G Model
RESUS 7047 1–7

ARTICLE IN PRESS

Resuscitation xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

ELSEVIER

EUROPEAN RESUSCITATION COUNCIL

Clinical paper

# Factors associated with the outcome of out-of-hospital cardiopulmonary arrest among people over 80 years old in Japan☆

Q1 Takashi Nagata[a,*], Takeru Abe[b], Manabu Hasegawa[c], Akihito Hagihara[d]

[a] Kyushu University, Faculty of Medical Sciences, Department of Advanced Medical Initiatives, Fukuoka, Japan
[b] Yokohama City University Medical Center, Advanced Critical Care and Emergency Center, Yokohama, Japan
[c] Ministry of Health, Welfare and Labor, Tokyo, Japan
[d] Kyusyu University Graduate School of Medicine, Department of Health Services Management and Policy, Fukuoka, Japan

ARTICLE INFO

*Article history:*
Received 11 August 2016
Received in revised form
27 December 2016
Accepted 14 January 2017

*Keywords:*
Out of hospital cardiac arrest
Older people
Signal detection analysis
Termination of resuscitation
Return of spontaneous circulation
Epinephrine

ABSTRACT

*Aim:* To determine if termination of resuscitation should be considered for older individuals, we sought to identify factors associated with clinical outcome following out-of-hospital cardiac arrest (OHCA) in people ≥80 years old and over.

*Methods:* A prospective, population-based, observational study was conducted for ≥80-year-old individuals who experienced out-of-hospital cardiac arrest and to whom resuscitation was provided by emergency responders between January 1, 2005 and December 31, 2012 (n = 377,577). The primary endpoint was 1-month survival. Signal detection analysis was applied to estimate predictive factors among 17 variables.

*Results:* Among all out-of-hospital cardiac arrest cases, 59.4% were of cardiac origin, and 1-month survival rate was 3.3%. Following signal detection analysis, cases of both cardiac and non-cardiac origin were categorized into three subgroups defined by return of spontaneous circulation (ROSC) and epinephrine use. One-month survival ranged between 1.2 and 41.0% for the three subgroups of cardiac origin and between 2.0 and 41.1% for the three subgroups of non-cardiac origin.

*Conclusions:* ROSC was the most significant predictor of 1-month survival among patients with cardiac and non-cardiac OHCA who were ≥80 years old. Absence of ROSC might be an important factor to the termination of resuscitation rule for OHCA in individuals who are ≥80 years old.



## Introduction

As populations age, the occurrence of out-of-hospital cardiopulmonary arrest (OHCA) also increases. Survival is markedly lower for cardiopulmonary arrest outside of a hospital in comparison to within a hospital. In addition, OHCA survival further declines as individuals get older.[1–5] Kitamura et al. showed in a nationwide study in Japan that the 2009 incidence rates of OHCA of cardiac origin among people 80–89 years old and >90 years old were 91.9 and 196.7, respectively, per 100,000 persons, while 1-month survival rates among people with OHCA of cardiac origin who were 80–89 years old and >90 years old were 1.6% and 0.5%, respectively.[6] Because Japan has a rapidly aging society, in which older individuals aged 65 years old and over account for more than 25% of the population, OHCA is poised to have an increasing effect on societal mortality. Q2

There are limited reports about resuscitation outcomes of older patients with OHCA. A study in Melbourne predicted that OHCA will increase among older individuals, but concluded that consequences of OHCA among older patients have improved annually.[4] Similarly, Kitamura et al. showed that survival among older people with OHCA improved from 1999 to 2011 due to multiple efforts, such as public access to automated external defibrillators (AED) and bystander-initiated CPR.[7]

In view of treatment costs and quality of life of OHCA patients, resuscitation outcomes are not favorable in older individuals.[8,9] In current discussions of how to conduct termination of resuscitation (TOR),[10–12] experts emphasize that TOR should not be determined based on patient age.[13] However, the incidence of refractory OHCA among older people, especially those ≥80 years old, has increased.[6] Therefore, to improve resuscitation outcomes for OHCA in all age groups with limited medical resources, implementation of TOR for older people should be considered in Western countries with

☆ A Spanish translated version of the abstract of this article appears as Appendix in the final online version at doi:10.1016/j.resuscitation.2017.01.014.

* Corresponding author at: Kyushu University, Faculty of Medical Sciences, Department of Advanced Medical Initiatives, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. Fax: +81 92 642 6224.
*E-mail address:* nagata.takashi@kyudai.jp (T. Nagata).

http://dx.doi.org/10.1016/j.resuscitation.2017.01.014
0300-9572/© 2017 Elsevier B.V. All rights reserved.



Please cite this article in press as: Nagata T, et al. Factors associated with the outcome of out-of-hospital cardiopulmonary arrest among people over 80 years old in Japan. Resuscitation (2017), http://dx.doi.org/10.1016/j.resuscitation.2017.01.014

rapidly aging societies.[11,14] In Japan, TOR is not currently performed in clinical settings, and the debate surrounding TOR has just begun.[10]

Because populations ≥65-year-old are estimated to increase in developed countries in the future, identifying factors conducive to improved prognosis of older patients with OHCA is socially and medically necessary. OHCA outcomes among older people are generally poor, and the discussion about TOR for older people is controversial.[15] Thus, the purpose of this study was to identify factors associated with clinical outcome following OHCA in people ≥80 years old.

## Methods

### *Study population*

The National Japan Utstein Registry at the Fire and Disaster Management Agency (FDMA) is a prospective, nationwide, population-based registry for OHCA.[16] This observational study included all OHCA cases aged 80–110 years old (defined as OHCA ≥80 years) registered between January 1, 2005, and December 31, 2012, treated by emergency medical service (EMS) personnel, and transported to hospitals during the study period. Compared with other age groups, individuals with OHCA ≥80 years have poor clinical outcomes, so this was the target population.[6] A detailed description of the Japan Utstein Registry has been reported previously.[17–19] The FDMA provided anonymous data, so written informed consent was waived. The ethical committee of Kyushu University Graduate School of Medicine approved the protocol for data analysis.

### *Study variables, outcomes, and predictors*

Data were collected prospectively by FDMA with a form that queries gender, age, cause of cardiac arrest, bystander witness status, first documented ECG, presence and type of CPR by bystander, and intubation and administration of epinephrine by EMS personnel.

The main outcome variable assessed in this study was 1-month survival after resuscitation.[20] Explanatory variables were categorized into three groups: demographic and transport, basic life support (BLS) provided by a bystander, and advanced life support provided by EMS personnel with Advanced Life Support skills (or "life-saving technician"). Demographic and transport information included gender, age, presence of life-saving technician in the ambulance, presence of medical doctor in the ambulance, time from emergency call to ambulance arrival on the scene, time from emergency call to hospital arrival, and initial electrocardiogram (ECG) waveform. Information about BLS provided by a bystander included chest compression, rescue breathing, and use of an AED. Information about advanced life support provided by EMS personnel included defibrillation, advanced airway device use, intravenous access, and epinephrine administration. Duration of time or number of cardiopulmonary resuscitation (CPR) cycles were not included in the dataset. Cause of cardiac arrest was diagnosed by the physician who contacted emergency responders in the ambulance, or in the hospital. Return of spontaneous circulation (ROSC), including transient return, was also documented. Cases with missing data for age and other variables were excluded from further analyses.

### *Statistical analysis*

The statistical analyses used in most prior studies of factors associated with OHCA outcomes are based on $\chi^2$ test with stratification, multivariate regression analysis, or linear regression analysis.[21,22] These statistical methods are effective when a model includes the interaction of two variables. However, if a model includes interaction of three or more variables, there is typically a problem of multi-colinearity, which complicates the interpretation of higher-order interactions. To address these problems, Kraemer and coworkers[23,24] has advocated a signal detection analysis (SDA) method, which recursively reveals the strongest interaction of factors among groups based on the largest $\chi^2$ statistic and significance probability ($p < 0.05$). Because multiple potential factors can mutually interact to influence resuscitation outcomes of older patients with OHCA, we used SDA to evaluate factors for resuscitation outcome.

First, study data for OHCA ≥80 years were randomly divided into two groups using a split-half method: one for prediction analysis (Sample 1, n = 188,745), and one for validation analysis (Sample 2, n = 188,832).[25,26] Randomization was performed using SPSS software (ver. 19; IBM, Armonk, NY, USA). Non-significant test results were considered to guarantee validity of randomization and, subsequently, homogeneity between samples 1 and 2.[25,26]

Next, SDA (ROC 5.0; ROC software, Austin, TX, USA) was applied to develop a prediction model for the outcome of ≥80 years cardiac and non-cardiac origin OHCA. SDA also was applied to each of five non-cardiac OHCA origins: stroke, respiratory disease, malignancy, external cause, and other. Based on past studies, analysis included 17 essential variables, including basic information (age, gender, medical staff ride, etc.), cardiac arrest witness, bystander CPR, and hospital diagnosis and treatment. These 17 variables produce in excess of millions of possible combinations, so logistic regression or linear regression cannot adequately analyze every combination. Therefore, we sought to develop a predictive model (prediction sample) of clinical outcomes for the OHCA ≥80 years cases by using SDA on nationwide Utstein-style data available in Japan and to subsequently confirm the validity of this model (validation sample).

SDA was performed on sample 1 to identify factors related to the proportion of cases evaluated as 1-month survival of the OHCA ≥80 years. SDA is a recursive partitioning and nonparametric process that assesses combinations of independent variables categorized into two subgroups according to selected criteria, for example, dichotomous variables or a certain cut-off point for continuous variables.[23,24] The SDA partitioning process identifies unknown combinations of certain independent variables to maximize both sensitivity and specificity in predicting patient outcome. The optimally efficient variable or cut-off point is determined by the maximum weighted-kappa coefficient.[23,24] After selecting the first variable, the program repeatedly partitions for each subgroup using all independent variables until stopping rules are applied. Stopping rules for partitioning processes were triggered when: (1) a subgroup contained <10 patients; (2) no significant variable was found ($p < 0.05$); and (3) <0 values were in the lower limits of the 95% confidence interval for maximum weighted-kappa coefficient.

The validation sample (Sample 2) was categorized into mutually exclusive subgroups based on information from SDA in the prediction sample (Sample 1). Analysis of variance (ANOVA) procedures for continuous variables and tests of independence for dichotomous or discrete variables were used. Two-tailed $p$-values <0.05 were considered statistically significant. Analyses were conducted using SPSS.

## Results

Out of 925,288 OHCA cases registered by the National Japan Utstein Registry from 2005 to 2012, this study included 377,577 cases of OHCA ≥80 years. Remaining registry cases were excluded according to selection criteria such as missing vari-



Please cite this article in press as: Nagata T, et al. Factors associated with the outcome of out-of-hospital cardiopulmonary arrest among people over 80 years old in Japan. Resuscitation (2017), http://dx.doi.org/10.1016/j.resuscitation.2017.01.014