

# **Call to Door Timing in Out-of-hospital Cardiac Arrest**

## **Study Protocol**

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## **1. Background**

Out-of-hospital cardiac arrest (OHCA) remains a significant global health challenge, with survival rates showing modest improvement but still remaining low. The chain of survival, including early recognition, initiation of CPR, rapid defibrillation, and effective advanced life support, is crucial for improving survival rates in sudden cardiac arrest cases. Efforts to reduce emergency medical services (EMS) response times have been instrumental in enhancing survival rates during the pre-pandemic period.

Recent studies have revealed that the coronavirus disease 2019 (COVID-19) pandemic has adversely affected EMS response times, potentially leading to delayed treatment for patients with OHCA. This has coincided with a sharp increase in OHCA mortality during the COVID-19 pandemic era. However, there is a lack of data regarding the clinical implications of the time delay from first emergency call to hospital arrival on the prognosis of OHCA patients. Therefore, this study aims to investigate the impact of time from call to hospital arrival (CtD time) on clinical outcomes in patients experiencing OHCA.

## **2. Methods**

**2.1. Patients:** Patients will be recruited from The Korea OHCA registry

**2.2. Time of recruitment:** January 1, 2016 – December 31, 2021

**2.3. Inclusion criteria:** Patients of out-of-hospital cardiac arrest were reported to The Korea OHCA Registry

**2.4. Exclusion criteria:**

- Non-cardiac origin (external cause including asphyxia, hanging, fall, drowning, traffic injury and drug overuse, respiratory, non-traumatic bleeding, malignancy, brain hemorrhage, other disease, unknown)
- Under 18 years of age
- Patients who did not receive any CPR
- Missing data

**2.5. Sample size calculation**

Between 2016 and 2021, 182,508 patients have been included in the Korea OHCA registry. Of these about 28% have been non-cardiac origin, about 0.5% have been under 18 years of age, about 25% has been did not receive any CPR, and about 4% has been missing data. Thus we assume that about 42% i.e. 76,505 patients will fulfil the inclusion criteria without exclusion criteria

**2.6. Hypothesis**

- 1) The study hypothesizes that a delayed time interval between primary emergency call and hospital arrival (Call-to-door time[CtD]) is significantly associated with decreased survival rates and unfavorable neurological outcomes in OHCA patients.
- 2) The COVID-19 pandemic has exacerbated the delays in CtD time, further hindering timely treatment and negatively impacting the survival rates and outcomes of OHCA patients.
- 3) The study aims to meticulously explore and quantify the impact of various delayed factors on the prognosis of patients experiencing OHCA, to provide a more comprehensive understanding of their influence.

### **3. Statistical Analysis Plan**

#### **3.1.Data source**

The data for this study was sourced from the Korea OHCA Registry, a collaborative database established by the Korea Centers for Disease Control and Prevention and the central fire services under the Korean government leadership.

#### **3.2. Analysis objectives**

The primary objective of the analysis is to investigate the impact of call-to-door (CtD) time on the clinical outcomes of patients experiencing OHCA. The study aims to discern the influence of delayed hospital arrival on survival rates and neurological outcomes, considering the potential exacerbations brought about by the COVID-19 pandemic.

#### **3.3. Analysis sets**

The study included patients selected from OHCA patients enrolled between January 2016 and December 2021. Exclusions were made based on criteria such as non-cardiac origin of arrest, age below 18, absence of CPR, and missing data.

#### **3.4.Endpoints and covariates**

The primary outcome is death from any cause at hospital discharge. Secondary outcomes include death from any cause within 6 and 24 hours, and neurological outcomes assessed using the Glasgow-Pittsburgh Cerebral Performance Category values at hospital discharge. Covariates considered in the analysis include demographics and significant clinical variables such as age and sex.

#### **3.5.Handling of missing data**

Cases with missing data were excluded from the study as part of the pre-analysis data cleaning process. The study aimed to maintain the integrity and reliability of the analysis by ensuring that only complete and accurate data sets were utilized in the evaluation.

#### **3.6.Statistical procedures**

All data were presented by the mean with standard deviation for continuous variables and frequency with percentage for categorical variables. The independent two-sample t-test, chi-squared or Fisher's exact test were used to compared differences in continuous or categorical

variables between the two groups. The Cox proportional hazards regression and logistic regression model were used to assess primary and secondary outcomes. The survival probability was estimated using Kaplan–Meier method, and the survival curves were compared between CtD time of <30 min and CtD time of  $\geq 30$  min groups by the log-rank test. Propensity-score matching and multivariable analyses were also utilized to adjust for confounding variables and assess the impact of CtD time on clinical outcomes. Landmark analysis also was conducted at 24 hours after hospital arrival. Data manipulation and statistical analyses were conducted using SAS version 9.3 (SAS Institute) and R software (version 4.1.1; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at  $P < 0.05$ . An independent statistician will conduct all statistical analyses to ensure objectivity and accuracy in the interpretation of the data.