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Clinical paper

Dynamic prediction of patient outcomes during ongoing cardiopulmonary resuscitation☆

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ABSTRACT

Purpose: The probability of the return of spontaneous circulation (ROSC) and subsequent favourable outcomes changes dynamically during advanced cardiac life support (ACLS). We sought to model these changes using time-to-event analysis in out-of-hospital cardiac arrest (OHCA) patients.
Methods: Adult (≥18 years old), non-traumatic OHCA patients without prehospital ROSC were included. Utstein variables and initial arterial blood gas measurements were used as predictors. The incidence rate of ROSC during the first 30 min of ACLS in the emergency department (ED) was modelled using spline-based parametric survival analysis. Conditional probabilities of subsequent outcomes after ROSC (1-week and 1-month survival and 6-month neurologic recovery) were modelled using multivariable logistic regression. The ROSC and conditional probability models were then combined to estimate the likelihood of achieving ROSC and subsequent outcomes by providing *k* additional minutes of effort.
Results: A total of 727 patients were analyzed. The incidence rate of ROSC increased rapidly until the 10th minute of ED ACLS, and it subsequently decreased. The conditional probabilities of subsequent outcomes after ROSC were also dependent on the duration of resuscitation with odds ratios for 1-week and 1-month survival and neurologic recovery of 0.93 (95% CI: 0.90–0.96, $p < 0.001$), 0.93 (0.88–0.97, $p = 0.001$) and 0.93 (0.87–0.99, $p = 0.031$) per 1-min increase, respectively. Calibration testing of the combined models showed good correlation between mean predicted probability and actual prevalence.
Conclusions: The probability of ROSC and favourable subsequent outcomes changed according to a multiphasic pattern over the first 30 min of ACLS, and modelling of the dynamic changes was feasible.

Introduction

Termination of resuscitation (TOR) in out-of-hospital cardiac arrest (OHCA) should be based on futility, and futility should be determined based on the objective estimation of possible outcomes from further effort that might be exerted. These outcomes are determined by achieving two important goals, the return of spontaneous circulation (ROSC) and post-resuscitation recovery. They are different physiologic processes, with the latter completely depending on the first. Therefore, we should consider both of these processes if we are to predict the clinical courses of patients in whom ROSC has not yet been achieved. This problem can be approached by objective estimation of both the likelihood of attaining ROSC and the conditional probabilities of post-resuscitation recovery assuming ROSC. However, this task is difficult because both of the processes are time-dependent. Firstly, the potential to achieve ROSC (e.g., resuscitability) changes over time.[1] Secondly, the conditional probability having any meaningful recovery after ROSC also changes based on the duration of resuscitation prior to ROSC.[2] Thirdly, combining the two estimates can also be difficult because it involves merging two constantly changing values.

The main hypothesis of this study was that the probabilities of achieving ROSC and subsequent favourable outcomes (1-week and 1-month survival and neurologic recovery within 6 months) can be simultaneously estimated as a function of initial patient

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conditions and the duration of ACLS in the emergency department (ED). To prove this hypothesis, we first modelled the incidence rate of the first ROSC as a function of the ACLS time variable *t*, which is the instantaneous chance of attaining ROSC at a particular point in time *t*, in patients who have been unresponsive until that point. Then, we modelled the conditional probabilities of subsequent recoveries after a ROSC as a function of the time duration required for the ROSC. Then, we combined these probabilities to estimate the chance of achieving ROSC and subsequent favourable outcomes given the duration of additional resuscitation efforts during an ongoing resuscitation. The primary goal of this study was to prove our main hypothesis that the dynamic prediction of multiple clinical outcomes during ongoing resuscitation is feasible. The secondary goal was to describe the dynamic changes in the probability of various clinical outcomes during ACLS in the ED.

Materials and methods

This was a single-centre, observational study of OHCA patients resuscitated in an ED from January 2008 to February 2015. A prospective OHCA registry was used as the data source.[3,4] The institutional review board at the study site approved the analysis and waived the requirement for informed consent.

Study setting

The study facility is an academic hospital located in a city with a population of 1,000,000 in South Korea with more than 80,000 ED visits annually. The Korean emergency medical service system is single-tiered and is provided by fire station-based emergency medical technicians (EMTs) hired by the government.[5] EMTs are classified into two levels: with level 1 (EMT intermediate in the US) and level 2 (EMT basic in the US).[6] All ambulances are equipped with an automated external defibrillator, and most of them are staffed by two to three EMTs. The level of prehospital CPR was restricted to basic life support (BLS), and prehospital administration of ACLS medications was not allowed according to the law.[5] Although placement of endotracheal tubes or laryngeal mask airways by level 1 EMTs is allowed, they are seldom used in the field, with a previous nationwide study showing that the BVM-only strategy was adopted in 87.9% of OHCA with presumed cardiac aetiology treated by level 1 EMTs.[6] Regarding ACLS and post-resuscitation care in the ED, our facility follows the most up-to-date American Heart Association (AHA) guideline, which was last updated in late 2014. We use manual compression with audio feedback (metronome). Arterial blood sampling is attempted immediately at the beginning of ACLS. Therapeutic hypothermia is recommended if indicated. Withdrawal of ongoing life-sustaining care is considered illegal because of the absence of laws or national guidelines in South Korea.[7]

Participants and data collection

The inclusion criteria were adult patients ($\geq$18 years old) who received ACLS upon ED arrival due to absence of a pulse. Cases of traumatic cardiac arrest due to penetrating or blunt trauma were excluded. The primary data source was a prospective ED OHCA registry.[3,4] The registry is maintained by ED research assistants and is reviewed monthly by a board-certified emergency physician. We selected predictors that are easily available during ongoing resuscitation, such as age, sex, cardiac arrest location, presence of witnesses, presumed aetiology, initial rhythm, time to BLS, prehospital low flow time and initial PaO_2, $PaCO_2$ and base deficit levels (Supplementary Table 1). The outcome variables were time to first ROSC (or termination), 1-week and 1-month survival and 6-month neurologic recovery, which was defined as a 6-month cerebral performance category (CPC) score of 1 or 2.[8]

Data analysis

The main prediction task that we performed through our modelling was to estimate the likelihood of achieving the first ROSC and other subsequent favourable outcomes by providing *k* additional minutes of resuscitation effort beginning at the *j*th minute of unresponsive resuscitation within the first 30 min after admission to the ED. The analytical procedures are briefly summarized as follows. Assuming that the decision to terminate ongoing resuscitation was based solely on the observed patient characteristics and the duration of the resuscitation effort, and thus resuscitation termination at each time point was conditionally independent of ROSC if the baseline covariate set was identical, we constructed a time-to-event model of ROSC using spline-based parametric survival analysis, which estimated the hazard (instantaneous incidence rate) of attaining the first ROSC as a function of an ACLS time variable *t*.[9,10] We additionally constructed three complementary multivariable logistic regression models using the Bayesian information criterion (BIC) for variable selection to estimate the conditional probabilities of achieving target outcomes (1-week and 1-month survival and neurologic recoveries within 6 months) given the time until ROSC and patient characteristics. Then, we combined each of the three complementary models with the time-to-event model of ROSC to estimate the likelihood of obtaining target outcomes by *k* minutes of additional resuscitative efforts during the first 30 min of ACLS in the ED. Overall calibration was tested by comparing mean predicted probability and the actual prevalence of the clinical outcomes.

Categorical variables were reported using frequencies and proportions, while continuous variables were reported using medians and interquartile ranges (IQRs). Wilcoxon's rank-sum test, the chi-square test, or Fisher's exact test was performed to describe differences between groups. All of the numerical variables were dichotomized at their medians before both univariable and multivariable regression analyses. *p*-Values <0.05 were considered significant. All of the statistical analyses were performed using the R package, version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

Dynamic prediction of ROSC during ED ACLS

The likelihood of attaining ROSC during ED ACLS can dynamically change. To model the phenomenon using time-to-event analysis, we first obtained its hazard function, which is, by definition, the instantaneous probability of attaining ROSC, conditional on there having not yet been ROSC. We first generated a multivariable Cox regression model with time-varying coefficients (TVCs), which yielded the final equation for $h_{rosc(t;Z)}$:

$$h_{rosc}(t;Z) = h_{rosc0}(t) \cdot \exp(\beta \cdot Z + \beta_{tv} \cdot \ln(t) \cdot z_{tv})$$

where $h_{rosc0}(t)$ is baseline hazard function of ROSC, and $\beta_{tv} \cdot \ln(t) \cdot z_{tv}$ are the TVC terms of variables with significant time-varying effects. Variable selection was performed by conducting univariable Cox regression analyses both with and without a TVC term. Variables were included if the *p*-value was less than 0.2 or if there was any statistically significant time-varying effect (*p* for TVC term <0.05), in which case the TVC term was also included. The proportional hazard assumption of the multivariable Cox model was assessed by examination of Schoenfeld residual plots, and additional TVCs were included if required. The overall fit of the model was tested with Gronnesby and Borgan's goodness-of-fit test.[11] After fitting the multivariable Cox model, we estimated the