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Clinical paper

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

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Abstract

Objectives: We evaluated the effect of sex and age on out-of-hospital cardiac arrest (OHCA) outcomes in a Canadian population.

Methods: This study was a retrospective analysis of the British Columbia (BC) Cardiac Arrest Registry (2011−16). We included adult, non-traumatic, EMS-treated OHCA. We stratified the cohort into four groups by age and sex: younger females (18−47 years of age), younger males (18−47 years of age), older females, and older males (>53 years old). We used logistic regression to examine the effect of sex and interaction effect of sex and age on ROSC and survival to hospital discharge.

Results: We included 8115 patients; 31.4% were females. Females had a lower proportion of OHCA in public locations, bystander witnessed arrests, and with initial shockable rhythms. Overall, females had greater adjusted odds of ROSC (OR 1.29, 95% CI 1.15−1.42, p < 0.001). The ROSC advantage was significant in females with non-shockable rhythms (OR 1.48, 95% CI 1.24−1.78, p < 0.001) and females of premenopausal age. However, there was no significant difference in survival to hospital discharge between females and males overall or by sex-age groups. Both younger females and younger males have higher odds of survival to hospital discharge compared to older females and males. Older females had the lowest survival rate among all other sex-age groups.

Conclusions: Female sex was associated with ROSC but not survival to hospital discharge. In the post-arrest phase, females, specifically those in the older age group, had a higher death rate, demonstrating the need for sex- and age-specific research in pre-and-post-OHCA care.

Keywords: Sex differences, Out of hospital cardiac arrest, Canada

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Introduction

Sudden unexpected OHCA is one of the leading 'causes' of death in the USA and other countries.[1,2] Approximately 400,000 sudden out-of-hospital cardiac arrests (OHCA) occur in North America annually.[3,4] Providing cardiac arrest victims with prompt and optimal out-of-hospital intervention improves the probability of return of spontaneous circulation (ROSC) and survival with good neurological function at hospital discharge.[5,6]

Health care providers and Emergency Medical Services (EMS) personnel use a systematic approach to treat cardiac arrest victims. This approach involves implementation of five critical actions known as the "chain of survival"[6]: (1) rapid activation of EMS, (2) rapid initiation of cardiopulmonary resuscitation (CPR), (3) early defibrillation, (4) early delivery of advanced cardiac life support, and (5) incorporation of post-resuscitative care. The implementation of these interventions increases the chances of survival.[6] The treatment-related factors found to be associated with survival are: shorter interval from arrest to commencement of CPR; witnessed arrest; provision of bystander CPR; quality of CPR; initial cardiac rhythm; and early defibrillation.[5−9]

In addition to treatment-related factors, patient-related factors, such as sex and age, may influence survival. Previous research has shown that there are sex-based disparities in the characteristics, intervention, and outcome of OHCA.[10−14] Most of the previous univariable analyses comparing OHCA characteristics between males and females reported that females had a lower proportion with an initial shockable rhythm, a lower proportion of arrest occurring in public locations, and were less likely to receive bystander CPR.[11,12,15−17] However, after adjusting for these characteristics, previous studies conducted in different countries reported contradictory results. Studies conducted in Japan and Switzerland reported that males and females have similar likelihoods of survival after multivariable adjustment.[17,18] A recent study in New Zealand reported no significant difference in one-month survival.[14] An Australian study reported survival to hospital arrival advantage in females but no difference in survival to hospital discharge.[19] Swedish studies reported one-month survival and survival to hospital discharge advantages in females.[12,20] In contrast, studies in the USA and Europe[15,21,22] showed higher survival at hospital discharge in males.

Other research reported females of premenopausal age have a higher probability of survival to hospital discharge than males in the same age group.[16,21,23] These studies suggested that the survival advantage in premenopausal females might be explained by potential protective effects of female sex hormones.

The primary objective of this study was to evaluate sex differences in achieving return of spontaneous circulation (ROSC) and survival to hospital discharge, and to examine the effect of premenopausal age on ROSC and survival to hospital discharge in a cohort of patients with OHCA in a Canadian population.

Method

Design and setting

This study examined prospectively collected data from the BC site of the Resuscitation Outcomes Consortium (ROC BC) Cardiac Arrest Epistry database.[24] The ROC BC database is one of 11 ROC sites that contributed to a North American population-based registry of EMS-attended OHCA (eight in the USA and three in Canada).[24] For this analysis, we examined data collected between 2011 and 2016 in the metropolitan regions of BC, an area of approximately 2.5 million inhabitants.[25] The database includes information on patient demographics, EMS scene arrival times, arrest location, bystander CPR, initial cardiac rhythm, EMS treatments, ROSC, and patients' status at hospital discharge.[24]

Prehospital medical care for OHCA in BC is a coordinated effort between the provincial BC Emergency Health Services (BCEHS) and municipal fire departments. Fire department first responders are trained in basic cardiopulmonary life support, including automated external defibrillator application. BCEHS units have either advanced life support or basic life support designations. BCEHS provides medical care for the entire province of BC, with centralized leadership and guidelines.

This study obtained ethical approval from the University of British Columbia - Providence Health Care Research Ethics Board.

Study population

We analyzed EMS-treated patients from the BC ROC registry. We excluded patients <18 years, cases witnessed by EMS, patients for whom sex data were missing, patients with "do not resuscitate" orders, and patients with traumatic arrest.

Key variables of interests and definitions

The independent variables were sex (female and male) and premenopausal age. Based on the estimation from the literature,[16,19,23,26], we considered 18−47 years old as a premenopausal age, and >53 years old as postmenopausal. We combined the age and sex variables into one variable named 'age-sex' and then stratified the cohort into four groups: premenopausal or younger females (18−47 years of age), younger males (18−47 years of age), older females (>53 years old), and older males (>53 years old). The average age of menopause in North American females is 51 years.[26] We excluded patients 48−52 years of age to reduce the risk of misclassification bias. The primary and secondary outcomes of interest were survival to hospital discharge and ROSC, respectively. Based on the standardized Utstein definitions,[27] ROSC is defined as the restoration of a spontaneous perfusing rhythm that results in a palpable pulse. Survival to hospital discharge describes OHCA patients who were discharged from hospital alive.

Data analysis

We calculated descriptive statistics for baseline characteristics and survival outcomes for the full cohort and stratified by sex and then compared the outcomes by initial rhythm (shockable and non-shockable). We employed multivariable logistic regression to examine the effect of sex on the outcomes. This was followed by a general comparison of the baseline characteristics and outcomes by age-sex. We initially compared younger females (18−47 years old) to males in the same age group and compared older females (>53 years old) to their age-matched males. To determine the effect of premenopausal age on the outcomes, we examined the interaction effect of age-sex using multivariable logistic regression. We created a dummy variable (age-sex) with the four categories mentioned above and specified the younger females' group as the reference group.

We used Student's t-test for continuous variables and Chi-Square test for categorical variables to examine the bivariate associations. For analyses of survival, we used logistic regression, adjusting for all Utstein variables known to be associated with improved survival,[24] including age, location of arrest, witness status, bystander CPR, initial cardiac rhythm, administration of epinephrine, and dispatch to EMS-arrival interval. We used Hosmer−Lemeshow's goodness of fit test to examine the goodness of fit of the logistic regression models. Prior to multivariable analyses, we examined multicollinearity by calculating the variance inflation factor (VIF); we considered VIF under 2.0 as no evidence of multicollinearity.[28] All analyses were performed using IBM SPSS version 26, Armonk, NY.

Results

Baseline characteristics for males and females

In total, 8328 cases met the inclusion criteria. Of those, 828 (9.9%) were excluded as they were witnessed by EMS, and an additional 213 (2.6%) were excluded due to missing data on one or more of the key variables (Fig. 1). The analytic dataset, therefore, included 7287 adult patients with OHCA. There were 2245 (30.8%) females and 5042 (69.2%) males. The summary statistics stratified by sex are shown in (Table 1). The mean age of females was significantly higher than the males (67.4 vs. 64.5 years, $p < 0.001$). Among females, there was a lower proportion of OHCA in public locations (9.8% vs. 21.5%, $p < 0.001$), a lower proportion of witnessed arrest (49.6% vs. 53.9%, $p < 0.001$), and a lower proportion with an initial shockable rhythm (14.0% vs. 29.1%, $p < 0.001$). With regards to the outcomes of interest, in the full cohort, no significant difference was observed for ROSC (36.1% vs. 36.9%, $p = 0.51$); however, survival to hospital discharge was significantly lower in females (9.1% vs. 14.6%, $p < 0.001$).
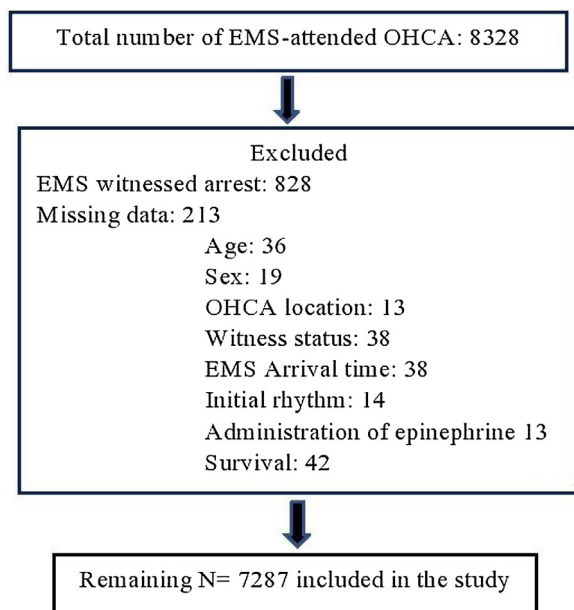

Total number of EMS-attended OHCA: 8328

Excluded
EMS witnessed arrest: 828
Missing data: 213
    Age: 36
    Sex: 19
    OHCA location: 13
    Witness status: 38
    EMS Arrival time: 38
    Initial rhythm: 14
    Administration of epinephrine 13
    Survival: 42

Remaining N= 7287 included in the study

Fig. 1 – Study flow diagram.

Effect of sex on ROSC and survival to hospital discharge

ROSC

Overall, 2670 (36.6%) patients in the cohort (N 7287) achieved ROSC. The proportion of females who achieved ROSC compared to males was 36.1% vs. 36.9% ($p = 0.51$). However, after adjusting for variables known to be associated with improved survival, females had significantly greater odds of ROSC than males (OR 1.29, 95% CI 1.15−1.44, $p < 0.001$) (Table 2). When outcomes were stratified by initial rhythms, the unadjusted analyses showed that females with non-shockable rhythms had a significantly higher rate of ROSC than males (30.9% vs. 26.6%, $p = 0.001$) and this ROSC advantage in females remained significant after adjusting for variables known to be associated with survival (OR 1.48, 95% CI 1.24−1.78, $p < 0.001$). No significant sex differences in unadjusted or adjusted ROSC were observed in the shockable rhythm subgroup (Table 2).

Survival to hospital discharge

Overall, 943 (12.9%) patients in the cohort (N 7287) survived to hospital discharge. The survival among female and male cases was 205/2245 (9.1%) and 738/5042 (14.6%), respectively ($p < 0.001$). However, after adjustment, multivariable logistic regression analysis showed that the difference in survival to hospital discharge was no longer significant (OR 1.09, 95% CI 0.91−1.32, $p = 0.37$) (Table 2). Unadjusted and adjusted analyses for the subgroups (shockable and non-shockable rhythms) showed no significant difference in survival to hospital discharge by sex.

All multivariable analyses were performed adjusting for age, public location, witnessed status, CPR status, shockable rhythm, administration of epinephrine, and EMS arrival time. The chi-square values for the models' Hosmer−Lemeshow tests were greater than 0.05, suggesting that the models fit the data well.[29] No VIF exceeded 2.0, indicating the absence of multicollinearity assumption was met.[28] All the predictors, except sex, made an independent, statistically significant contribution to the models.

Baseline characteristics for males and females

Of the cohort (N = 7287), 833 patients aged 48−52 were excluded. The analytic dataset for age-sex groups, therefore, included 6454 adult patients with EMS-attended OHCA. Of those, 660 (10.2%) were younger males, 1709 (26.5%) were younger females, 1388 (21.5%) were older females, and 2697 (41.8%) were older males. A comparison of OHCA characteristics and outcomes by sex, stratified by age-groups, is shown in Table 3. The proportion of premenopausal females who survived to hospital discharge compared to younger males was 14.8% vs. 18.9% ($p = 0.02$), and the proportion of older females who achieved ROSC compared to older males was 6.1% vs. 10.8% ($p < 0.001$). Similar to the full cohort, baseline characteristics predictive of OHCA were not in favour of females in this age-sex groups (Table 3).

Effect of sex and age on ROSC and survival to hospital discharge

ROSC

After adjusting for the baseline characteristics, results showed that, compared to the reference group (younger females), younger males, older females, and older males had lower odds of ROSC (younger male OR 0.76, 95% CI 0.63−95 $p = 0.01$; older female OR 0.75, 95% CI 0.61−0.92, $p < 0.006$; and older males OR 0.63, 95% CI 0.52

Table 1 – Sex differences in baseline characteristics and survival.

Variables	Total N = 7287	Females n = 2245	Males n = 5042	P-value*
Age (Mean ± SD)	65.4 ± 7.9	67.4 ± 18.8	64.50 ± 17.4	<0.001
Arrest in public location	1305 (17.9%)	219 (9.8%)	1086 (21.5%)	<0.001
Dispatch to EMS arrival (6 min or less)	2941 (40.4%)	910 (40.5%)	2031 (40.3%)	0.84
Bystander witnessed	3831 (52.6%)	1113 (49.6%)	2718 (53.9%)	<0.001
Bystander CPR	3179 (43.6%)	898 (40.0%)	2281 (41.0%)	0.86
Shockable initial rhythm	1784 (24.5%)	315 (14.0%)	1469 (29.1%)	<0.001
Administration of epinephrine	5561 (76.3%)	1642 (73.1%)	3919 (77.7%)	<0.001
Transported to hospital	4390 (56.5%)	991 (48.2%)	2399 (51.3%)	<0.001
Survival outcomes				
ROSC	2670 (36.6%)	810 (36.1%)	1860 (36.9%)	0.51
Alive at hospital discharge	943 (12.9%)	205 (9.1%)	738 (14.6%)	<0.001

* P-value <0.05 is significant; student's t-test for continuous variable and Chi-square test for categorical variables.

Table 2 – Effect of sex on ROSC and survival to hospital discharge.

	Females vs. males (%)	P-value	Adjusted OR [a] (females vs. males)	P-value
ROSC				
Full cohort (N = 7287)	(36.1% vs. 36.9%)	0.51	1.29 (1.15−1.44)	<0.001
Shockable rhythm (n = 1784)	(67.6% vs. 61.9%)	0.07	1.21 (0.96−1.52)	0.11
Unshockable rhythm (n = 5503)	(30.9% vs. 26.6%)	0.001	1.48 (1.24−1.78)	<0.001
Survival to hospital discharge				
Full cohort (N = 7287)	(9.1% vs. 14.6%)	<0.001	1.09 (0.90−1.32)	0.37
Shockable rhythm (n = 1784)	(36.2% vs. 38.2%)	0.51	1.06 (0.81−1.40)	0.67
Unshockable rhythm (n = 5503)	(4.7% vs. 5.0%)	0.69	1.09 (0.83−1.42)	0.54

[a] Odds ratios with 95% CIs, adjusting for age, public location, witnessed status, CPR status, shockable rhythm, administration of epinephrine, and EMS arrival time. Initial rhythm was adjusted for in the full cohort analysis.

−0.76, $p < 0.001$). This ROSC advantage in younger females was observed in the group with non-shockable rhythms but not in the group with shockable rhythm. Both females and males in the older age groups, overall and by initial rhythm, had significantly lower odds of achieving ROSC than younger females (Table 4).

Survival to hospital discharge
With regards to survival to hospital discharge, no significant difference was detected between younger females and their age-matched males either overall (OR 0.02, 95% CI: 0.74−1.41, $p = 87$) or by initial rhythm (shockable OR 1.10, 95% CI 0.61−1.75, $p = 91$; non-shockable OR 0,98 95% CI 0.64−1.50). Both males and females in the older age groups has significantly lower odds of survival to hospital discharge than younger females (Table 4).

Discussion

We examined the effect of sex on survival outcomes on EMS-treated OHCAs over six years, from the metropolitan regions in BC treated by a single EMS system. We found substantial differences in baseline characteristics predictive of OHCA outcomes not in favour of females. While crude ROSC and survival to hospital discharge was significantly lower in females, after adjustment, female sex was associated with higher probability of ROSC but was no longer associated with survival to hospital discharge. These trends were observed in the full cohort and in the subgroup with non-shockable rhythm.

We further examined the interaction effect of sex and age on survival outcomes. Our analyses revealed that, similar to the full

cohort, premenopausal females had greater odds of achieving ROSC compared to their age-matched males. This effect was noticed in premenopausal females with non-shockable rhythm but not in females with shockable rhythm. There was no significant difference in survival to hospital discharge between females of premenopausal age and their age-matched males. Hence, our results do not support the previous findings suggesting survival to hospital discharge advantages in premenopausal females.[16,21,23,30]

The discrepancies between our findings and other studies reporting premenopausal females have better survival[16,21,23,30] could also be explained by issues related to inclusion, methodology, and analysis. Topjian et al. reported survival at hospital discharge advantage in younger females. However, Topjian et al. included in-hospital cardiac arrest only in their study.[30] Akahane et al. reported neurologic outcome advantage in females aged 40−59 years. However, Akahane et al. included EMS-witnessed and non-cardiac etiology cases.[17] A North American study reported that females aged 15−45 years had a higher probability of survival to hospital discharge compared to younger males. Of note, this study analyzed nested data but did not account for nested data structure effects on their analyses. Not accounting for the effect of nested data structure could lead to finding association that does not exist (type 1 error).[26] It is worth mentioning that none of the above-mentioned studies, including our study, defined premenopausal status based on actual hormone levels, but rather used age as a proxy of female sex hormones. Another plausible explanation for the discrepancies between our findings and these data is that there could be systemic differences in the prehospital EMS protocols and treatment. Perhaps the EMS care provided for OHCA patients is not the same in all regions. Our result

Table 3 – Sex-age group differences in baseline characteristic and outcomes (N = 6454).

Variable	Females 18−47y n = 660	Males 18−47y n = 1709	P-value	Females >53y n = 1388	Males >53y n = 2697	P-value[a]
Age, median (IQR)	42.2 ± 11.6	43.8 ± 11.1	0.002	79.7 ± 8.6	77.6 ± 8.2	<0.001
Public location	94 (14.2%)	462 (27.0%)	<0.001	98 (7.1%)	435 (16.1%)	<0.001
Dispatch to EMS arrival (6 min or less)	264 (40.0%)	684 (40.0%)	0.99	565 (40.7%)	1092 (40.5%)	0.89
Bystander witness	359 (54.4%)	970 (56.8%)	0.29	642 (46.3%)	1380 (51.2%)	0.003
Bystander CPR	211 (32.0%)	650 (38.0%)	0.006	604 (43.5%)	1327 (49.2%)	0.001
Administration of epinephrine	472 (71.5%)	1291 (75.5%)	0.04	1016 (73.2%)	2140 (79.3%)	<0.001
Initial rhythm						
Shockable (n = 1512)	106 (16.1%)	476 (27.9%)	<0.001	172 (12.4%)	758 (28.1%)	<0.001
Unshockable (n = 4942)	554 (83.9%)	1233 (72.1%)	<0.001	1216 (87.6%)	1939 (71.9%)	<0.001
Survival outcomes						
ROSC	257 (38.9%)	661 (38.7%)	0.91	470 (33.9%)	955 (35.4%)	0.33
Survival to hospital discharge	98 (14.8%)	323 (18.9%)	0.02	84 (6.1%)	292 (10.8%)	<0.001

[a] P-value <0.05 is significant; student's t-test for continuous variable and Chi-square test for categorical variables.

Table 4 – Effect of age-sex on ROSC and survival to hospital discharge overall and by initial rhythm.

	Full cohort N = 6454 OR (95% CIs)[a]	P-value	Shockable rhythm n = 1512 OR (95% CIs)	P-value	Unshockable rhythm n = 4942 OR (95% CIs)	P-value
ROSC						
Females 18−47y (ref)						
Males 18−47y	0.76 (0.63−0.95)	0.01	0.75 (0.45−1.25)	0.27	0.78 (0.63−0.98)	0.03
Females >53y	0.75 (0.60−0.92)	0.006	0.63 (0.33−0.97)	0.04	0.77 (0.61−0.96)	0.02
Males >53y	0.63 (0.52−0.76)	<0.001	0.57 (0.35−0.95)	0.03	0.62 (0.50−0.76)	<0.001
Survival to hospital discharge						
Female 18−47y (ref)						
Males 18−47y	1.02 (0.74−1.41)	0.87	1.10 (0.61−1.75)	0.91	0.98 (0.64−1.50)	0.93
Females >53y	0.30 (0.21−0.43)	<0.001	0.21 (0.11−0.41)	<0.001	0.34 (0.21−0.54)	<0.001
Males >53y	0.42 (0.30−0.57)	<0.001	0.36 (0.21−0.61)	<0.001	0.45 (0.30−0.69)	<0.001

[a] Odds ratio with 95% CI, younger female (18−47y) is the reference group, adjusting for age, public location, witnessed status, CPR status, shockable rhythm, administration of epinephrine, and EMS arrival time. Initial rhythm was adjusted for in the full cohort analysis.

suggests that the BC-EMS system provides OHCA resuscitation with no sex disparity in resuscitation efforts. A previous study in BC showed no difference in the provision of bystander CPR and chest compression rate by EMS rescuers when comparing males and females with OHCA.[31]

The reasons for the high proportion of females with ROSC are unclear. There must be another unmeasured (hidden) factor that improved odds of ROSC in females. This can be the influence of the estrogen hormone.[16,21,23] The estrogen hormone may have a protective effect, but its effect is limited to a short post-arrest period and disappears during in-hospital post-arrest course. Put differently, the estrogen hormone appeared to assist females in achieving ROSC but was not effective in improving survival to hospital discharge.

On the other hand, our findings are consistent with findings from an Australian study that reported survival to hospital arrival advantage in females but no difference in survival to hospital discharge.[19] Additionally, our results do not contradict findings from two other studies.[14,17] A recent study in New Zealand reported no association between sex and one-month survival,[14] while another study in Japan reported no statistical sex differences in 30-day survival. However,

this latter study included only patients with witnessed arrest and shockable rhythm.[17]

We also found other important sex-age differences in survival. Among the four sex-age groups, older females' group had the lowest rates of ROSC and survival to hospital discharge. Furthermore, among the four sex-age groups, older females had the lowest proportion of OHCA occurring in public locations, the lowest proportion of bystander CPR, and the lower proportion with an initial shockable rhythm. These differences in prehospital characteristics, including an initial non-shockable rhythm, might have contributed to the lower survival in older females. As initial cardiac rhythm is associated with preceding no-flow duration,[32] it is possible that the initial rhythms in females in general and older females in particular may be partially related to delays in CPR. It also may be related to differences in the etiology of cardiac arrest. Nonetheless, novel methods to identify older female OHCAs in private locations (for example, personal wearable monitors) to alert bystanders and professional responders may confer substantial benefits. Other initiatives that could improve survival in older females include making more automated external defibrillators (AED) accessible and training

more residents in basic life support and the use of AED. These initiatives increase survival rate for both females and males.[5,33]

Other possible explanation for the low survival to hospital discharge in females could be sex-specific differences in post-resuscitation interventions. These differences in care may be due to a perception of poor prognosis, given the unfavourable baseline characteristics. This clinician prognostication may then contribute to poor post-ROSC outcomes.[34] Disparities in post-ROSC interventions between females and males has been previously reported.[35] Bosson et al. found that females were less likely to receive post-ROSC coronary angiography compared to males.[35] Such a sex-specific difference could explain why fewer females left hospital alive than males. The reasons for differences in post-arrest interventions could be gender-related, such as inequitable care. Yet, sex-specific reasons cannot be disregarded. Females may have different requirements concerning post-arrest coronary angioplasty. They may have different optimal hemodynamic targets to guide vasopressor treatment.

This study has a number of limitations. First, the analyses were limited to the BC ROC data and may not be generalizable to other North American jurisdictions or elsewhere in the world. Second, data on some variables, such as ethnicity and comorbidities were incomplete in the dataset, and therefore not included in the analyses. Third, the etiology of arrest among women may be systematically different from men and may have significant effects on outcomes. Fourth, data on in-hospital treatment variables were not available and therefore not included in the analyses. If these variables were adjusted for, the results might have been affected. Finally, we used premenopausal age (18−47) as a surrogate of female sex hormones. We did not examine the actual effect of female sex hormones due to a lack of actual data on estrogen.

Conclusion

There are significant differences in OHCA characteristics between males and females. After adjusting for these characteristics, females had 1.29 greater odds of ROSC compared to males. This ROSC advantage was obvious in females with non-shockable rhythms and females of premenopausal age. However, female sex was not associated with outcomes at hospital discharge. Both older females and older males have lower survival rate compared to younger females and males. Survival rate in older females was lowest among all four sex-age groups. Our results suggest that premenopausal status, defined by age, may have some association with ROSC but has no association with survival to hospital discharge. Further research into sex and age-specific differences in pre- and post-arrest care is required.

Conflicts of Interest

None.

CRediT authorship contribution statement

Emad Awad: Conceptualization, Methodology, Software, Formal analysis, Visualization, Writing - original draft. **Karin Humphries:** Supervision, Conceptualization, Methodology, Writing - review & editing. **Brian Grunau:** Methodology, Data curation, Writing - review & editing. **Floyd Besserer:** Methodology, Writing - review & editing. **Jim Christenson:** Supervision, Writing - review & editing.

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