Comparison between epinephrine and no epinephrine groups in patients with shockable rhythms

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

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

Comparison between epinephrine and no epinephrine groups in patients with nonshockable rhythms

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

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

Adjusted population

Comparison when the initial rhythm was shockable

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

Comparison when the initial rhythm was nonshockable

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

DISCUSSION

Our study was performed with a large cohort of OHCA patients and based on a time-dependent propensity score-matched analysis. This methodology enabled us to assess the link between epinephrine use and survival in the real-world setting by limiting the inherent bias of the impact of time to injection on patient survival. Regarding survival, in both groups with nonshockable rhythms or with shockable rhythms, we observed that the epinephrine use was associated with a decrease in 30-day survival compared to controls. Some other studies have also highlighted negative impacts of epinephrine on 30-day survival (9,15,30), while others did not (7,12,13). However, previous findings did not support robust conclusions regarding the efficacy of epinephrine due to methodological issues (10,11) or conflicting results (13–15).

In our adjusted analysis, epinephrine use was never associated with a better outcome. We always observed deleterious effects of epinephrine 30 days after OHCA. The results regarding D30 survival are in agreement with those of the studies by Hagihara *et al.* (15) and Olasveengen *et al.* (11). Those studies also found deleterious effects of epinephrine 30 days after the OHCA. In the Olasveengen *et al.* study, they reported a 48% lower change of survival when epinephrine was injected than when epinephrine was not injected (11). However, some recent studies noted

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

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

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

Our results may be explained by the pharmacology of epinephrine. The α1 and β stimulation increases myocardial perfusion pressure. Hence, the higher rate of immediate survival in patients with nonshockable rhythms in unadjusted populations can at least partially be explained by these effects (34). However, the action of epinephrine has deleterious effects on mid-term survival and neurological outcomes (35,36) (myocardial dysfunction (37,38),

development of new arrhythmias (37,38), cerebral microcirculation impairment) (30,34,39). Our results related to mid-term survival can also be partially explained by these effects.

Our study was based on reliable French national registry-based data. The RéAC registry provided an overview of real-life professional practices and conditions regarding OHCA (2). We used a validated time-dependent propensity-score matching method to reduce bias. Our study provided consistent results that bolstered the limited literature regarding the issue of epinephrine efficacy. In addition, we stratified our results according to the initial patient rhythm on MMT arrival. Guidelines regarding epinephrine use differ based on if the initial patient rhythm is shockable or not (20). Furthermore, some studies have suggested that the impact of epinephrine differs according to the initial rhythm identified (7,16). Hence, our results were not influenced by the time to epinephrine injection and the patient's rhythm.

Limitations

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

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

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

CONCLUSIONS

The currently recommended use of epinephrine does not seem to have any benefit on mid-term outcomes, regardless of the patients' initial rhythm and after adjustment for time imbalances. Questions such as the optimal epinephrine dose or the association with other drugs still have to be investigated within the context of a global therapeutic strategy surrounding the use of epinephrine.

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ARTICLE SUMMARY

1. Why is this topic important?

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

2. What does this study attempt to show?

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

3. What are the key findings?

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

4. How is patient care impacted?

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

Legends to figures

Fig. 1 Flow chart

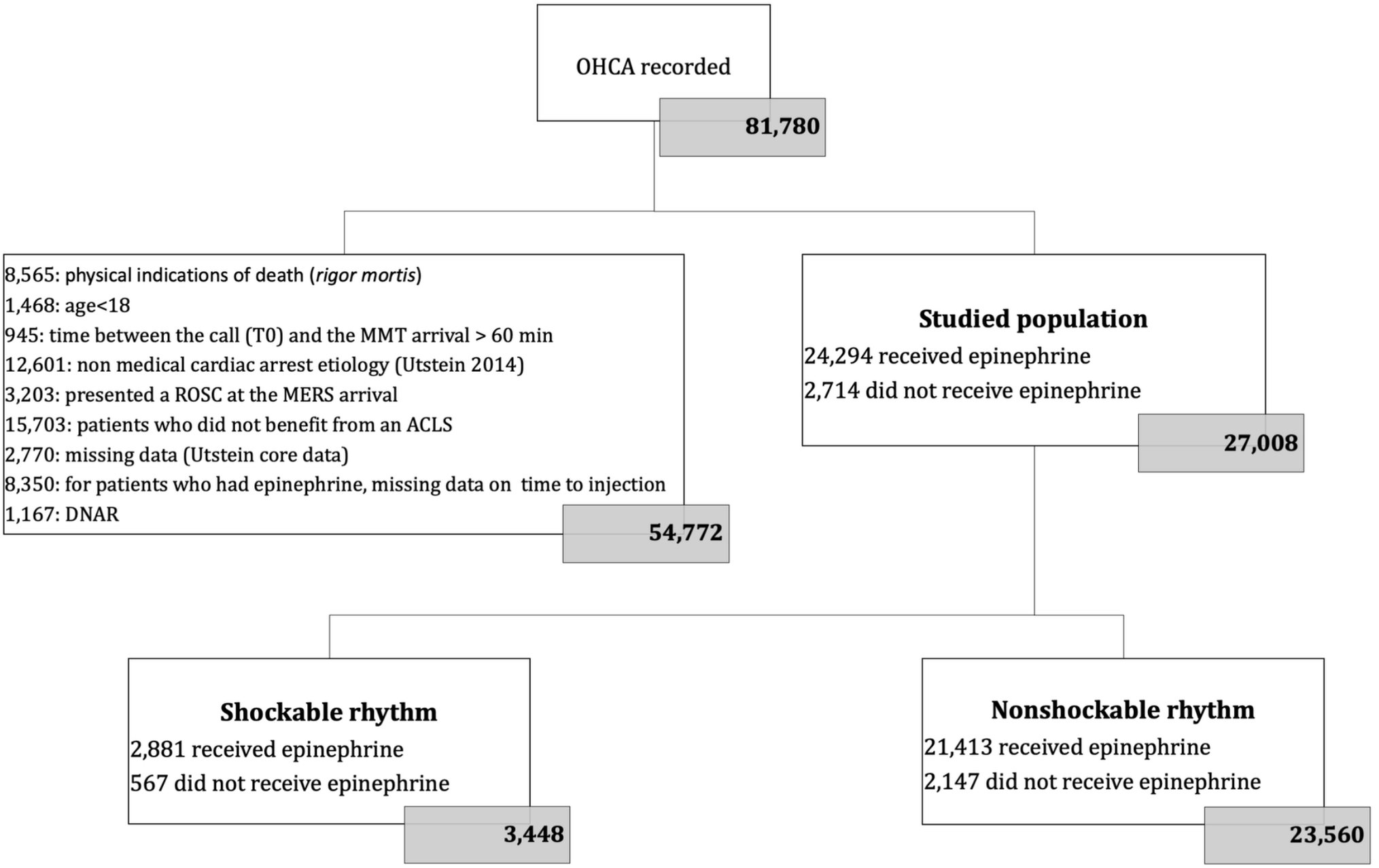
OHCA: out-of-hospital cardiac arrest, DNAR: do not attempt resuscitation, MMT: mobile medical team, ROSC: return of spontaneous circulation, MERS: mobile emergency and resuscitation service

Fig. 2 Comparison of endpoints in shockable group

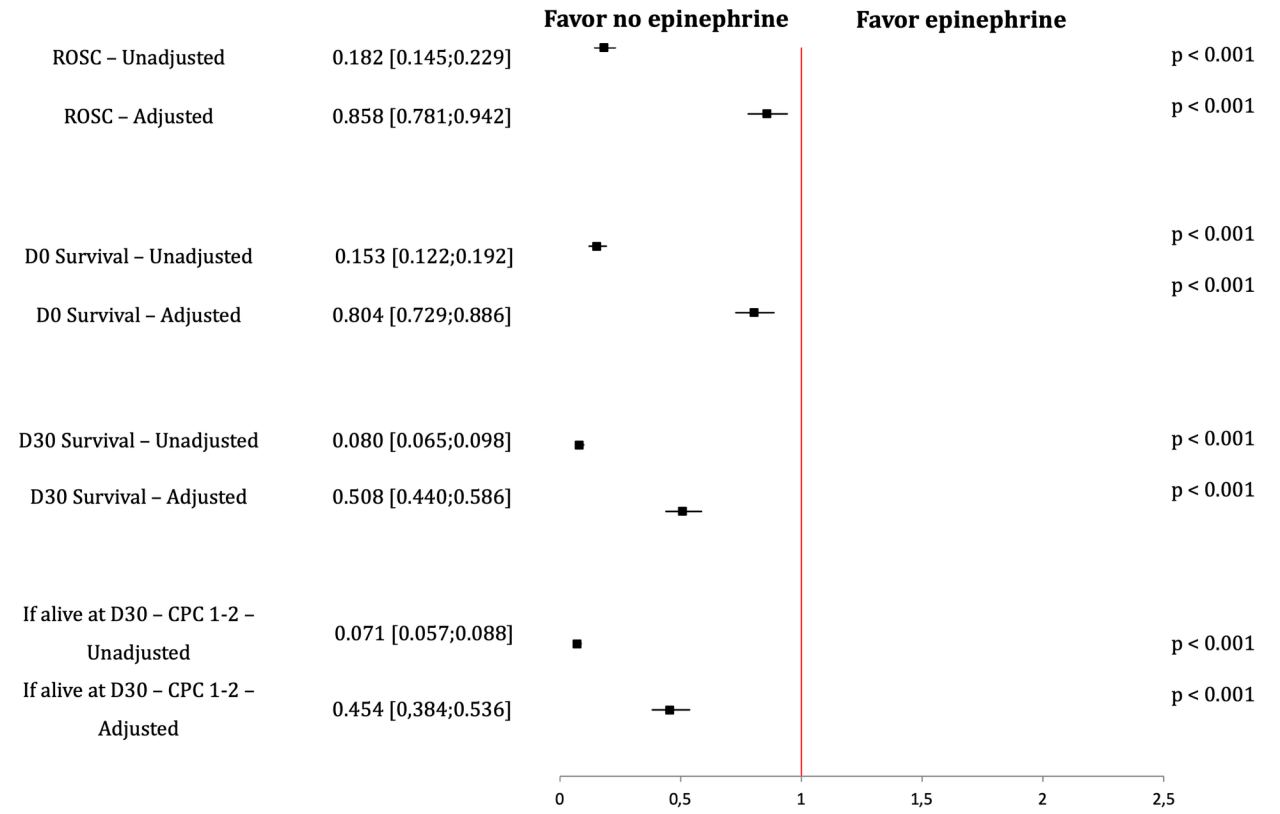
ROSC: return of spontaneous circulation; D30: 30 days

Fig. 3 Comparison of endpoints in nonshockable group

ROSC: return of spontaneous circulation; D30: 30 days


OHCA recorded
81,780
8,565: physical indications of death (*rigor mortis*)
1,468: age<18
945: time between the call (T0) and the MMT arrival > 60 min
12,601: non medical cardiac arrest etiology (Utstein 2014)
3,203: presented a ROSC at the MERS arrival
15,703: patients who did not benefit from an ACLS
2,770: missing data (Utstein core data)
8,350: for patients who had epinephrine, missing data on time to injection
1,167: DNAR
54,772
Studied population
24,294 received epinephrine
2,714 did not receive epinephrine
27,008
Shockable rhythm
2,881 received epinephrine
567 did not receive epinephrine
3,448
Nonshockable rhythm
21,413 received epinephrine
2,147 did not receive epinephrine
23,560

Shockable rhythm – OR (95% CI)



Nonshockable rhythm – OR (95% CI)

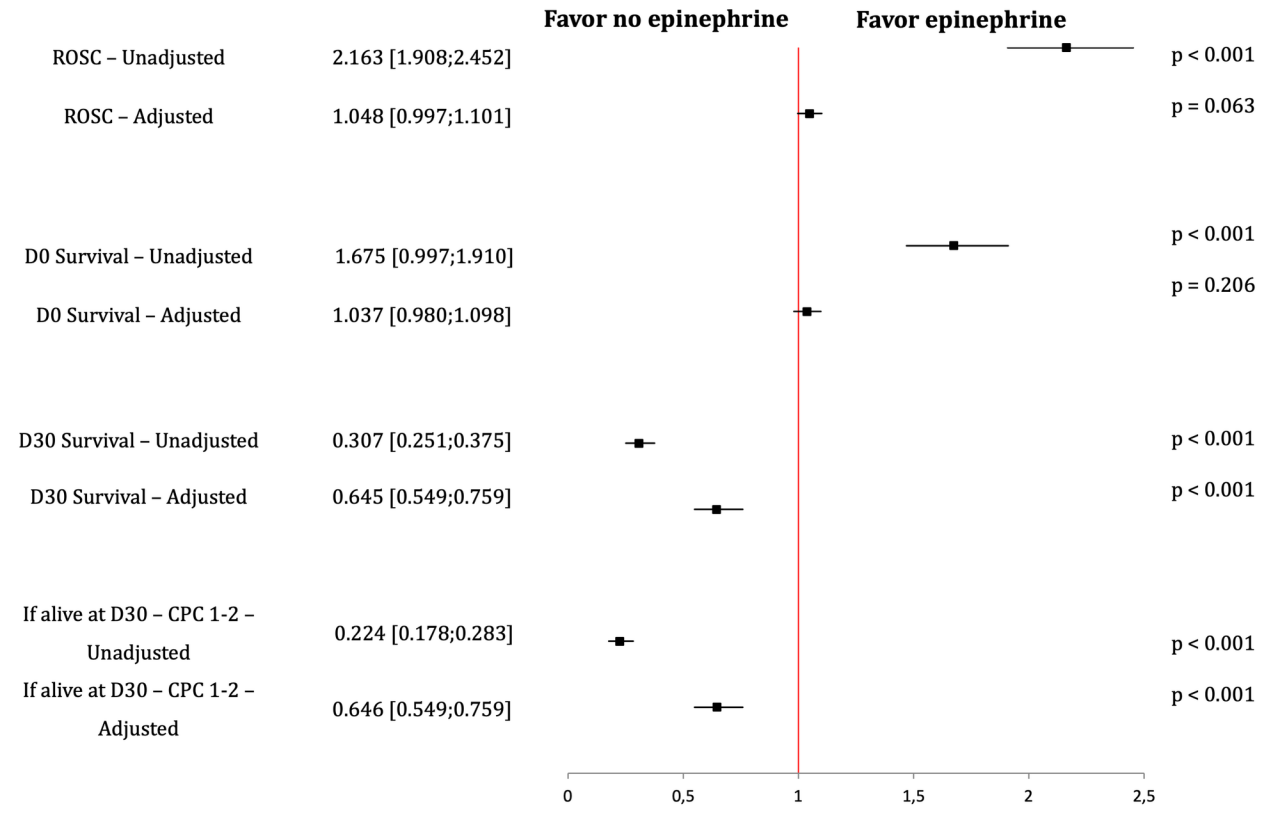


Table 1. Population characteristics and global analysis[a]

	Description	Comparison		
Characteristics	Studied Population 27,008	Epinephrine 24,294	No Epinephrine 2,714	*P*
Cases per year				
- 2011	349 (1.3)	326 (1.3)	23 (0.9)	
- 2012	2699 (10.0)	2421 (10.0)	278 (10.2)	
- 2013	5120 (19.0)	4585 (18.9)	535 (19.7)	<0.001
- 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
BLS				
- 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
Times				
- 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
ACLS				
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
Survival				
- 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[b]	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.

[a]*Data are expressed as frequencies. (%) for qualitative variables or median (Q1;Q3) for quantitative variables*

[b]*140 missing values*

Table 2 Comparison between epinephrine and no epinephrine according to cardiac rhythms[a]

	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.
[a]Data are expressed as frequencies (%) for qualitative variables or median (Q1;Q3) for quantitative variables