Thrombolysis during resuscitation for out-of-hospital cardiac arrest caused by pulmonary embolism increases 30-day survival: findings from the french national cardiac arrest registry

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Thrombolysis during resuscitation for out-of-hospital cardiac arrest caused by pulmonary embolism increases 30-day survival: findings from the French National Cardiac Arrest Registry

Running Title: Thrombolysis PE-related OHCA increases survival

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Conflicts of interest
The authors have no conflicts of interest to declare.

Acknowledgements

The RéAC registry was supported by the French Society of Emergency Medicine (SFMU), a patient foundation – Fédération Française de Cardiologie, the Mutuelle Générale de l'Education Nationale (MGEN), the University of Lille and the Institute of Health Engineering of Lille. The authors declare that the funding sources had no role in the conduct, analysis, interpretation or writing of this manuscript.

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Word count

Paper: 2500

Abstract: 233

ABSTRACT

Background: Pulmonary embolism (PE) represents 2% to 5% of all causes of out-of-hospital cardiac arrest (OHCA) and is associated with extremely unfavorable prognosis. In PE-related OHCA, inconsistent data showed that thrombolysis during cardiopulmonary resuscitation (CPR) may favor survival.

Methods: It was a retrospective, observational, multicenter study from July 2011 to March 2018. All adult OHCA, managed by a mobile intensive care unit, and with a diagnosis of pulmonary embolism confirmed on hospital admission were included. The primary end point was day-30 survival in a weighted population.

Results: Of the 14,253 patients admitted to the hospitals, 328 had a final diagnosis of PE and 246 were included in the analysis. In the group that received thrombolysis during resuscitation (n=58), 14 received alteplase (24%), 43 tenecteplase (74%) and 1 streptokinase (2%). Thirty-day survival was higher in the thrombolysis group than in the control group (16% vs 6%, *P*=0.005; adjusted log-rank test) but the good neurological outcome was no significantly different (10% vs 5%; adjusted relative risk = 1.97 CI95[0.70–5.56]). Median duration of stay in the intensive care unit (ICU) was 1 (0-5) day in the thrombolysis group and 1 (0-3) day in the control group (*P*=0.23).

Conclusions: In OHCA patients with confirmed PE and admitted with recuperation of spontaneous circulation in the hospital, there was significantly higher 30-day survival in those who received thrombolysis during CPR compared with patients who did not receive thrombolysis.

Keywords: Out-of-hospital cardiac arrest, Thrombolytic therapy, Pulmonary embolism, Cardiopulmonary resuscitation

Introduction

Out-of-hospital cardiac arrest (OHCA) accounts for 600,000 deaths each year in industrialized countries [1,2]. OHCA can be of cardiac or non-cardiac origin [3]. Pulmonary embolism (PE) represents 2% to 5% of OHCA and is associated with very unfavorable prognosis [4-9].

Thrombolytic therapy during resuscitation in all-cause OHCA has been evaluated by four randomized controlled trials that did not demonstrate improvement in survival [4,10-12]. But it should be noted that the TROICA trial was stopped in the interim analysis because of futility [4]. A higher proportion of any intracranial hemorrhage was also reported in patients who received thrombolytic therapy, indeed in TROICA trial the rate of intracranial hemorrhage in the tenecteplase group was about 5 times higher but without an increase in symptomatic intracranial hemorrhage and major non-intracranial hemorrhage [4].

Thrombolysis reduces mortality, decreases the risk of developing chronic thromboembolic pulmonary hypertension and improves the quality of life in patients with massive PE [13,14]. A meta-analysis has also suggested that thrombolysis reduces mortality in patients with submassive PE, but with increased major bleeding complications including intracranial hemorrhage [15]. In OHCA caused by PE (PE-related OHCA), inconsistent data has reported that thrombolysis during resuscitation could favor the return of spontaneous circulation (ROSC) and survival [5,16,17]. The most recent American Heart Association (AHA) [18] and European Resuscitation Council (ERC) [19] guidelines therefore recommended that thrombolysis be used when cardiac arrest is suspected as being caused by PE, even if robust evidence is lacking.

The objective of this present study was to first evaluate whether thrombolysis during cardiopulmonary resuscitation (CPR) was effective in the case of PE-related OHCA before evaluating it on suspected PE. To do this, we analyzed a large observational, multicenter cohort to assess if thrombolysis during resuscitation improved 30-day survival in PE-related OHCA.

Methods

Study Design

We performed a retrospective cohort study analysis based on data extracted from the French National OHCA Registry (RéAC) from July 2011 to March 2018. RéAC is a cohort which includes all OHCA managed by mobile intensive care units (MICU) in France. A MICU consists of an ambulance driver, a nurse, and a senior emergency physician as a minimum team. A detailed description of the emergency medical system in France has been previously published [20]. The RéAC form meets the requirements of the French Emergency Medical

Service organizations and is structured according to the Utstein universal style [21]. Data is then entered in the secured RéAC database (www.registreac.org) [22].

The present study was approved by the French Advisory Committee on Information Processing in Health Research (CCTIRS) and the French National Data Protection Commission (CNIL, authorization no. 910946). It was approved as a medical assessment registry without requirement for patient consent [22].

Patient Population

We selected in the RéAC database for all OHCA that occurred in adults (≥18 years of age), managed by a MICU, and with a diagnosis of pulmonary embolism confirmed on hospital admission. We excluded all other causes of OHCA and patients who had ROSC prior to mobile intensive care unit management because they could not receive thrombolysis during CPR. Patients were classified in two groups: those who received thrombolytic therapy during CPR and those who did not. Following the initial treatment out of the hospital by MICU, the therapies initiated in the intensive care units (ICU) were left at the discretion of the physicians in charge (including initial or complementary thrombolytic therapy).

Diagnosis of pulmonary embolism

PE was diagnosed on hospital admission by computed tomography pulmonary angiography (CTPA) (definite PE) or echocardiogram (probable PE). CTPA is the method of choice for imaging the pulmonary vasculature in patients with suspected PE [23-25]. Echocardiographic examination is also recommended as part of the diagnostic work-up in suspected PE with shock [24-26].

Outcomes

The primary end point was 30-day survival, irrespective of Glasgow-Pittsburgh Cerebral Performance Categories (CPC). The secondary endpoints were survival at 24 hours, length of stay in the ICU, and neurological outcome (CPC). Outcomes were collected by blinded assessors.

Statistical analyses

Continuous variables were reported as medians with interquartile range (IQR) and categorical variables were summed as patient counts and percentages.

In order to obtain unbiased estimations of the average treatment effects, we used inverse probability of treatment weighting (IPTW). This method was performed in two steps: first, an estimation of the propensity score of treatment (thrombolysis during cardiopulmonary resuscitation) with a logistic model, and then an estimation of the effect of treatment on 30-day survival, weighted on the propensity score. Since the study population was small, this conservative procedure was preferred to propensity score matching. The small sample

size also forced us to carefully select the variables to be included in the propensity score calculation. Indeed, the inclusion of variables not or weakly correlated to the outcome (30-day survival) increases the variance of the effect and is related to low reduction of bias [27]. The variables included for the propensity score were therefore limited to variables related to the outcome – whether or not related to exposure (thrombolysis during resuscitation). Observations with missing data for the variables included in the multivariate models were excluded (n=2).

The primary endpoint was reported by Kaplan-Meier estimators, adjusted according to the IPTW method. The significance of the differences in survival between the two groups was measured using the log-rank test adapted to these estimators.

Analyses were performed using R software 3.5.1 version and required IPW survival library [28] for survival analysis.

Results

Patient characteristics

From July 2011 to March 2018, 85,519 cardiac arrests were recorded in the RéAC database as reported in **Figure 1**. A total of 14,253 subjects were admitted to hospitals (admitted with ROSC or for ECMO). Of those, 328 (2.3%) presented pulmonary embolism with 82 excluded owing to ROSC (n=69; 21%) or unknown ROSC status (n=13; 3%) before MICU management on site. These subjects who achieved an early ROSC (n=69) had a survival rate of 42% at day-30 and those whose ROSC status was not known had a survival rate of 23%. Finally, the population analyzed was composed of 58 patients in the thrombolysis group and 188 patients in the control group. The main characteristics of the study patients are reported in **Table 1**. Median age was 62 (48-73) with a male proportion of 48%. Most of the patients had a non-shockable rhythm when the mobile intensive care unit arrived at the scene (99%). The no-flow duration (time between collapse and initiation of BLS) was estimated to be more than 5 minutes in 28% of the cases. 26 subjects (11%) were admitted at hospital without ROSC with the MICU, of whom 15 (6%) had an ECMO and 11 (4%) had ROSC at the hospital.

In the group of patients who received thrombolysis during cardiopulmonary resuscitation, tenecteplase was the thrombolytic agent the most used (n=43; 74%) with a median dose of 45mg (minimum=35; maximum=50) known for 21 subjects), 14 subjects (24%) received alteplase (median dose=50mg (minimum=50; maximum=80) known for 7 subjects) and one streptokinase (2%; dose unknown). Patient characteristics and resuscitation

management were balanced between the 2 groups except for initial rhythm recorded by medical team, low-flow duration (time between initiation of BLS and ROSC) and epinephrine dose during CPR.

The most important variables associated with 30-day survival were: professional rescuers as bystanders (52% in survivors vs 28%; *P*=0.02), estimated no-flow duration >5 min (10% vs 29%; *P*=0.05) (time between collapse and initiation of BLS), epinephrine dose during cardiopulmonary resuscitation (2 mg vs 6 mg; *P*<0.001) and inotropic support (38% vs 68%; *P*=0.006) (data detailed in Supplemental Table 1).

Primary and secondary endpoints

On day 30, there was a total of 21 survivors (9%) including 9 in the thrombolysis group (16%) and 12 in the control group (6%) (*P*=0.055; unweighted Fisher's exact test).

The population was successfully weighted (i.e. standardized mean difference <0.1) on 7 variables shown in **Figure 2**. Survival at day-30 was higher in the thrombolysis group than in the control group (*P*=0.005; adjusted log-rank test) on the weighted population (**Figure 3**). In thrombolysis group 6 (10%) had a good neurological outcome at day-30 (i.e. CPC 1-2) versus 9 (5%) in control group (Adjusted relative risk=1.97 CI95[0.70–5.56]). On the thrombolysis group, there were 4 survivors among them who received alteplase (29%) and 5 tenecteplase (12%; *P*=0.20; unweighted Fisher's exact test)

Survival at 24 hours was 66% in the thrombolysis group and 63% in the control group (*P*=0.76). Median of length of stay in the ICU was 1 (0-5) day in the thrombolysis group and 1 (0-3) day in the control group (*P*=0.23).

Subjects in the thrombolysis group would not die of hemorrhage any more than those in the control group (6% vs 5%; *P*=0.73). On the other hand, irreversible coma appeared slightly less frequent as a cause of death in the thrombolysis group (2% vs 11%; *P*=0.05) (**Table 1**).

Discussion

We assessed thrombolysis during resuscitation for PE-related OHCA in a large prospective cohort. There was significantly higher 30-day survival in patients who received thrombolysis during CPR compared with patients who did not receive it.

PE-related OHCA is rare, representing 2.3% of all OHCA with ROSC managed by a mobile intensive care unit in our cohort. This is comparable to other studies [5,6,8,9] with an incidence of 3.5% reported in the largest trial assessing thrombolysis during CPR performed by Böttiger et al [4]. They evaluated 30-day survival with a Kaplan-Meier survival model of patients who received either tenecteplase or placebo during resuscitation of a

witnessed OHCA presumed to be cardiac in origin. They did not demonstrate a beneficial effect of thrombolysis under these conditions. However, of the 1,050 subjects included, only 37 had confirmed PE, with 2 out of 15 survivors (13%) in the tenecteplase group versus 0 out of 22 (0%) in the placebo group (relative risk=7.19 [0.37-139.9]; *P*=0.31) [4]. Recently, Bougouin et al. showed that thrombolysis was associated with improved survival rates on hospital discharge in patients with PE-related OHCA (adjusted Odds Ratio=12.5 [1.8-89.1]; *P*=0.01) [5]. They analyzed the Sudden Death Expertise Center registry [29] which included 82 patients with suspected PE. In Lederer's observational study, 30-day survival after PE-related OHCA was 32% (n=6/19) in patients receiving recombinant tissue plasminogen activator (rt-PA) [30]. In another cohort of 42 subjects with in- or out-of-hospital cardiac arrest caused by PE, Kürkciyan et al. showed a higher rate of ROSC (81% vs 43%, *P*=0.03) in patients who received rt-PA (n=21). However, they did not provide survival data on hospital discharge [9]. In a retrospective cohort, Janata et al. found a higher proportion of survival at 24 hours in patients receiving thrombolysis (n=19/36 [53%] *vs* n=7/30 [23%]); *P*=0.01). The difference was not significant on hospital discharge (n=7/36 [19%] *vs* n=2/30 [7%]; *P*=0.15) [31]. Owing to methodological limitations, the effect of thrombolytic therapy during CPR therefore remained unclear. We assessed 246 subjects with PE-related OHCA, 58 of whom received thrombolysis during cardiopulmonary resuscitation. Tenecteplase was used more frequently than ateplase, both of which were studied in pulmonary embolism [32] and cardiac arrest due to suspected pulmonary embolism [17]. We didn't find any difference in survival rates between these two molecules. Therefore, in routine care, one or the other of these molecules could be used, nevertheless tenecteplase is not yet approved by FDA for this indication (PE). To the best of our knowledge, this is the largest prospective cohort. Moreover, we adjusted the 2 groups of treatment before the survival analysis to place them in the closest conditions to an RCT. Survival rate was low in our study, about 9%. However, subjects who achieved ROSC before MICU arrival at the scene were excluded from the analysis because they were not eligible for thrombolysis during CPR. These subjects had a higher survival rate (42%), as well as subjects with unknown ROSC status (23%). In total, among all confirmed PE (n=328), the survival rate after admission to ICU was 16%. Compared to other PE-related OHCA studies, Kürkciyan et al. had a survival rate of 12% in subjects who achieved ROSC [9] and 22% for Bouguoin et al. in subjects admitted to ICU [5].

Determining the cause of an OHCA during resuscitation remains challenging. A diagnostic concordance study comparing the out-of-hospital physician's presumed diagnosis and the diagnosis made in the hospital showed concordance in 74% of the cases [33]. With regard to the diagnosis of PE-related OHCA outside the hospital (n=21/211), its sensitivity was low (43%) and its specificity was very high (94%) [33]. The factors

associated with PE-related OHCA were: previous thromboembolism and non-shockable rhythm. In this population with these 2 factors, the proportion of pulmonary embolism was 34% (sensitivity=24%; specificity=98%) [34]. The use of echocardiography during resuscitation could improve these results. Indeed, the presence of an acute pulmonary heart or a thrombus in the right cavities visualized on echocardiography guides the diagnosis of PE [35-37]. AHA and ERC guidelines therefore suggest the use of ultrasound during resuscitation for diagnostic and prognostic purposes [38,39]. However, acute pulmonary heart can be related to acute circulatory failure and be non-specific of pulmonary embolism as recently highlighted [40].

Limitations

First of all, thrombolytic therapy during cardiopulmonary resuscitation was not assigned by random allocation. In our prospective cohort, we performed an IPTW survival analysis and made adjustments for selection bias and confounding factors. Under these conditions, the measured effect was considered comparable to randomized trials [41]. However, we could not adjust the groups to the initial cardiac rhythm recorded by the mobile intensive care unit because there were no patients with ventricular fibrillation (VF) in the control group. Nevertheless, this imbalance was compensated by the fact that among the 3 subjects in VF in the thrombolysis group, only one survived on day 30, the other two died on day 0. In addition, this electric rhythm variable was not associated with the outcome in our cohort (i.e. survival on day 30) (P=0.14) as well as defibrillation before MICU management on site (P=0.61).

Secondly, an inherent limitation of this type of registry analysis is the lack of completeness of data which may have resulted in not being completely exhaustive in the selection of the population. The dose of fibrinolytic agent used was known in less than half of the subjects due to a lack of accuracy and completeness. The data only covered deaths caused by bleeding, but not all hemorrhage complications such as intracranial hemorrhage. Similarly, the method of confirming embolism either by CTPA or echocardiogram was not known for each patient.

Lastly, we were not able to include all suspected PE-related OHCA because this variable is not clearly available in the registry. In our database there were a total of 1300 adults who received thrombolysis during CPR and 567 of them achieved ROSC (44%). However, this population was not only composed of suspected PE but also of suspected acute coronary syndrome with a better prognosis.

Conclusion

We assessed thrombolysis during cardiopulmonary resuscitation for PE-related OHCA in a large prospective cohort. We found that thrombolysis during cardiopulmonary resuscitation was associated with higher 30-day survival in PE-related OHCA. A large RCT is needed to confirm these results in case of OHCA presumed to be PE in origin.

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Legends to figures

Figure 1. Flow Chart of Patient Inclusion

OHCA, out-of-hospital cardiac arrest; ARVD, arrhythmogenic right ventricular dysplasia; PE, pulmonary embolism; ROSC, return of spontaneous circulation; MICU, mobile intensive care unit; CPR, cardiopulmonary resuscitation

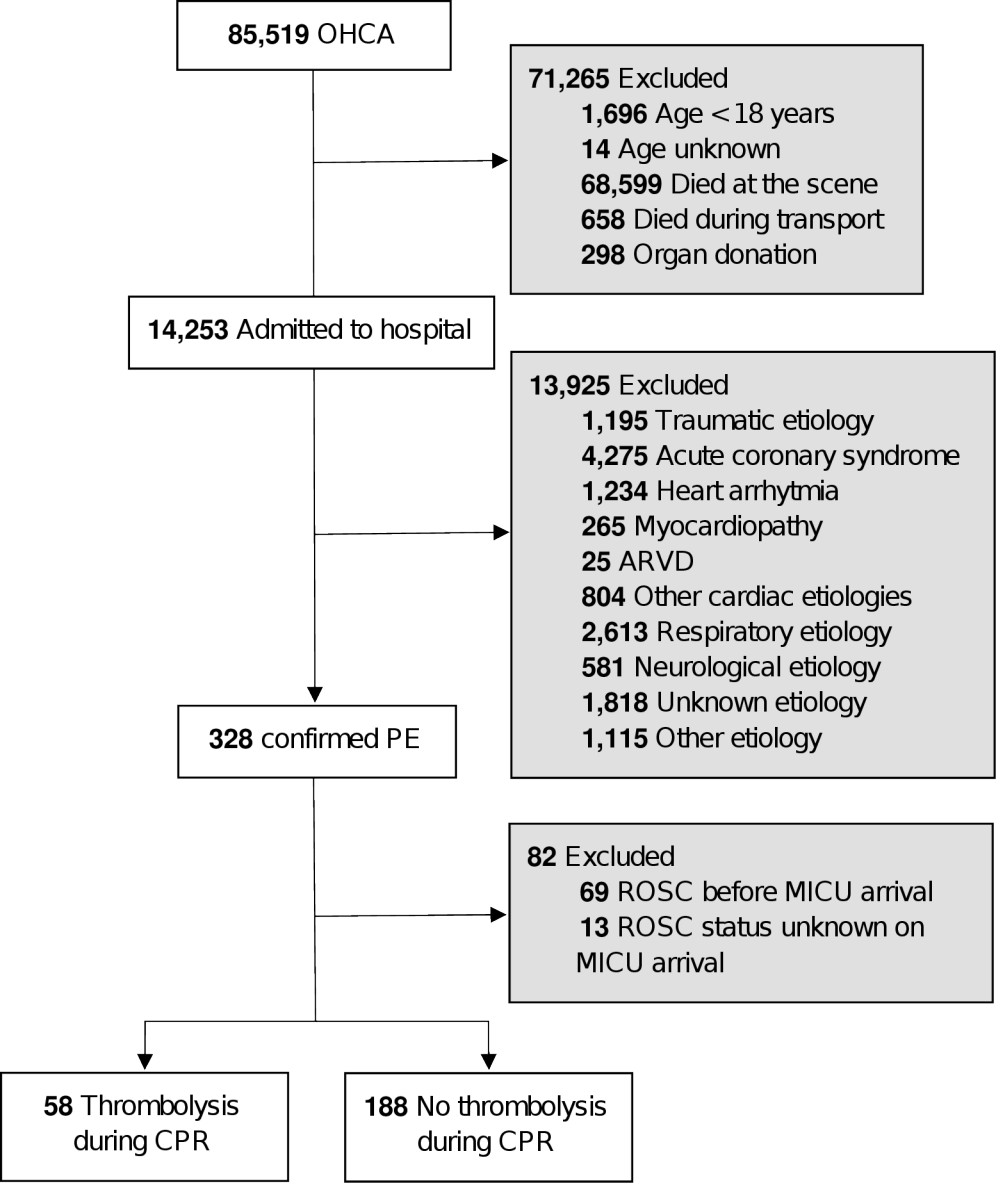
Figure 2. Standardized Mean Difference before and after adjustment

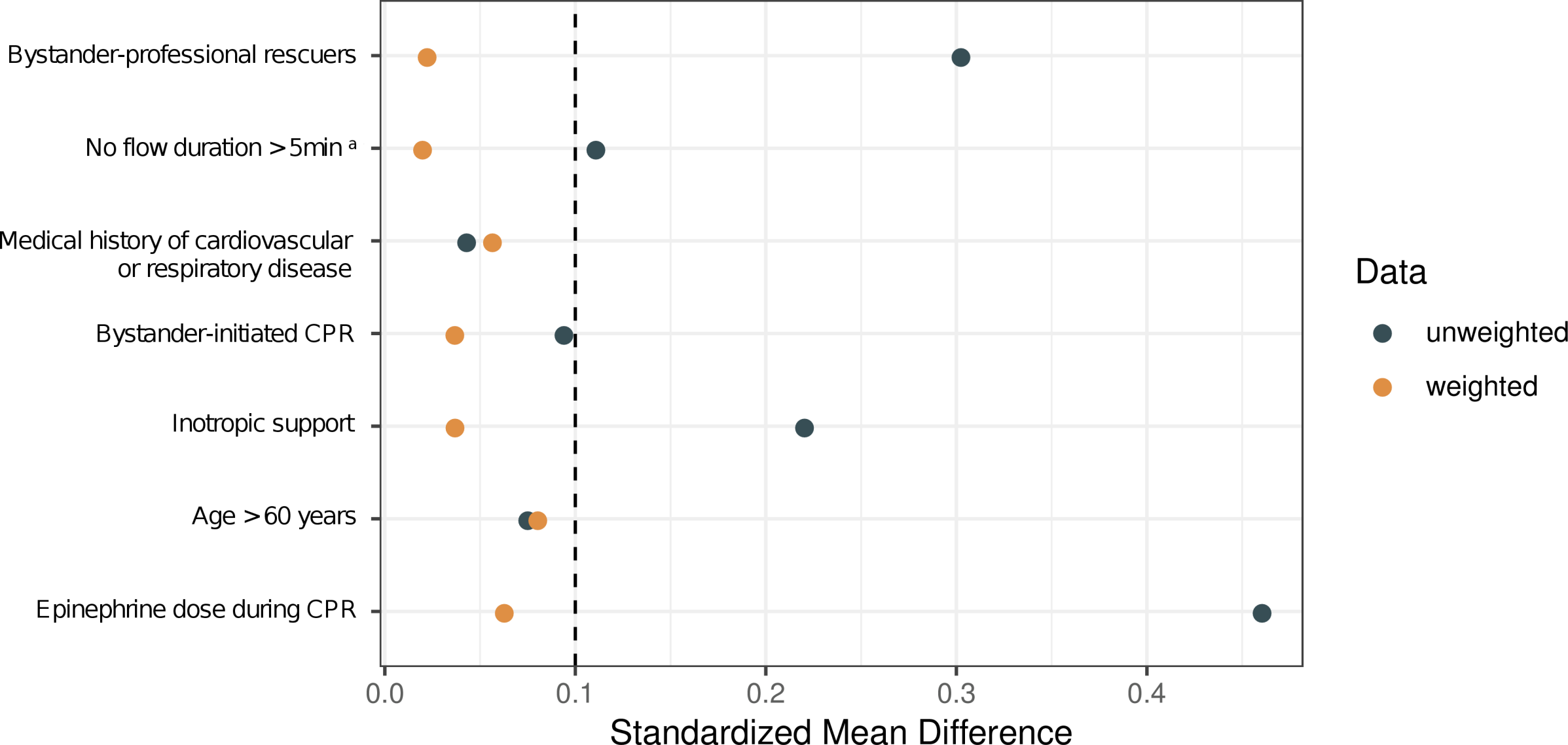
CPR, cardiopulmonary resuscitation

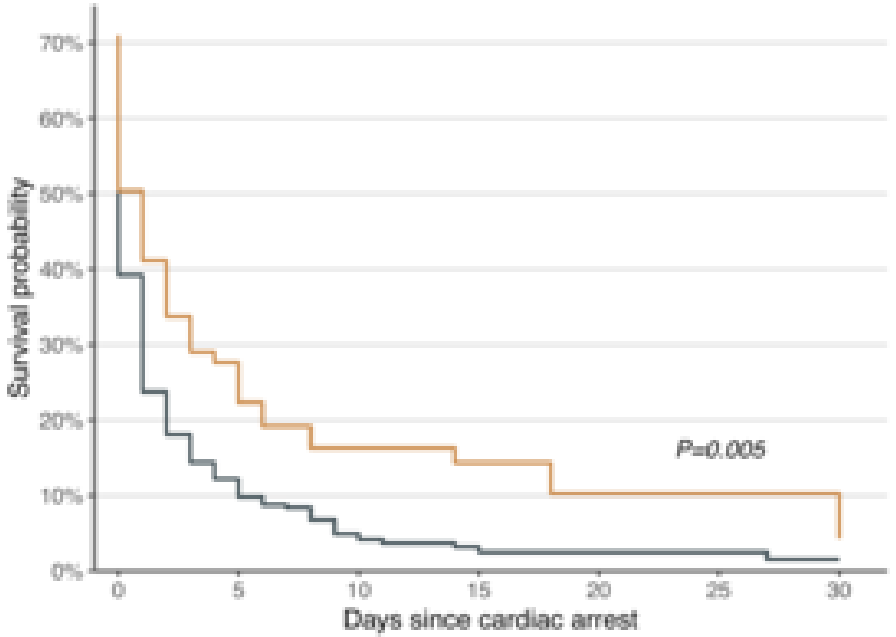
Figure 3. Adjusted Kaplan–Meier Survival Curves on weighted population

Author contributions

FJ and BL had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. FJ wrote the first draft of the paper, with all other authors making important critical revisions. All authors have read and approved the final version of the manuscript.


85,519 OHCA
71,265 Excluded
1,696 Age < 18 years
14 Age unknown
68,599 Died at the scene
658 Died during transport
298 Organ donation
14,253 Admitted to hospital
13,925 Excluded
1,195 Traumatic etiology
4,275 Acute coronary syndrome
1,234 Heart arrhytmia
265 Myocardiopathy
25 ARVD
804 Other cardiac etiologies
2,613 Respiratory etiology
581 Neurological etiology
1,818 Unknown etiology
1,115 Other etiology
328 confirmed PE
82 Excluded
69 ROSC before MICU arrival
13 ROSC status unknown on MICU arrival
58 Thrombolysis during CPR
188 No thrombolysis during CPR


Bystander-professional rescuers
No flow duration >5min [a]
Medical history of cardiovascular or respiratory disease
Bystander-initiated CPR
Inotropic support
Age >60 years
Epinephrine dose during CPR
0.0
0.1
0.2
0.3
0.4
Standardized Mean Difference
Data
unweighted
weighted



Number at risk (adjusted sample)

Thrombolysis	242	84	56	36	32	32	23
No thrombolysis	247	43	16	7	7	3	2

Table 1. Characteristics of patients and cardiac arrest management

Characteristic	Fibrinolysis Group (n=58)	Control Group (n=188)	*P* Value
Age, median (IQR), y	60.5 (45.5-69)	62.5 (50-73)	0.33
Male, n (%)	30 (52)	87 (46)	0.47
Location, n (%)			0.42
Home / Private place	36 (62)	133 (71)	
Public place	14 (24)	33 (17)	
Health facility	3 (5)	13 (7)	
Other	5 (9)	9 (5)	
Known medical history, n (%)			
Cardiovascular disease	21 (36)	68 (36)	>0.99
Respiratory disease	4 (7)	29 (15)	0.09
Diabetes	7 (12)	26 (14)	0.73
Cancer	4 (7)	16 (9)	>0.99
Bystander-witnessed cardiac arrest, n (%)	49 (84)	163 (87)	0.67
Bystander-professional rescuers, n (%)	24 (41)	51 (27)	0.04
Bystander-initiated CPR, n (%)	35 (60)	122 (65)	0.63
Estimated no-flow duration[a] > 5 min, n (%)	14 (24)	54 (29)	0.47
Time between emergency call and MICU arrival at the scene, median (IQR), min	19.5 (14-33)	20 (13-31)	0.98
Defibrillation before MICU arrival at the scene, n (%)	5 (9)	8 (4)	0.19
Initial cardiac rhythm recorded by MICU, n (%)			0.01
Asystole	38 (66)	141 (75)	
PEA	17 (29)	47 (25)	
VF	3 (5)	0 (0)	
Low-flow duration[b], median (IQR), min	35 (21-66)	24 (15-36)	<0.001
Injection route, n (%)			0.59
Peripheral intravenous	51 (88)	171 (91)	
Intraosseous	7 (12)	15 (8)	
Central intravenous	0 (0)	2 (1)	
Epinephrine dose during CPR, median (IQR), mg	8 (3-13)	5 (3-8)	0.001
Inotropic support, n (%)	33 (57)	127 (68)	0.14
Amiodarone administration, n (%)	4 (7)	8 (4)	0.48
Defibrillation administered by MICU, n (%)	9 (16)	21 (11)	0.38
Endotracheal intubation by MICU, n (%)	58 (100)	187 (99)	>0.99
ECMO, n (%)	5 (9)	20 (11)	0.64
Death causes, n (%)	n=49	n=176	
Irreversible coma	1 (2)	20 (11)	0.052
Cardiovascular failure	24 (49)	74 (42)	0.39
Hemorrhage	3 (6)	9 (5)	0.73
Septic shock	0 (0)	1 (1)	>0.99
Hypoxia	2 (4)	5 (3)	0.65
Multi-system organ failure	18 (37)	55 (31)	0.47
Undetermined	1 (2)	12 (7)	0.31

Abbreviations: CPR: cardiopulmonary resuscitation; MICU: mobile intensive care unit; PEA: pulseless electrical activity; VF: ventricular fibrillation; $ETCO_2$: end-tidal capnography; IQR: interquartile range. *P* values were calculated by using $\chi 2$ test, Fisher's exact test or Mann-Whitney U test.

[a] No-flow duration: time between collapse and initiation of basic life support (missing value, n=2).
[b] Low-flow duration: time between initiation of basic life support and return of spontaneous circulation (missing value, n=14).