Supplementary Online Content

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

eAppendix. Supplemental Methods

Time-dependent propensity score calculation

The propensity score was calculated using a nonparsimonious multivariable Cox proportional hazards model. The outcome for the Cox model was time to intubation during the cardiac arrest. Patients were censored if the resuscitation ended (with or without return of spontaneous circulation [ROSC]) without intubation. All variables presented in Table 1 were included in the model including quadratic and cubic terms of age[1] and year as a categorical variable with each year a separate category. Since administration of epinephrine is associated with outcomes in in-hospital cardiac arrest[2,3], we entered receipt of the first epinephrine dose in the Cox model as a time-dependent covariate. The potential confounding effects of epinephrine could depend on the initial rhythm and we therefore also entered an interaction between epinephrine administration and the first documented rhythm to the model. Timing of the first defibrillation in patients with a shockable rhythm is also associated with outcomes[4]. For those with a shockable rhythm, we therefore entered the first defibrillation in the Cox model as a time-dependent covariate. We chose all variables *a priori* based on prior work[1,2,4-10] and/or clinical reasoning as well as availability in the GWTG-R registry. The propensity score for each patient was then derived from the Cox model as the hazard component (i.e. the linear predictor) at any given minute from the model.[11,12] The proportional hazards assumption was tested by including an interaction between each variable (except time-varying variables) and the natural logarithm of time. Given the large sample size, the proportional hazards assumption was determined to be met if the p-value from the interaction was > 0.01. Variables not meeting the proportional hazards assumption were included as time-varying covariates allowing the variables' association with intubation to change every five minutes (i.e. different hazard ratios at 0 – 4, 5 – 9, and 10 – 15 minutes).

Rationale for the time-dependent propensity score and risk set matching approach

Traditional propensity score matching allows for matching of exposed and unexposed patients based on a set of measured characteristics at a given point in time.[13,14] However, when covariates and the exposure (i.e. intubation) are time-dependent it is desirable that the distribution of covariates are balanced not only at baseline but also at any given time where the patients are at risk of the exposure.[11] For example, the risk of intubation (as quantified by the propensity score) might depend on whether or not the patient has received epinephrine. As receipt of epinephrine may also be associated with outcomes[2,3], it is essential that the exposed and unexposed patients are balanced on this covariate to avoid biased results. Simply adding a variable with yes vs. no epinephrine administration at any time during resuscitation is not optimal, as epinephrine might have been given after the intubation. Moreover, the association between a variable (e.g. location of the event) and intubation may vary over time. By allowing variables not meeting the proportional hazards assumption to vary over time, a more flexible model is created and we ensure that the exposed and unexposed are better balanced at any given time-point.

As also described elsewhere[3,12,15], the use of risk set matching is essential to reduce bias when assessing interventions during cardiac arrest. First, the duration of a cardiac arrest is associated with intubation i.e. the longer the cardiac arrest the higher the chance of the patient being intubated. As such, if one were to simply compare intubated to nonintubated patients, this would essentially be comparing patients with longer vs. shorter duration of cardiac arrest. As an extreme example, one could imagine that all patients were intubated at minute 10. The comparison of intubated vs. nonintubated patients would then be a comparison of patients with ROSC or termination of resuscitation < 10 minutes to patients with ROSC or termination of resuscitation ≥ 10 minutes. Since the duration of the cardiac arrest (i.e. time to ROSC) is strongly associated with outcomes[16,17] and termination without ROSC is rarely performed before 10 minutes this would create severely biased results. Secondly, since interventions during cardiac arrest including intubation could theoretically influence the duration of the cardiac arrest (e.g. intubation leading to rapid ROSC), one cannot simply adjust for the duration of the cardiac arrest as early ROSC could be a mediator of the potential effect of intubation on outcomes such as survival to hospital discharge.

Lastly, the practical importance of using risk set matching is evident from two observational studies regarding epinephrine administration in out-of-hospital cardiac arrest. The two studies used the same database but one used time-dependent propensity score matching[12] whereas the other used traditional propensity score matching[18], ultimately yielding differing results with important differences in the conclusions of the paper. While it is obviously unclear which study had the correct results, the findings do indicate that the concepts discussed above are not purely theoretical.

Interpretation of the effect estimates

The interpretation of the results from the analyses using time-dependent propensity scores and risk set matching is different from that obtained from traditional logistic regression or propensity score–matched analysis. The effect estimate (i.e. risk ratio) from the current study should be interpreted as the risk of the outcome (e.g. survival) in a patient being intubated during cardiac arrest at a given minute (from 0 to 15) compared to a similar patient (based on characteristics at that minute) who was not intubated before or at that minute ("as yet untreated").[19] These "as yet untreated" patients include those being intubated at a later time point as well as patients never intubated. We believe this interpretation is more clinically relevant as a clinician might consider intubating a patient at any given minute with future events being unknown.[15] That said, the effect estimates obtained from this approach (assuming no confounding, no selection bias, and no information bias) would likely be closer to one (i.e. less of an effect) compared to a randomized controlled trial comparing intubation to strictly no intubation.

Multiple imputation

We performed multiple imputation assuming that the data were "missing at random".[20] Data were missing or inconsistent on at least one variable for 35,731 patients (25%) with a median number of missing variables of 0 (quartiles: 0, 0, mean: 0.5, standard deviation: 1.4). In order to account for this, missing values for intubation, categorical covariates, and the outcomes (ROSC, survival and good functional outcome) were imputed using the fully conditional specification method[21] and a total of 20 data sets were created[22]. Time to intubation and time to the end of resuscitation were then imputed for each of the 20 data sets using Poisson distributions and time to epinephrine/defibrillation was imputed using zero-inflated Poisson distributions for those receiving epinephrine/defibrillation.[3,23,24] We then performed the time-dependent propensity score matching and modified Poisson regression on each of these 20 data sets and combined the results using SAS “proc mianalyze”. For this analysis, we accounted for the matching and not hospital-level clustering.

Non–time-dependent propensity score matching

As a *post hoc* analysis, we conducted a non–time-dependent propensity score–matched analysis. For this analysis, the propensity score was calculated based on a logistic regression model with intubation within the first 15 minutes (but otherwise irrespective of timing) as the outcome. This model included all variables included in our main analysis except administration of epinephrine and receipt of defibrillation since these are time-dependent and therefore cannot be included in a meaningful way. Based on the propensity score, patients were then matched using a nearest neighbor-matching algorithm with a maximum caliber of 0.01 of the propensity score. After the matching, similar analyses were performed as for our time-dependent propensity score–matched cohort. However, as discussed above, this approach has important limitations and the results should be interpreted with caution.

eReferences

1. Andersen LW, Bivens MJ, Giberson T, et al. The relationship between age and outcome in out-of-hospital cardiac arrest patients. Resuscitation 2015;94:49-54.

2. Donnino MW, Salciccioli JD, Howell MD, et al. Time to administration of epinephrine and outcome after in-hospital cardiac arrest with non-shockable rhythms: retrospective analysis of large in-hospital data registry. BMJ 2014;348:g3028.

3. Andersen LW, Kurth T, Chase M, et al. Early epinephrine in in-hospital cardiac arrest patients with an initial shockable rhythm: a propensity score matched analysis. BMJ 2016;353.

4. Chan PS, Krumholz HM, Nichol G, Nallamothu BK, American Heart Association National Registry of Cardiopulmonary Resuscitation I. Delayed time to defibrillation after in-hospital cardiac arrest. N Engl J Med 2008;358:9-17.

5. Chan PS, Nichol G, Krumholz HM, Spertus JA, Nallamothu BK, American Heart Association National Registry of Cardiopulmonary Resuscitation I. Hospital variation in time to defibrillation after in-hospital cardiac arrest. Arch Intern Med 2009;169:1265-73.

6. Chan PS, Nallamothu BK, Krumholz HM, et al. Long-term outcomes in elderly survivors of in-hospital cardiac arrest. N Engl J Med 2013;368:1019-26.

7. Girotra S, Nallamothu BK, Spertus JA, et al. Trends in survival after in-hospital cardiac arrest. N Engl J Med 2012;367:1912-20.

8. Meaney PA, Nadkarni VM, Kern KB, Indik JH, Halperin HR, Berg RA. Rhythms and outcomes of adult in-hospital cardiac arrest. Crit Care Med 2010;38:101-8.

9. Peng TJ, Andersen LW, Saindon BZ, et al. The administration of dextrose during in-hospital cardiac arrest is associated with increased mortality and neurologic morbidity. Crit Care 2015;19:160.

10. Nadkarni VM, Larkin GL, Peberdy MA, et al. First documented rhythm and clinical outcome from in-hospital cardiac arrest among children and adults. JAMA 2006;295:50-7.

11. Lu B. Propensity score matching with time-dependent covariates. Biometrics 2005;61:721-8.

12. Nakahara S, Tomio J, Takahashi H, et al. Evaluation of pre-hospital administration of adrenaline (epinephrine) by emergency medical services for patients with out of hospital cardiac arrest in Japan: controlled propensity matched retrospective cohort study. BMJ 2013;347:f6829.

13. Rosenbaum PR, Rubin DB. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. The American Statistician 1985;39:33-8.

14. D'Agostino RB, Jr. Propensity scores in cardiovascular research. Circulation 2007;115:2340-3.

15. Andersen LW, Raymond TT, Berg RA, et al; American Heart Association's Get With The Guidelines–Resuscitation Investigators. Association between tracheal intubation during pediatric in-hospital cardiac arrest and survival. JAMA 2016;316:1786-97.

16. Chan PS, Spertus JA, Krumholz HM, et al. A validated prediction tool for initial survivors of in-hospital cardiac arrest. Arch Intern Med 2012;172:947-53.

17. Wang CH, Huang CH, Chang WT, et al. Monitoring of serum lactate level during cardiopulmonary resuscitation in adult in-hospital cardiac arrest. Crit Care 2015;19:344.

18. Hagihara A, Hasegawa M, Abe T, Nagata T, Wakata Y, Miyazaki S. Prehospital epinephrine use and survival among patients with out-of-hospital cardiac arrest. JAMA 2012;307:1161-8.

19. Li P, Propert K, Rosenbaum P. Balanced risk set matching. Journal of the American Statistical Association 2001;96:13.

20. Li P, Stuart EA, Allison DB. Multiple Imputation: A Flexible Tool for Handling Missing Data. JAMA 2015;314:1966-7.

21. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res 2007;16:219-42.

22. Bodner TE. What improves with increased missing data imputations? Structural Equation Modeling: A Multidisciplinary Journal 2008;15:651-875.

23. 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.

24. Andersen LW, Berg KM, Saindon BZ, et al. Time to epinephrine and survival after pediatric in-hospital cardiac arrest. JAMA 2015;314:802-10.

eTable 1. Definitions of Preexisting Conditions

Variable	Definition
History of myocardial infarction	Documented diagnosis of myocardial ischemia (acute coronary syndrome)/infarction prior to this admission
Myocardial infarction this admission	Documented diagnosis of myocardial ischemia (acute coronary syndrome)/infarction this admission.
History of heart failure	Documented diagnosis of congestive heart failure prior to this admission
Heart failure this admission	Documented diagnosis of congestive heart failure this admission prior to the cardiac arrest
Respiratory insufficiency	Evidence of acute or chronic respiratory insufficiency within 4 hours up to the time of the event, defined by any of the following: • PaO_2/FiO_2 ratio < 300 (in the absence of preexisting documented cyanotic heart disease) • PaO_2 < 60 mm Hg (in the absence of preexisting documented cyanotic heart disease) • SaO_2 < 90 % (in the absence of preexisting documented cyanotic heart disease) • $PaCO_2$, $EtCO_2$ or $TcCO_2$ > 50 mm Hg • Spontaneous respiratory rate > 40/min or < 5/min • Requiring noninvasive ventilation (e.g., bag-valve-mask, mask or nasal continuous/bi-level positive airway pressure, negative pressure ventilation)
Diabetes mellitus	Documented diagnosis of Type I or Type II diabetes mellitus
Renal insufficiency	Evidence of renal insufficiency prior to the event, defined by any of the following: • Requiring ongoing dialysis or extracorporeal filtration therapies • Creatinine > 2 mg/dL within 24 hours up to the time of the cardiac arrest
Metastatic/hematologic malignancy	Any solid tissue malignancy with evidence of metastasis, or any blood borne malignancy
Hypotension/hypoperfusion	Evidence of hypotension within 4 hours up to the time of the event, defined by any of the following: • Systolic blood pressure < 90 mm Hg or mean arterial pressure < 60 mm Hg • Vasopressor/inotropic requirement after volume expansion (except for dopamine ≤ 3 mcg/kg/min) • Intra-aortic balloon pump
Pneumonia	Documented diagnosis of active pneumonia, where antibiotics have not yet been started or the pneumonia is still being treated with antibiotics

eTable 1. Definitions of preexisting conditions (continued)	
Variable	**Definition**
Baseline depression in central nervous system function	Evidence of chronically depressed central nervous system function including a motor, cognitive, or functional baseline deficit (at time of system entry)
Metabolic/electrolyte abnormality	Evidence of metabolic/electrolyte abnormality within 4 hours up to the time of the event, defined by any of the following: • Sodium < 125 or > 150 mEq/L • Potassium < 2.5 or > 6 mEq/L • pH < 7.3 or > 7.5 (arterial) • Lactate > 2.5 mmol/L, • Blood glucose < 60 mg/dL
Septicemia	Bloodstream infection where antibiotics have not yet been started or the infection is still being treated with antibiotics. Documentation of "presumed sepsis" without confirmatory positive blood cultures would not constitute septicemia
Acute central nervous system nonstroke event	Evidence of decreased mental status, delirium, or coma not due to acute stroke within 4 hours up to time of the event
Hepatic insufficiency	Evidence of hepatic insufficiency within 24 hours up to the time of the event, defined by any of the following: • Total bilirubin > 2 mg/dL and aspartate aminotransferase > 2 times normal • Cirrhosis
Acute stroke	Documented diagnosis during this hospitalization of stroke, ischemic stroke, or hemorrhagic stroke
Major trauma	Evidence of multi-system injury or single system injury associated with shock or altered mental status during this admission and prior to the cardiac arrest

eTable 2. Intubation Confirmation Method(s) in Those Intubated Within 15 Minutes

Confirmation method	Intubation within 15 min (n = 70,279)[a]
Expired carbon dioxide detector	47,872 (68)
Flexible/fiberoptic laryngoscope	376 (1)
Esophageal detector device	485 (1)
Other (except auscultation)	50,189 (71)
None documented	5058 (7)

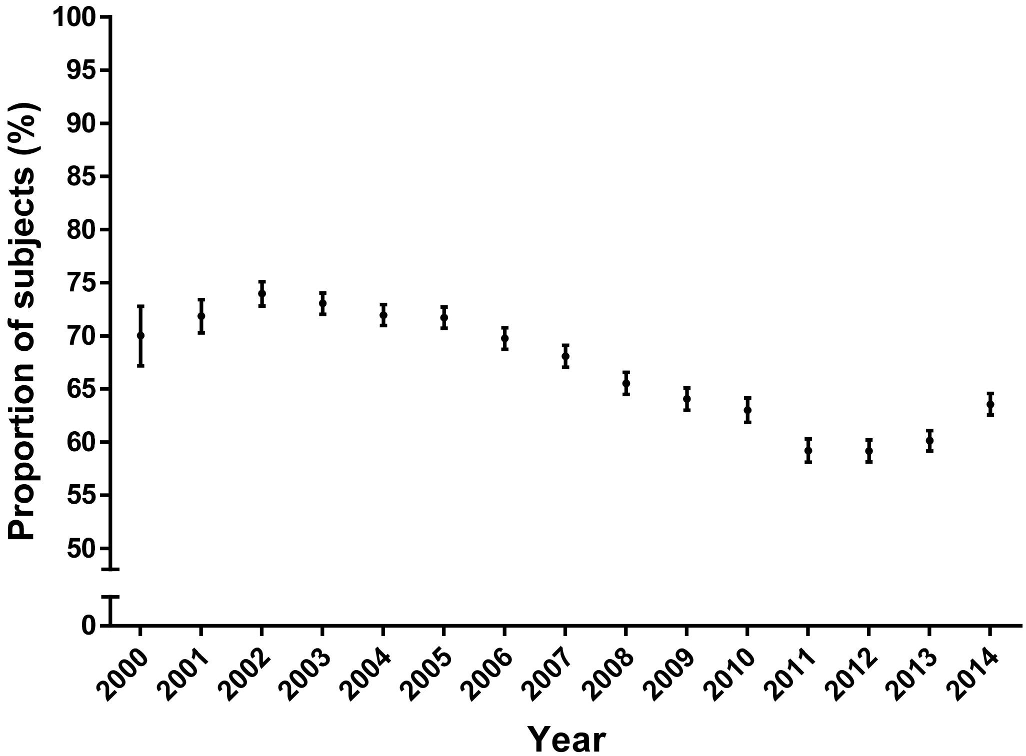
[a] Data missing on 1,336 patients

eTable 3. Documented Drugs Administered During the Cardiac Arrest Other Than Epinephrine

Drug	All patients (n = 107,351)[a]
Vasoactive drugs other than epinephrine	
Norepinephrine	11,274 (11)
Phenylephrine	3314 (3)
Dobutamine	2371 (2)
Dopamine	19,519 (18)
Other vasopressor	2904 (3)
Antiarrhythmic drugs	
Amiodarone	18,256 (17)
Lidocaine	9051 (8)
Atropine	65,507 (61)
Procainamide	189 (0)
Adenosine	379 (0)
Others	
Sodium bicarbonate	52,383 (49)
Calcium chloride/carbonate	27,349 (25)
Dextrose bolus	6425 (6)
Magnesium sulfate	10,077 (9)

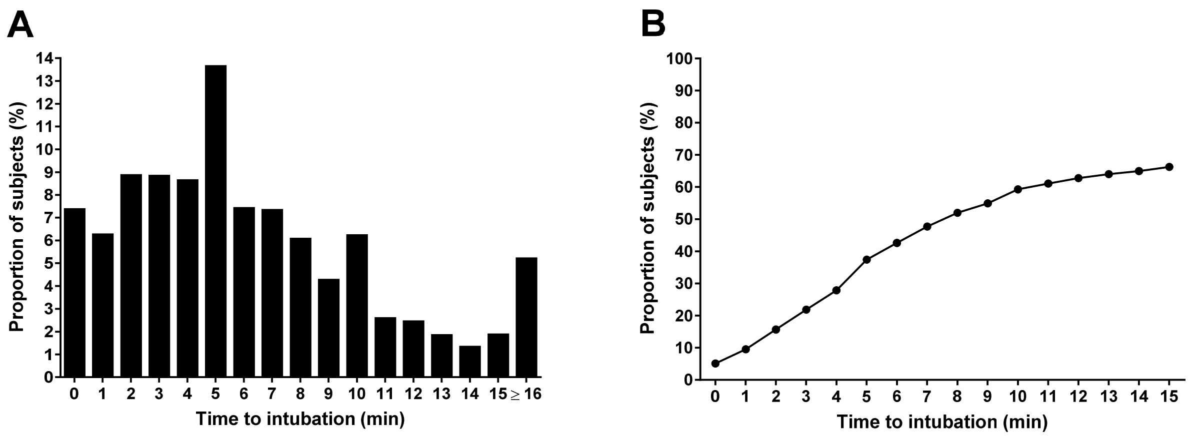
[a] Data missing on 728 patients

eFigure 1. Proportion of In-Hospital Cardiac Arrest Patients Intubated Within 15 Minutes Over Time



Proportion of patients with in-hospital cardiac arrest intubated within 15 minutes according to year. The error bars represent exact binomial 95% confidence intervals. There was a significant decrease in the proportion of patients intubated ($p < 0.001$ for trend).

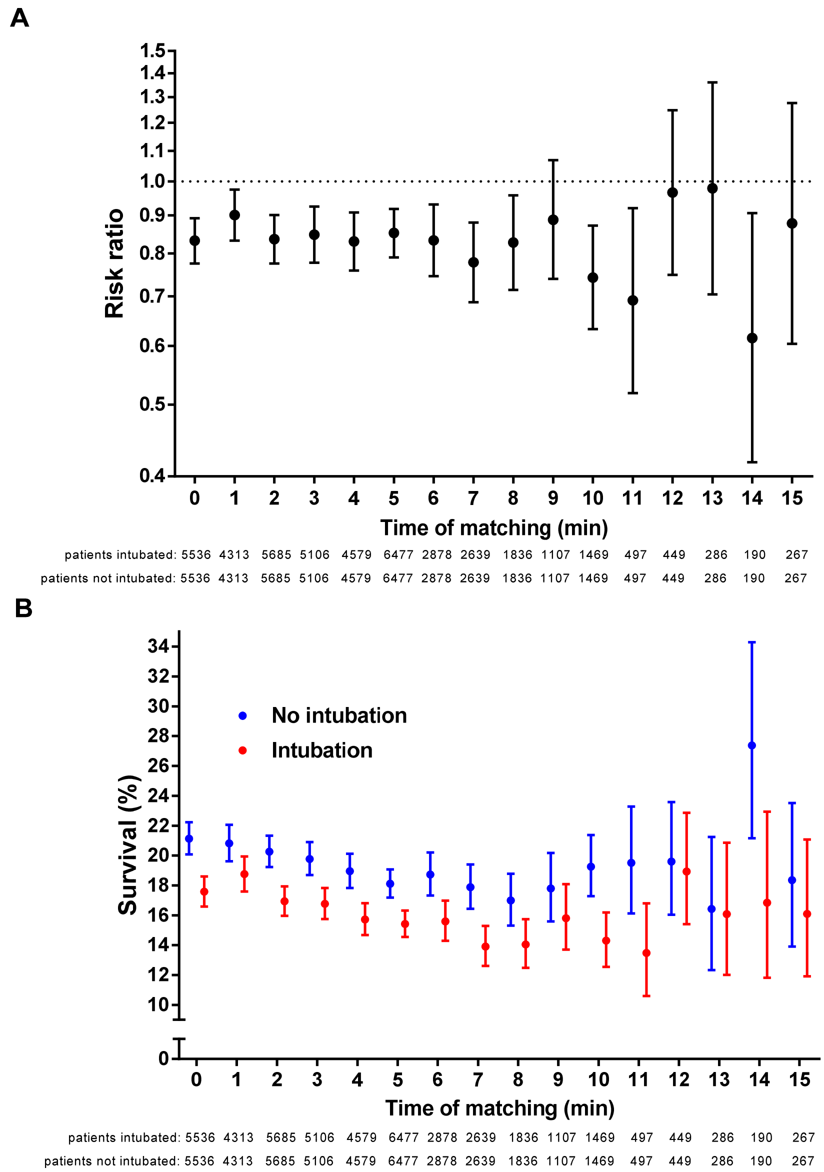
eFigure 2. Distribution of Time to Intubation in Those Intubated (A) and Cumulative Proportion of Patients Intubated in the Entire Cohort (B)



A: Distribution of the time to intubation in those intubated (n = 75,579). In those intubated within the first 15 minutes, the median time to intubation was 5 minutes (quartiles: 3, 8)

B: The cumulative proportion of patients intubated within the first 15 minutes in the full cohort (n = 108,079). 66% of all patients, corresponding to 95% of those intubated, were intubated within the first 15 minutes.

eFigure 3. Risk Ratios (A) and Survival to Hospital Discharge (B) Comparing Intubation to No Intubation According to the Time of Matching



A: Risk ratios for the comparison of intubation to no intubation in the matched cohort according to the minute of matching for the outcome survival to hospital discharge. Values below one indicates that intubation was associated with decreased survival. When time of matching was treated as a linear continuous variable, there was no interaction between intubation and the time of matching (p = 0.22).

B: Survival to hospital discharge in the matched cohort according to intubation and minute of matching with 95% exact binomial confidence intervals.

The sample size for each minute is provided below the figure.