Predictors of neurological outcome after out-of-hospital cardiac arrest: sex-based analysis: do males derive greater benefit from hypothermia management than females?

Emad M. Awad1,2*, Karin H. Humphries2,3,4, Brian E. Grunau2,5,6, Colleen M. Norris7 and Jim M. Christenson2,5,6

Abstract

Background: Previous studies of the effect of sex on after out-of-hospital cardiac arrest (OHCA) outcomes focused on survival to hospital discharge and 1-month survival. Studies on the effect of sex on neurological function after OHCA are still limited. The objective of this study was to identify the predictors of favorable neurological outcome and to examine the association between sex as a biological variable and favorable neurological outcome OHCA.

Methods: Retrospective analyses of clustered data from the Resuscitation Outcomes Consortium multi-center randomized controlled trial (2011–2015). We included adults with non-traumatic OHCA and EMS-attended OHCA. We used multilevel logistic regression to examine the association between sex and favorable neurological outcomes (modified Rankin Scale) and to identify the predictors of favorable neurological outcome.

Results: In total, 22,416 patients were included. Of those, 8109 (36.2%) were females. The multilevel analysis identified the following variables as significant predictors of favorable neurological outcome: younger age, shorter duration of EMS arrival to the scene, arrest in public location, witnessed arrest, bystander CPR, chest compression rate (CCR) of 100–120 compressions per minute, induction of hypothermia, and initial shockable rhythm. Two variables, insertion of an advanced airway and administration of epinephrine, were associated with poor neurological outcome. Our analysis showed that males have higher crude rates of survival with favorable neurological outcome (8.6 vs. 4.9%, \( p < 0.001 \)). However, the adjusted rate was not significant. Further analyses showed that hypothermia had a significantly greater effect on males than females.

Conclusions: Males had significantly higher crude rates of survival with favorable neurological outcome. However, the adjusted rate was not statistically significant. Males derived significantly greater benefit from hypothermia management than females, but this can possibly be explained by differences in arrest characteristics or in-hospital treatment. In-depth confirmatory studies on the hypothermia effect size by sex are required.

Keywords: Resuscitation, Cardiac arrest, Sex differences, Neurological outcome

Introduction

Sudden out-of-hospital cardiac arrest (OHCA) is a serious medical emergency affecting more than 350,000 North Americans yearly [1, 2]. Providing patients suffering from OHCA with optimal prehospital intervention improves the probability of return of spontaneous...
circulation (ROSC) [3–9]. Even OHCA patients who receive prehospital resuscitation and achieve ROSC are at risk of developing anoxic brain complications, including coma and death [10].

Many studies examined the predictors of survival with good neurological outcomes and identified the contributors to favorable neurological outcome as: younger age, shorter time to ROSC, witnessed arrest, initial rhythm being a shockable rhythm, and arrest due to cardiac etiology [9, 11–13]. In addition to prehospital treatment-related predictors, there is evidence suggesting that sex may influence survival. Previous studies of the effect of sex on OHCA outcomes focused on survival to hospital discharge [14–18] and 1-month survival [16, 19, 20]. Some other studies assessed the effect of sex on OHCA neurological outcome; however, they reported contradictory results. While some reported no significant difference by sex [15, 21], others reported male sex is associated with a favorable neurological function [22, 23]. In contrast, a recent study reported neurological outcome advantage in females [24]. The primary objective of this study was to assess whether sex as a biological variable has any association with favorable neurological outcome after OHCA. The secondary objective was to identify the predictors of favorable neurological outcome.

**Methods**

**Design and setting**

We analyzed data from the Resuscitation Outcome Consortium (ROC) Continuous Chest Compression (CCC) trial (June 2011 to May 2015) [25]. The ROC is a resuscitation research network with 10 clinical regions in the USA and Canada [26]. The ROC CCC trial was a cluster-randomized, trial that included 114 emergency medical service (EMS) agencies across eight sites in the USA and Canada. The participating EMS agencies were grouped into 47 clusters. The CCC trial included adults with non-traumatic OHCA who received chest compressions provided by EMS and excluded OHCA witnessed by EMS, patients pronounced dead on EMS arrival, and those with “do not resuscitate” orders. The trial examined the effect of chest compressions provided continuously (CCC) versus chest compressions interrupted for ventilation, on survival [25]. The trial results showed no significant difference in survival or neurological function between the continuous versus interrupted chest compression groups. A detailed report of the CCC trial has been published [25].

**Study population**

From the CCC database, we created an analytic data set that included males and females 18 years and older, with non-traumatic, EMS-attended OHCA. Cases with non-cardiac etiology of arrest and cases missing data on any of the key variables were excluded.

**Key variables of interest and measurements**

The outcome variable of interest was neurological function at hospital discharge measured using a modified Rankin Scale (mRS), a scale from zero to six, where a scale of zero represents no neurological deficit and a scale of six means death [27]. For this study, a mRS of >3 was coded as (0) and indicated unfavorable neurological function, and a mRS of ≤3 was coded as [1] and indicated favorable neurological function.

In addition to “sex,” a total of 10 independent variables known to be associated with short-term survival were screened as possible predictors for the neurological outcome. These included the following: age (per year), the interval from the 9-1-1 call to first to EMS arrival to the scene (per minute), location of arrest (public vs. private), bystander witnessed status (witnessed vs. unwitnessed), bystander cardiopulmonary resuscitation (CPR) (yes vs. no), chest compression rate (CCR), initial cardiac arrest rhythm (shockable vs. nonshockable), advanced airway placement (yes vs. no), administration of epinephrine (administered vs. not administered), and induction of hypothermia. Patients who had in-hospital cooling or continued hypothermia for prehospital at temp of 32 to 35 °C were coded as “yes.”

**Statistical analysis**

We calculated descriptive statistics for baseline characteristics for the full cohort and stratified by sex. Continuous variables were presented as medians and interquartile ranges, as they were not normally distributed. Categorical variables were presented as counts and percentages. To explore associations between the potential predictors including “sex” and neurological outcome, we performed bivariate analyses using chi-square test for the categorical variables and point biserial correlation for the continuous variable. Bivariate relationships were assessed at a 5% level of significance.

To further examine the effect of sex and identify the significant prehospital predictors of favorable neurological outcome, we employed multilevel (hierarchical) logistic regression. Multilevel modeling was necessary to account for the nesting of patients within 47 clusters [28]. We ran the hierarchical logistic regression analyses as follows: first, we built an intercept-only model (null model) and estimated the intercept (γ00) and variance (τ2). γ00 represents the average log odds of survival with favorable neurological outcome across all clusters, and τ2 represents the variance of clusters’ average log odds of survival with favorable neurological outcome [29]. Second, we calculated the intraclass correlation coefficient (ICC) and the design effect (DE). A DE value greater than
two was considered an indication of the need for multi-
level analysis [28]. Third, using a forward and backward
variable selection technique, we built a series of multi-
variable mixed models (random intercept models with
patient-level predictors). This allowed us to account for
the clustering effect (patients nested within clusters). In
these models, we included patient-level variables known
to be associated with survival [30]. The patient-level vari-
ables were modeled as fixed effects, and the cluster was
modeled as a random effect. The dependent variable was
neurological function at hospital discharge (favorable vs. unfavorable). Fourth, to further examine the effect of
sex, we stratified the sample by sex and ran the mod-
els in each of the sex subgroups. We then compared the
predictors in each model for both the significance and
effect sizes. Fifth, we examined for possible interactions
between sex and other variables. We used the Akaike
information criterion (AIC) to evaluate the overall fit of
the models [31]. All analyses were performed using R
version 4.0.1, Vienna, Austria. Ethics approval for this
study was obtained from the University of British Colum-
ia - Providence Health Care Research Ethics Board.

Results
Patients' characteristics and univariate analyses
A total of 23,711 OHCA cases were included in the CCC
trial database. After excluding patients who did not meet
the inclusion criteria and those with missing data on any
of the key variables, 22,416 patients were eligible and
included in the analysis (Fig. 1). Of those, 8109 (36.2%) 
were females, 3249 (14.5%) arrested in a public location,
10,403 (46.4%) received bystander CPR, and 5187 (23.1%) 
had an initial shockable rhythm. The summary statistics
for the study variables and the bivariate analyses results
are shown in Table 1. When comparing the females to
the males, the unadjusted analyses showed that females
had a lower proportion of OHCA in public locations
(10.1% vs. 17.0%, p < 0.001), a lower proportion with an
initial shockable rhythm (14.1% vs. 28.3%, p < 0.001),
and a lower proportion received hypothermia interven-
tion (13.3% vs. 17.0%, p < 0.001). Among the full cohort,
survival to hospital discharge was 8.7%, and survival with
good neurological function was 7.3%. Males have higher
 crude rates of survival to hospital discharge than females
(10.2% vs. 6.0%, p < 0.001) and survival with favorable
neurological outcome (8.6 vs. 4.9%, p < 0.001) (Table 2).

Multivariable logistic regression analyses
Null model
In the intercept-only model (null model), the estimated
intercept $\gamma_0$ was $-2.65$, while the estimated variance of
the random effects $\tau^2$ was $0.25$ (95% CI 0.15–0.40, $p < 0.001$). This indicates that there was significant variability
in the intercept among clusters. To allow further assess-
ment for the clustering effect, we computed the ICC:

\[
ICC = \frac{\tau^2}{\tau^2 + \frac{n}{\pi}} 
\]

where $\pi = 3.14$ [32]

![Fig. 1 Study flow diagram](image)
ICC and DE values suggested that multilevel analysis is needed.

**Random intercept with level one predictors model**

In the series of models produced by the forward and backward variable selection procedure, sex remained statistically significant in favor of males. Only after adding two variables (hypothermia and initial rhythm) was sex no longer significant with \( p \) value slightly above the significance level (OR M vs. F 1.16, 95% CI 0.99–1.36, \( p = 0.06 \)). The effects of all other potential predictors remained significant (Table 3).

To further examine the effect of sex, we stratified the sample by sex and ran the models in each of the sex subgroups. We then compared the predictors in each model for both the significance and effect sizes. The significance and effect sizes were very similar in the male and female models except in the effect of hypothermia and initial rhythm. Hypothermia and initial rhythm had larger effect sizes in males than females (Table 4). This suggests that the effect of hypothermia and initial rhythms depend on the levels of “sex” variable (effects modification by sex). We thus ran three new models: 1—all predictors and the initial shockable rhythm by sex interaction, 2—all predictors, the initial rhythm by sex interaction, and hypothermia management by sex interaction, and 3—all predictors and the hypothermia management by sex interaction only (Table 5). The results of these analyses showed that the initial shockable rhythm by sex interaction was significant in favor of males. However, after adding the

**Table 1** Patients’ characteristics and univariate associations with favorable neurological outcome

| Study variable | N = 22,416 | Favorable neurological outcome | \( P \) value |
|----------------|------------|--------------------------------|--------------|
| EMS arrival interval (min) | Median = 5.5 (4.2–6.9) | \( r_{pb} = 0.05^{a} \) | < 0.01 |
| Age (years) | Median = 69 (57–81) | \( r_{pb} = 0.13^{b} \) | < 0.01 |
| Sex | | | |
| Female | 8109 (36.2%) | 395 (4.9%) | < 0.001 |
| Male | 14,307 (63.8%) | 1234 (8.6%) | |
| Location of arrest | | | |
| Non-public | 19,167 (85.5%) | 946 (4.9%) | < 0.001 |
| Public | 3249 (14.5%) | 683 (21.0%) | |
| Bystander witnessed | | | |
| Unwitnessed | 12,845 (57.3%) | 325 (2.5%) | < 0.001 |
| Witnessed | 9571 (42.7%) | 1304 (13.6%) | |
| Bystander CPR | | | |
| No | 12,013 (53.6%) | 568 (4.7%) | < 0.001 |
| Yes | 10,403 (46.4%) | 1061 (10.2%) | |
| Initial rhythm | | | |
| Nonshockable | 17,229 (76.9%) | 328 (1.9%) | < 0.001 |
| Shockable | 5187 (23.1%) | 1301 (25.1%) | |
| Chest compression rate per min | | | |
| 50–99 | 3599 (16.1%) | 196 (5.4%) | < 0.001 |
| 100–120 | 17,705 (78.9%) | 1370 (7.7%) | |
| > 120 | 1112 (5.0%) | 63 (5.7%) | |
| Advanced airway | | | |
| No | 4958 (22.1%) | 597 (36.6%) | < 0.001 |
| Yes | 17,458 (77.9%) | 1032 (5.9%) | |
| Admin of Epinephrine | | | |
| No | 3950 (17.6%) | 899 (22.8%) | < 0.001 |
| Yes | 18,466 (82.4%) | 730 (4.0%) | |
| Hypothermia management | | | |
| No | 18,906 (84.3%) | 1061 (10.2%) | < 0.001 |
| Yes | 3510 (15.7%) | 1000 (28.5%) | |

\( ^{ab} \) Point biserial correlation coefficient
hypothermia by sex interaction, the initial rhythm by sex was no longer significant. Moreover, after removing initial rhythm by sex and including hypothermia by sex interaction only, the hypothermia by sex remained significant, i.e., hypothermia was significantly more effective in males than females, holding all other predictors constant (Table 5). The AIC showed that the last model that include all predictors and hypothermia by sex interaction was the best-fit model and therefore was accepted as the final model (Table 6). In this final model, the following variables were found to have a statistically significant positive impact on good neurological outcome: younger age, shorter duration of EMS arrival to the scene, arrest in public location, witnessed arrest, bystander CPR, CCR of 100–120 compressions per minute, initial shockable rhythm, and hypothermia by sex interaction.

The predictor with the largest effect size was the initial shockable rhythm. The model indicated that patients with an initial shockable rhythm had 6.53 times greater odds of survival with good neurological function than those with unshockable rhythm, holding all other predictors constant (95% CI 5.47–7.80, \( p < 0.001 \)). Two variables, insertion of an advanced airway and administration
of epinephrine, were associated with poor neurological outcome. The model also revealed a significant interaction between sex and hypothermia. Males derived greater benefit from hypothermia management than females, holding all other predictors constant (sex*hypothermia 1.61, 95% CI 1.18–2.19, \( p = 0.003 \)) (Table 6).

Discussion
We identified the significant predictors of survival with good neurological function at hospital discharge in a cohort of patients with OHCA from multiple North American regions. Our adjusted analysis revealed the following variables had a positive impact on favorable
neurological function: younger age, shorter duration of EMS arrival to the scene, arrest in a public location, witnessed arrest, bystander CPR, quality of CPR represented by 100–120 chest compressions per minute, initial shockable rhythm, and induction of an advanced airway. Two variables had negative impacts on neurological function, insertion of an advanced airway, and administration of epinephrine. Our analysis showed that the crude rate of neurological intact survival was higher in males than females. Our results also revealed that males derived significantly greater benefit from hypothermia management than females.

With the exception of age, all of the significant predictive variables were event or treatment characteristics. Of note, many of these variables are modifiable, for example bystander CPR, induction of hypothermia, EMS arrival time, and insertion of an advanced airway. Initiatives and strategies that can improve treatment characteristics, such as strategies to shorten duration of EMS arrival to the scene and training more residents in basic life support bystander CPR, could improve survival with good neurological outcomes [3].

An initial shockable rhythm was the predictor with the largest effect size. This finding is consistent with the findings of previous studies that reported a positive association between an initial shockable rhythm and survival [8, 11, 33]. Additionally, our analyses showed that advanced airway management and administration of epinephrine were associated with decreased odds of favorable neurological outcome. The insertion of an advanced airway may interrupt chest compressions, which results in decreased blood flow to the brain. This is a plausible explanation of the negative impact of advanced airway management on neurological outcome. In line with our results, a RCT compared an epinephrine group with a placebo group to determine if administration of epinephrine during OHCA is effective. The trial found that the proportion of survivors with severe neurologic damage was higher in the epinephrine group than in the placebo group (31.0% vs. 17.8%) [34]. A possible explanation of the negative impact of epinephrine is perhaps the peripheral vasoconstriction effect of epinephrine as reported in a previous animal study [35]. However, other animal studies showed an increase of cerebral flow with bolus doses of epinephrine [36]. Our dataset had limited data on epinephrine bolus doses. It is worth mentioning that advanced airway and epinephrine are indicated for patients with prolonged resuscitation; perhaps those with unshockable rhythms. Therefore, in our study, confounding by indication cannot be disregarded.

Our adjusted analysis also showed that the odds of good neurological function among those who received a CCR between 100 and 120 compressions per minute was 1.6 times higher than that of patients who received 50–99 compressions per minutes. Similar finding was reported by Idris et al. [37]. Interestingly, our analysis showed that chest compressions delivered at a rate higher than 120 compressions per minutes was associated with poor neurological function. A plausible explanation for this is that compressions delivered too quickly (> 120/min) may not allow the chest to recoil during CPR, resulting in poor blood flow to the brain.

With regards to the effect of sex, the bivariate analysis showed that males had a significantly higher rate of

### Table 6
Hierarchical multivariable regression model for favorable neurological outcome. Included one interaction (sex * hypothermia)

| Variable                        | Full cohort N = 22,416 | OR (95% CI) | P value |
|---------------------------------|------------------------|-------------|---------|
| EMS arrival interval (per min)  |                        | 0.92 0.80–0.94 | < 0.001 |
| Age (per year)                  |                        | 0.97 0.96–0.97 | < 0.001 |
| Sex                             |                        | Male 0.95 0.77–1.16 | 0.59    |
| Location of arrest              |                        | Public 1.78 1.53–2.07 | < 0.001 |
| Witness status                  |                        | Witnessed 3.01 2.57–3.54 | < 0.001 |
| CPR status                      |                        | No CPR Ref |         |
| Chest compression rate          |                        | Yes 1.28 1.17–1.48 | < 0.001 |
| Initial cardiac rhythm          |                        | Nonshockable Ref |       |
| Epinephrine                     |                        | Yes 6.53 5.47–7.80 | < 0.001 |
| Advanced airway                 |                        | No Ref |         |
| Hypothermia management          |                        | Yes 0.59 0.49–0.70 | < 0.001 |
| Sex * hypothermia               |                        | 4.94 3.76–6.48 | < 0.001 |

AIC 161549.14
neurologically intact survival. However, this advantage disappeared after adjustment. In the series of models produced by the multivariable analyses, sex remained statistically significant until we added hypothermia and initial rhythm. Only in the models that included initial shockable rhythm and/or hypothermia was the variable “sex” no longer statistically significant. This suggests that sex as a biological variable has no impact on neurological function once initial shockable rhythm and hypothermia management are taken into account. Nevertheless, it is important to note survival with good neurological outcome was lower in females.

Our unadjusted analysis demonstrated significant bivariate correlation between sex and initial rhythm. A similar correlation was shown in a recent North American study that reported females had a lower proportion of OHCA with an initial shockable rhythm compared to males [17]. Our analysis also showed significant bivariate correlation between sex and hypothermia. Females had a lower proportion of receiving hypothermia management compared to males (13.3% vs. 17.0%, p < 0.001). While an initial shockable rhythm and hypothermia management contribute significantly to favorable neurological outcome, the lower proportion of females with an initial shockable rhythm and receiving hypothermia thus contribute to the lower crude rate of neurological intact survival in females. It is possible that the initial unshockable rhythms in females may be related to delays in CPR [21]. It also may be related to differences in the etiology of cardiac arrest. Novel procedures that lead to early identification of OHCA in females may confer considerable benefits. The reason for sex differences in hypothermia management is not clear; it could be gender-related reasons, such as inequitable care, or sex-specific reasons, such as different requirements concerning hypothermia intervention.

To further examine the effect of sex on the outcome in relation to the baseline characteristics, we stratified the sample by sex and ran the analysis for each of the sex subgroups. We then compared the effect of predictors in each model. We found that hypothermia and initial rhythm had noticeably larger effect sizes in males than females, while the magnitude of the effects of the other predictors were similar. The marked difference in the effect size by sex, with much lower ORs in females than males, suggests possible interaction effects. Examination of possible interactions revealed that males derived significantly greater benefit from hypothermia management than females. These results suggest effect modification of hypothermia by sex. While the benefit of hypothermia for males was obvious, it could be due to other confounders related to pre-arrest status, arrest characteristics, or in-hospital treatments that influence the outcome, i.e., the higher effect size of hypothermia for males could be just a consequence that males had more favorable presenting initial rhythms, more witnessed arrests, or more post arrest percutaneous coronary interventions than females. In-depth investigation of the reasons for the observed differences in the effect sizes of hypothermia is required.

Of note, the proportion of survivors with favorable neurological outcome in the cohort who did not receive hypothermia intervention was low (3.3%). This indicates that selection bias might have been introduced: patients deemed to have poor neurological outcome may have been declined for hypothermia. Thus, no hypothermia was associated with poor neurological outcome, when really it is just a marker of patients having poor clinical status.

This study analyzed data from 47 clusters that participated in the ROC CCC trial. One strength of this study is that it applied multilevel analysis to account for clustering effect. Not accounting for clustering effect can produce inaccurate results, including incorrect estimates of the standard errors for the level-one predictors, and increases in the odds of finding a relationship when one does not exist, i.e., inflated type 1 error [28].

Our study has several limitations. First, the study analyzed data from multiple North American regions and the results may not be generalizable elsewhere in the world. Second, our study is vulnerable to unmeasured confounders. Data on some variables, such as comorbidities, year, and time of the event were incomplete in the dataset and, therefore, not included in the analysis. Fourth, the study focused on prehospital interventions. Data on other in-hospital treatment variables, such as cardiac interventions and revascularization, were not available in the dataset and therefore not included in the analyses. In addition to sex differences in OHCA characteristics, there may be some differences in post arrest care. Females less often presenting with shockable rhythms and less often receiving invasive coronary interventions [15, 21]. These are possible confounders that may explain the observed difference in the effects of hypothermia by sex.

Conclusions
We found 10 predictors of neurological function, eight predictors of favorable neurological outcome, and two predictors of poor neurological outcome, after OHCA. The predictors of favorable neurological function include younger age, shorter duration of EMS arrival to the scene, arrest occurring in a public location, witnessed arrest, bystander CPR, chest compression rate of 100–120 compressions per minute, initial shockable
rhythm, and induction of hypothermia. The predictors of poor neurological outcome include insertion of an advanced airway and administration of epinephrine. Males with OHCA have higher crude rates of neurologically intact survival. However, the adjusted rate was not statistically significant. This suggests that sex as a biological variable has no independent effect on neurological function. The magnitude of the effect of the hypothermia on neurological outcome was higher in males than females, suggesting effect modifications of hypothermia by sex. The observed differences may be due to sex differences in OHCA characteristics, differences in post arrest care, or differences in other hidden confounders. In-depth confirmatory studies on the hypothermia effect size by sex are required.

Acknowledgements
This paper was prepared using ROC CCC trial data. The authors thank NHLBI and BioLINCC for providing us with the data. The authors also thank ROC research teams in the USA and Canada and the CIHR, NIH, and the Heart and Stroke Foundation of Canada for supporting the original data collection.

Authors’ contributions
All authors contributed to the study’s conception and design. Material preparation, data collection, and analysis were performed by Emad M. Awad, Karin H. Humphries, and Brian E. Grunau. The first draft of the manuscript was written by Emad M. Awad and revised by Brian E. Grunau, Colleen M. Norris, and Jim M. Christenson. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding
No fund was received for this study.

Availability of data and materials
The data that support the findings of this study are available from [the National Heart, Lung, and Blood Institute (NHLBI), Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC), but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of BioLINCC.

Declarations

Ethics approval and consent to participate
Ethics approval for this study was obtained from the affiliated University of British Columbia - Providence Health Care Research Ethics Board. We certify that the study was performed in accordance with the Declaration of Helsinki ethical standards. No written informed consent was obtained from patients as this was a secondary data analysis. No informed consent was obtained from the participants in the initial CCC trial. The trial meets all requirements for exception from informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1 Faculty of Medicine, Experimental Medicine, University of British Columbia, 2775 Laurel Street, 10th Floor, Room 10117, Vancouver, BC VS1 1M9, Canada.
2 BC RESURRECT: BC Resuscitation Research Collaborative, Vancouver, British Columbia, Canada.
3 Division of Cardiology, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada.
4 BC Centre for Improved Cardiovascular Health, Vancouver, British Columbia, Canada.
5 Department of Emergency Medicine, St. Paul’s Hospital, Vancouver, British Columbia, Canada.
6 Department of Emergency Medicine, University of British Columbia, Vancouver, British Columbia, Canada.
7 Departments of Nursing, Medicine, and School of Public Health, University of Alberta, Edmonton, Alberta, Canada.

Received: 9 May 2022 Accepted: 19 August 2022 Published online: 05 September 2022

References
1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. Circulation. 2020;141(9):2.
2. Heart and stroke foundation of Canada. Addressing cardiac arrest (Internet). 2019. Available from: https://www.heartandstroke.ca/medical/pdf-files/canada/2017-position-statements/final-en-addressingcardiacarreststatement-nov-2019.pdf?Rev=a388eeef4069747dcb4ab6353d36b3f7b266hash=9e273a3232e8908e45e115b59b9dc9d5
3. Hellenberg J, Herlitz J, Lindqvist J, Riva G, Bohm K, Rosenqvist M, et al. Improved survival after out-of-hospital cardiac arrest is associated with an increase in proportion of emergency crew—witnessed cases and bystander cardiopulmonary resuscitation. Circulation. 2008;118(4):389–96.
4. Meaney PA, Bobrow BJ, Mancini ME, Christenson J, de Caen AR, Bhanji F, et al. Cardiopulmonary resuscitation quality: Improving cardiac resuscitation outcomes both inside and outside the hospital: a consensus statement from the American Heart Association. Circulation. 2013;128(4):417–35.
5. Rukuddede MJ, Ramadoss R, Rajase V, Grzeskowiak LE, Rajagopalan RE. Early clinical prediction of neurological outcome following out of hospital cardiac arrest managed with therapeutic hypothermia. Indian J Crit Care Med. 2015;19(6):304.
6. Maia Hansen C, Kragholm K, Pearson DA, Tyson C, Monk L, Myers B, et al. Association of bystander and first-responder intervention with survival after out-of-hospital cardiac arrest in North Carolina, 2010-2013. JAMA. 2015;314(3):255.
7. Grunau B, Humphries K, Sterntrom R, Pennington S, Scheuermeyer F, van Diepen S, et al. Public access defibrillators: gender-based inequities in access and application. Resuscitation. 2020;150:17–22.
8. Awad E, Humphries K, Grunau B, Besserer F, Christenson J. The effect of sex and age on return of spontaneous circulation and survival to hospital discharge in patients with out of hospital cardiac arrest: a retrospective analysis of a Canadian population. Resusc Plus. 2021;5:100084.
9. Martinell L, Nielsen N, Herlitz J, Karlsson T, Horn J, Wise MP, et al. Early predictors of poor outcome after out-of-hospital cardiac arrest. Crit Care. 2017;21(1):96.
10. Khot S, Tirschwell D. Long-term neurological complications after hypoxic-ischemic encephalopathy. Semin Neurol. 2006;26(4):422–31.
11. Wibrandt I, Norsted K, Schmidt H, Schierbeck J. Predictors for outcome among cardiac arrest patients: the importance of initial cardiac arrest rhythm versus time to return of spontaneous circulation, a retrospective cohort study. BMC Emerg Med. 2015;15(1):13.
12. Ameloot K, Genbrugge C, Mees I, Eertmans W, Jans F, Dekeynne C, et al. Venous congestion associated with reduced cerebral oxygenation and worse neurological outcome after cardiac arrest? Crit Care. 2016;20(1):146.
13. Shinozaki K, Oda S, Sadahiro T, Nakamura M, Hirayama Y, Watanabe E, et al. Blood ammonia and lactate levels on hospital arrival as a predictive biomarker in patients with out-of-hospital cardiac arrest. Resuscitation. 2011;82(4):404–9.
14. Johnson MA, Haukoos JS, Larabee TM, Daugherty S, Chan PS, McNally B, et al. Females of childbirth age have a survival benefit after out-of-hospital cardiac arrest. Resuscitation. 2013 May;84(5):639–44.
15. Karlsson V, Dankiewicz J, Nielsen N, Kern KB, Mooney MR, Riker RR, et al. Association of gender to outcome after out-of-hospital cardiac arrest – A REPORT from the International Cardiac Arrest Registry. Crit Care. 2015;19(1):182.
16. Herlitz J, Engdahl J, Svensson L, Young M, Ångquist K-A, Holmberg S. Is female sex associated with increased survival after out-of-hospital cardiac arrest? Resuscitation. 2004;60(2):197–203.
17. Awad E, Christenson J, Grunau B, Tallon J, Humphries K. Sex differences in out-of-hospital cardiac arrest interventions within the province of British Columbia. Canada Resuscitation. 2020;148:128–34.
18. Safdar B, Stolz U, Stiell IG, Cone DC, Bobrow BJ, DeBoer M, et al. Differential survival for men and women from out-of-hospital cardiac arrest varies by age: Results from the OPALS study. Acad Emerg Med. 2014;21(12):1503–11.
19. Adelsson A, Hollenberg J, Karlsson T, Lindqvist J, Lundin S, Silfverstolpe J, et al. Increase in survival and bystander CPR in out-of-hospital shockable arrhythmia: bystander CPR and female gender are predictors of improved outcome. Experiences from Sweden in an 18-year perspective. Heart. 2011;97(17):1391.
20. Dicker B, Conaglen K, Howie G. Gender and survival from out-of-hospital cardiac arrest: a New Zealand registry study. Emerg Med J. 2018;35(6):367–71.
21. Awad EM, Humphries KH, Grunau BE, Christenson JM. Premenopausal-aged females have no neurological outcome advantage after out-of-hospital cardiac arrest: a multilevel analysis of North American populations. Resuscitation. 2021;166:58–65.
22. Vogelsong MA, May T, Agarwal S, Cronberg T, Dankiewicz J, Dupont A, et al. Influence of sex on survival, neurologic outcomes, and neurodiagnostic testing after out-of-hospital cardiac arrest. Resuscitation. 2021;167:66–75.
23. Winter-Jensen M, Kjaergaard J, Wanscher M, Nielsen N, Wetterstov J, Cronberg T, et al. No difference in mortality between men and women after out-of-hospital cardiac arrest. Resuscitation. 2019;96:78–84.
24. Kotini-Shah P, Del Rios M, Khosla S, Pugach O, Vellano K, McNally B, et al. Sex differences in outcomes for out-of-hospital cardiac arrest in the United States. Resuscitation. 2021;163:6–13.
25. Nichol G, Leroux B, Wang H, Callaway CW, Sopko G, Weisfeldt M, et al. Trial of continuous or interrupted chest compressions during CPR. N Engl J Med. 2015;373(23):2203.
26. Davis DP, Garberson LA, Andrusiak DL, Hostler D, Daya M, Pirrallo R, et al. A descriptive analysis of emergency medical service systems participating in the Resuscitation Outcomes Consortium (ROC) network. Prehospital Emerg Care. 2007;11(4):369–82.
27. Huybrechts KF, Caro JJ, Xenakis JJ, Vemmos KN. The prognostic value of the modified rankin scale score for long-term survival after first-ever stroke. Cerebrovasc Dis. 2008;26(4):381–7.
28. Peugh JL. A practical guide to multilevel modeling. J Sch Psychol. 2010;48(1):85–112.
29. McMahon JM, Pouget ER, Tortu S. A guide for multilevel modeling of dyadic data with binary outcomes using SAS PROC NLMIXED. Comput Stat Data Anal. 2006;50(12):3663–80.
30. Morrison LJ, Nichol G, Rea TD, Christenson J, Callaway CW, Stephens S, et al. Rationale, development and implementation of the Resuscitation Outcomes Consortium Epistry—Cardiac Arrest. Resuscitation. 2006;78(2):3663–80.
31. Liu X. Chapter 11. In: Applied ordinal logistic regression using stata: from single-level to multilevel modeling. Thousand Oaks: SAGE Publications, Inc.; 2016. p. 408–10.
32. Wu S, Crespi CM, Wong WK. Comparison of methods for estimating the intraclass correlation coefficient for binary responses in cancer prevention cluster randomized trials. Contemp Clin Trials. 2012;33(5):869–80 Available from: https://linkinghub.elsevier.com/retrieve/pii/S1551714412001310.
33. Al-Dury N, Ravn-Fischer A, Hollenberg J, Israelsson J, Nordberg P, Stromsoe A, et al. Identifying the relative importance of predictors of survival in out of hospital cardiac arrest. A machine learning study. Scand J Trauma Resusc Emerg Med. 2020;28(1):60.
34. Perkins GD, Ji C, Deakin CD, Quinn T, Nolan JP, Scomparin C, et al. A randomized trial of epinephrine in out-of-hospital cardiac arrest. N Engl J Med. 2018;379(8):711–21.
35. Ristagno G, Sun S, Tang W, Castillo C, Weil MH. Effects of epinephrine and vasopressin on cerebral microcirculatory flows during and after cardiopulmonary resuscitation*. Crit Care Med. 2007;35(9):2145–9.
36. Putzer G, Martini J, Spraired P, Hornung R, Pinggera D, Abram J, et al. Effects of different adrenaline doses on cerebral oxygenation and cerebral metabolism during cardiopulmonary resuscitation in pigs. Resuscitation. 2020;156:223–9.
37. Idri S, Guffey D, Pepe PE, Brown SP, Brooks SC, Callaway CW, et al. Chest compression rates and survival following out-of-hospital cardiac arrest. Crit Care Med. 2015;43(4):840–8.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.