Supplemental Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

Propensity score analysis

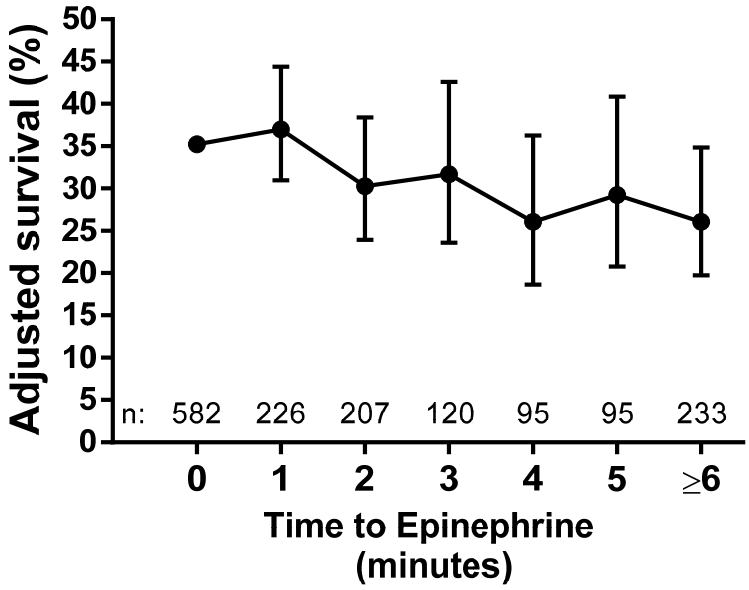
The propensity score was calculated using multivariable logistic regression with generalized estimating equations with an exchangeable (compound symmetry) variance-covariance structure to account for hospital clustering. For the calculation of the propensity score, the dependent variable was administration of epinephrine at minute zero (as compared to after minute zero). We included all covariates that were included in our main model. We next performed modified Poisson regression with inclusion of time to epinephrine adjusting for the propensity score categorized in quintiles.

Non-linearity analysis

To assess whether there were a nonlinear relationship between time to epinephrine and our primary outcome of survival to hospital discharge we added polynomial terms (quadratic and cubic) to the multivariable model with survival to hospital discharge (the primary outcome) as the dependent variable.

Multiple imputations

In order to account for missing data on covariates, time to epinephrine and the outcomes, we performed imputation of missing data in a 3-step manner as follows. First, we imputed values for missing data on covariates. Eighty-one patients had missing data on one or more of four covariates (time of day, insertion or reinsertion of an airway, hospital teaching status and hospital type). Missing covariate values were imputed with the most prevalent age group (neonate, infant, child, adolescent) and sex-specific category. Next, we performed imputations for missing data on time to epinephrine which was missing on 228 patients. Time to epinephrine follows an approximate zero-inflated Poisson distribution and we therefore performed multiple imputations using this distribution.[1] All covariates from the main model were used in the imputation model and we created a total of 10 new data sets. Lastly, for each of these 10 data sets we imputed the outcome (28 missing for survival) using the "logistic" function in SAS "proc mi". We then performed the main analysis on these 10 data sets and combined the results across the 10 datasets using SAS "proc mianalyze" in order to obtain one overall assessment of the effect of time-to-epinephrine on the primary survival outcome. This was repeated for our secondary outcomes.



eFigure 1. Time to epinephrine and survival to hospital discharge (n = 1,558) – Multivariable analysis

The adjusted survival to hospital discharge for the various categories was calculated by multiplying the survival at 0 min (the reference category) with the relative risk for each category obtained from the multivariable model. There was a significant decrease in the risk of survival to hospital discharge when treating time to epinephrine as a continuous variable (RR: 0.95 [95%CI: 0.93 – 0.97] per minute delay, $p < 0.001$). Error bars indicate 95% confidence intervals

eTable 1. Drug interventions during the event[a]	All Patients (n = 1,558) - No. (%)
Vasoactive drugs	
Doses of epinephrine	3 (2, 6)
Norepinephrine	40 (3)
Phenylephrine	9 (1)
Dobutamine	37 (2)
Dopamine	192 (13)
Antiarrhythmic drugs	
Amiodarone	31 (2)
Lidocaine	64 (4)
Adenosine	1 (0)
Atropine	568 (37)
Procainamide	2 (0)
Others	
Sodium bicarbonate	860 (56)
Calcium chloride or gluconate	595 (39)
Dextrose bolus	114 (7)
Magnesium sulfate	51 (3)

[a] Data missing on 81 patients for total doses of epinephrine and for 26 patients for other interventions. Continuous variables are presented as medians with 1st and 3rd quartiles and categorical variables as counts (frequencies)

eTable 2. Sensitivity analyses for various definitions of neurological outcome at hospital discharge[a]					
		Bivariable		Multivariable[c]	
Good Neurological Outcome	**Overall**	**RR (95%CI)[b]**	**p-value**	**RR (95%CI)[b]**	**p-value**
PCPC of 1 or 2, or no increase in PCPC from baseline	388 / 1386 (21%)	0.94 (0.91 – 0.98)	0.002	0.96 (0.92 – 0.99)	0.02
PCPC of 1, 2, or 3	257 / 1395 (18%)	0.92 (0.88 – 0.96)	< 0.001	0.94 (0.90 – 0.98)	0.003
PCPC of 1, 2, or 3, or no increase in PCPC from baseline	296 / 1389 (21%)	0.94 (0.91 – 0.98)	0.001	0.96 (0.92 – 0.99)	0.01

[a] PCPC = pediatric cerebral performance category

[b] Per minute delay in epinephrine

[c] The multivariable model included the following variables: age group, gender, year of the arrest, illness category, pre-existing mechanical ventilation, whether the patient was monitored, whether the event was witnessed, location of arrest, time of week, time of day, first documented pulseless rhythm, hospital type and hospital teaching status

eTable 3. Propensity analysis and multiple imputations[a]				
	Propensity score analysis (n = 1,558)		Multiple imputations (n = 1,895)	
Outcome	**RR (95%CI)[b]**	**p-value**	**RR (95%CI)[b]**	**p-value**
ROSC	0.97 (0.95 – 0.98)	< 0.001	0.98 (0.96 – 0.99)	0.001
24-hour survival	0.96 (0.95 – 0.98)	0.001	0.97 (0.95 – 0.99)	0.002
Survival to hospital discharge	0.95 (0.92 – 0.98)	< 0.001	0.95 (0.93 – 0.98)	< 0.001
Favorable neurological outcome	0.94 (0.90 – 0.99)	0.01	0.95 (0.90 – 1.00)	0.04

[a] ROSC = return of spontaneous circulation

[b] Per minute delay in epinephrine

eTable 4. Outcomes according to epinephrine category[a]		
	Epinephrine category	
Outcome	≤ 5 min	≥ 5 min
ROSC	445/1,325 (66)	120/233 (49)
24-hour survival	664/1,325 (50)	81/233 (35)
Survival to hospital discharge	438/1,325 (33)	49/233 (21)
Favorable neurological outcome	196/1176 (17)	21/219 (10)

[a] ROSC = return of spontaneous circulation

References

1. Pahel BT, Preisser JS, Stearns SC, Rozier RG. Multiple imputation of dental caries data using a zero-inflated Poisson regression model. J Public Health Dent 2011;71:71-8.