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Clinical paper

Females of childbearing age have a survival benefit after out-of-hospital cardiac arrest☆,☆☆

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ABSTRACT

Background: There is controversy regarding the association between age and being female and survival to hospital discharge after out-of-hospital cardiac arrest (OHCA). We hypothesized that younger females (aged 12–49 years) would be independently associated with increased survival after OHCA when compared to other age and sex groups.
Methods: We conducted a secondary analysis of prospectively collected data from 29 United States cities that participate in the Cardiac Arrest Registry to Enhance Survival (CARES). Patients were included if they were ≥12 years of age and had a documented resuscitation attempt from October 1, 2005 through December 31, 2009. Hierarchical multivariable logistic regression analyses were used to estimate the associations between age and sex groups and survival to hospital discharge.
Results: Females were less likely to have a cardiac arrest in public, was witnessed, or was treatable with defibrillation. Females in the 12–49 year old age group had a similar proportion of survival to hospital discharge when compared to age-matched males (females 11.6% vs. males 11.2%), while males ≥50 years old were more likely to survive when compared to age matched females (females 6.9% vs. males 9.6%). Age stratified regression models demonstrated that 12–49 year old females had the largest association with survival to hospital discharge (OR 1.55, 95% CI 1.20–2.00), while females in the ≥50 year old age group had a smaller increased odds of survival to hospital discharge (OR 1.18, 95% CI 1.03–1.35), which only lasted until the age of 55 years (OR 1.12, 95% CI 0.97–1.29).
Conclusions: Younger aged females were associated with increased odds of survival despite being found with poorer prognostic arrest characteristics.

1. Introduction

Out-of-hospital cardiac arrest (OHCA) accounts for approximately 300,000 deaths annually in the United States.[1] There are known sex disparities in OHCA characteristics, specifically females are more likely to arrest at older ages, arrest at home, have an unwitnessed arrest, and be found in non-shockable rhythms (i.e., pulseless electrical activity or asystole).[2–5] Although each of these characteristics is associated with poorer outcomes, currently there is no consensus on whether females with cardiac arrest are less likely to survive to hospital discharge.

Three recent studies, two Japanese studies of OHCA patients[6,7] and another United States study of in-hospital cardiac arrest (IHCA) patients[8] suggest there may also be an interaction between age and sex on survival from cardiac arrest. These studies have found that females of childbearing age are more likely to survive to hospital discharge when compared to other age and sex groups. It is postulated that this may be due to a protective effect provided by sex hormones in women of childbearing age, as this survival benefit is not seen among females who are >50 years of age or age-matched male counterparts. These findings are further supported by basic

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science research demonstrating that female sex hormones may have a role in decreasing the reperfusion injury thought to mediate poor outcomes in patients who experience cardiac arrest.[7–14]

Although the two clinical studies on OHCA from Japan and the IHCA study from the United States report associations between sex and age and survival after cardiac arrest, no studies have been conducted on a racially heterogeneous population from different communities. As such, we utilized the Cardiac Arrest Registry to Enhance Survival (CARES) to further determine if females from a heterogeneous patient population within the United States had increased odds of survival after OHCA. We hypothesized that within this population, females of child-bearing age would have increased odds of surviving OHCA.

2. Methods

2.1. Study design, setting, and population

Data were obtained from the CARES dataset, which is funded by the Centers for Disease Control and Prevention and supported by Emory University.[15] The communities that contribute to CARES include a catchment area of approximately 22 million people from 29 cities across the United States (Appendix Table 1). CARES is an EMS-based registry for OHCA, composed of a limited standard set of data elements from three sources: 911 call centers, EMS providers, and receiving hospitals. Data from submitted reports are linked and reviewed by an independent data analyst from Emory University. Detailed information on the design and development of this registry as well as the data elements included in the registry is published elsewhere.[15]

This was a secondary data analysis of prospectively collected data submitted to CARES from October 1, 2005 through December 31, 2009. All 911-activated cardiac arrest patients for whom resuscitation was attempted and the etiology was presumed to be cardiac were included in the study sample. Exclusion criteria included: not being of presumed cardiac etiology, age <12 years, missing data for sex, or if survival to hospital discharge could not be determined.

Because the CARES registry contains only de-identified data, our study was considered exempt by the Colorado Multiple Institutional Review Board.

2.2. Data collection and processing

All data were entered into a web-based platform (Sansio Corporation, Minneapolis, MN) and an Excel file (Microsoft Corporation, Redmond, WA) was generated. All data analyses were conducted using Stata 11 (Stata Corporation, College Station, TX). Patient-level characteristics collected in the registry included: age, sex, race/ethnicity (as coded by the EMS provider), location of the arrest (public vs. private residence), whether the arrest was witnessed (by someone other than the first responder/EMS provider), whether CPR was initiated by the bystander, use of an automated external defibrillator, initial cardiac rhythm, return of spontaneous circulation (ROSC), and survival to hospital admission and discharge. Bystander CPR was defined as any time CPR was performed by a person who was not part of the medical or EMS teams.

Age cutoffs were initially defined as the average age of menarche in the United States (12 years)[16] and the average age of menopause in the United States (49 years).[17] Two principal age groups were created consisting of ages from 12 to 49 years and patients aged greater than 49 years.

2.3. Statistical analysis

In order to confirm that our age categories were associated with survival, we used bivariate fractional polynomial regression to evaluate the non-linear relationship between patient age and survival to hospital discharge among females. The best fit resulted in a two-order transformation ($b_0 + b_1(\text{age})^2 + b_2(\text{age})^3$). We then plotted the probability of survival to hospital discharge for females using these transformations in a separate logistic regression model (Appendix figure 1). This demonstrated an inflection point at approximately 50 years of age, confirming our initial age categorization.

Baseline characteristics between age and sex groups were compared using the chi-square test for categorical variables. To estimate associations between individual- and site-specific characteristics, including specifically the relationships between age, sex, and survival, we used hierarchical logistic regression analyses. This statistical approach allowed us to account for 20,018 individual cardiac arrest patients nested within 29 distinct cities. To determine the extent to which city-specific factors have effects independent of individual characteristics, we used a random intercept model to partition the variance between catchment areas and the individual-level characteristics. Individual level effects were then added as fixed effects to the model to examine their independent contributions. Individual and site-specific characteristics included in the model were: age, sex, race/ethnicity, witnessed by bystander, witnessed by EMS, location of arrest, bystander CPR, use of a public AED, and initial rhythm. In order to test whether there was effect modification between age and sex we included an interaction term between age and sex.

To minimize bias and preserve study power, we used multiple imputation to handle missing values. We and others have previously demonstrated the validity of multiple imputation for imputing missing out-of-hospital values under a variety of conditions.[18–20] Individual-level race/ethnicity was coded as unknown in approximately 25% of our sample, whereas arrest witnessed by a bystander, initial presenting rhythm, and location of the arrest had missing values in less than 3% of the dataset. The multiple imputation model included the following variables: age, sex, race/ethnicity, witnessed arrest, initial rhythm, AED use, arrest location, regional site, prehospital disposition, and survival to hospital discharge. Ten imputed datasets were created using imputation by flexible chain equations based on bootstrapped samples from the complete dataset.

2.4. Sensitivity analysis

We performed a sensitivity analysis (Appendix Table 2) to examine the independent association between sex and survival to hospital discharge across different age ranges. Age ranges of 5–49 years, 12–65 years, >55 years, and >65 years were used in our fully adjusted model and imputed datasets. An additional analysis using only complete cases was performed on the 12–49 year old age group.

3. Results

3.1. Population

Initially, 20,018 patients were eligible for inclusion. Patients were excluded for not having a presumed cardiac etiology ($n = 37$), age <12 years ($n = 391$), missing sex data ($n = 8$), or missing survival to hospital discharge data ($n = 184$). A total of 19,398 patients were therefore included in the study sample (Fig. 1).

3.2. Stratified by sex

Table 1 displays demographic, clinical, and EMS characteristics of the patients stratified by sex. Of 19,398 patients, 7634 (39.5%) were female with a median age of 69 (interquartile range [IQR]: