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Sex Differences in Survival From Out-of-Hospital Cardiac Arrest in the Era of Regionalized Systems and Advanced Post-Resuscitation Care

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Background—The purpose of this study was to evaluate sex differences in out-of-hospital cardiac arrest (OHCA) characteristics, interventions, and outcomes.

Methods and Results—This is a retrospective analysis from a regionalized cardiac arrest system. Data on patients treated for OHCA are reported to a single registry, from which all adult patients were identified from 2011 through 2014. Characteristics, treatment, and outcomes were evaluated with stratification by sex. The adjusted odds ratio (OR) for survival with good neurological outcome (cerebral performance category 1 or 2) was calculated for women compared to men. There were 5174 out-of-hospital cardiac arrests (OHCAs; 3080 males and 2094 females). Women were older, median 71 (interquartile range [IQR], 59–82) versus 66 years (IQR, 55–78). Despite similar frequency of witnessed arrest, women were less likely to present with a shockable rhythm (22% vs 35%; risk difference [RD], 13%; 95% CI, 11–15), have ST-segment elevation myocardial infarction (23% vs 32%; RD, 13%; 95% CI, 7–11), or receive coronary angiography (11% vs 25%; RD, 14%; 95% CI, 12–16), percutaneous coronary intervention (5% vs 14%; RD, 9%; 95% CI, 7–11), or targeted temperature management (33% vs 40%; RD, 7%; 95% CI, 4–10). Women had decreased survival to discharge (33% vs 40%; RD, 7%; 95% CI, 4–10) and a lower proportion of good neurological outcome (16% vs 24%; RD, 8%; 95% CI, 6–10). In multivariable modeling, female sex was not associated with decreased survival with good neurological outcome (OR, 0.9; 95% CI, 0.8–1.1).

Conclusions—Sex-related differences in OHCA characteristics and treatment are predictors of survival outcome disparities. With adjustment for these factors, sex was not associated with survival or neurological outcome after OHCA. (***J Am Heart Assoc***. 2016;5:e004131 doi: 10.1161/JAHA.116.004131)

Key Words: heart arrest • men • mortality • resuscitation • women

Out-of-hospital cardiac arrest (OHCA) is a major public health problem affecting ≈300 000 people in the United States each year.[1] Past studies demonstrate that

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there are sex differences in survival from cardiac arrest. Studies have consistently found more favorable arrest characteristics in men, including younger age and a higher frequency of initial shockable rhythm, witnessed arrest, and bystander cardiopulmonary resuscitation (CPR).[2–5] However, there is conflicting evidence regarding patient outcomes (survival and neurological outcome). Whereas some studies have reported improved survival in women,[2,3,6] particularly those of childbearing age,[7] others show no difference or even lower survival in women.[4,5,8,9]

The implications for differences in care also remain undefined. The majority of past studies included patients treated before regional systems of care and advanced postresuscitation management, including widespread adoption of early percutaneous coronary intervention (PCI) and targeted temperature management (TTM). A recent meta-analysis of these studies reported increased survival in women, but outcomes may be very different with current management approaches.[10]

The 2014 Academic Emergency Medicine Consensus Conference Cardiovascular Resuscitation Working Group

identified OHCA epidemiology as a research priority, noting that exploring sex-specifics in OHCA can allow targeted improvements in resuscitation and outcomes.[11] The goal of this study was to evaluate sex differences in OHCA characteristics, interventions, and outcomes, including survival to hospital discharge and survival with good neurological outcome, in a large regional cardiac system of care with established PCI and TTM protocols.

Methods

This is a retrospective study of registry data from the Los Angeles (LA) County Emergency Medical Services (EMS) system. The study was reviewed and approved with exemption of informed consent by the institutional review board.

LA County is a large metropolis, comprising 88 cities spanning over 4000 square miles with a population of 10.2 million. LA County EMS operates a regional cardiac system of care for patients with ST-segment elevation myocardial infarction (STEMI) and/or OHCA that has been previously described.[12,13] EMS providers transport patients resuscitated from OHCA to 1 of 35 currently designated cardiac arrest receiving centers. These centers are capable of providing immediate coronary angiography and primary PCI 24 hours per day, 7 days per week, and have cardiovascular surgeons available. In addition, all centers are required to have a robust quality improvement program and internal policies for PCI, fibrinolysis, and TTM. Cardiac arrest receiving centers submit data on all adult patients with return of spontaneous circulation (ROSC) post-OHCA to a single registry maintained by the LA County EMS Agency. Data abstraction from prehospital and hospital records is completed by registered nurses (RNs) in the departments of emergency medicine, cardiology, and/or quality improvement. Completeness and accuracy of the entered data is reviewed by the EMS Agency with verification performed during site visits.

The database was queried from 2011 through 2014 for all adult patients with OHCA. Study variables included age, sex, race/ethnicity, initial cardiac rhythm, arrest location, witness, bystander CPR, electrocardiogram (ECG) findings (STEMI or no STEMI), length of stay, induction of hypothermia, and whether the patient received coronary angiography and PCI. STEMI was indicated in the database if STEMI was identified on the ECG, either in the field by software interpretation or in the emergency department by physician interpretation. The primary outcome of the study was survival to hospital discharge with good neurological outcome in women compared to men, as defined by a Cerebral Performance Category (CPC) score at hospital discharge of 1 or 2. A CPC of 1 corresponds to a return to normal or mildly impaired cerebral function and independence with activities of daily living

(ADL). A CPC of 2 corresponds to moderate cerebral disability but sufficient function to remain independent with the ADL. The CPC scores documented by physician, nurse, or occupational therapy assessment at the time of discharge were abstracted from the medical record and recorded in the database.

Patient characteristics, interventions, and outcomes were evaluated by sex for the entire cohort as well as the subgroup of witnessed cardiac arrest with initial shockable rhythm. The adjusted odds ratio (OR) for survival with good neurological outcome was calculated for women compared to men. All data were entered into Microsoft Excel (Microsoft Corporation, Redmond WA) and transferred to SAS software (version 9.4; SAS Institute Inc., Cary, NC) for analysis. We report the neurologically intact survival rates as proportions with risk differences and exact binomial confidence intervals. Adjusted ORs and their *P* values were calculated using logistic regression and the chi-square test. Variables in regression, which included patient characteristics (age, sex), arrest characteristics (initial rhythm, witness, and bystander CPR), and interventions (coronary angiography, PCI, and TTM), were selected based on previous knowledge of their contribution to cardiac arrest outcomes. In order to specifically evaluate the confounding effects of hospital treatment on the association of sex with outcome, we constructed 2 primary models: the first limited to baseline patient and arrest characteristics without hospital interventions and the second inclusive of all variables above entered simultaneously into the model. In addition, we accounted for clustering by hospital with generalized estimating equations (GEEs) using the *proc genmod* option in SAS 9.4. We used the "exchangeable" covariance structure for the GEE analysis. Given that there is evidence that women are less likely to undergo treatments, such as coronary angiography and TTM,[8,14–16] as part of a sensitivity analysis, the sex-effect estimate was evaluated in an additional model, one in which the interaction terms between sex and TTM and between sex and coronary angiography were included. Regression analysis was limited to subjects with complete data. Model fit was determined by assessing the Hosmer–Lemeshow fit statistic.

Results

There were 5174 OHCAs in the registry during the study period, including 3080 males and 2094 females. Table 1 shows the characteristics, treatment, and outcome stratified by sex. Women were older, median 71 (interquartile range [IQR], 59–82) versus 66 years (IQR, 55–78). Despite a similar frequency of witnessed arrest, women were less likely to present with a shockable rhythm (22% vs 35%; risk difference [RD], 13%; 95% CI, 11–15) compared to men.

Table 1. Characteristics, Treatment and Outcome by Sex (N=5174)

	Male		Female		Risk Difference (95% CI)	
	N	%	N	%		
Age, median/IQR, y	66	55 to 78	71	59 to 82	5	(4, 6)
Race/ethnicity						
Black	330	11	353	17	6%	(4, 8)
Asian	391	13	214	10	−3%	(−5, −1)
Hispanic	680	22	442	21	−1%	(−3, 1)
White	1480	48	960	46	−2%	(−5, 8)
Pacific Islander/Hawaiian	25	1	12	1	0%	(−1, 1)
Other/unknown	174	6	113	5	−1%	(−2, 3)
Initial shockable rhythm	1090	35	453	22	−13%	(−15, −11)
Witnessed	2559	83	1687	81	−2%	(−4, 0.1)
Bystander CPR	1255	41	821	39	−2%	(−5, 1)
STEMI	989	32	487	23	−9%	(−11, −7)
Coronary angiography	781	25	239	11	−14%	(−16, −12)
PCI (% of catheterizations)	420	54	112	47	−9%	(−0.2, −14)
TTM	1243	40	686	33	−7%	(−10, −4)
Survival to hospital discharge	1186	39	674	32	−7%	(−10, −4)
Length of stay*, median/IQR	7	4–13	7	4–14	−0.74	(−1, −0.4)
CPC 1–2	732	24	345	16	−8%	(−10, −6%)

CPC indicates cerebral performance category; CPR, cardiopulmonary resuscitation; IQR, interquartile range; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TTM, targeted temperature management.
*Among survivors.

Regarding interventions, women were less likely to have STEMI on the ECG (23% vs 32%; RD, 13%; 95% CI, 7−11), receive emergent coronary angiography (11% vs 25%; RD, 14%; 95% CI, 12−16), PCI (5% vs 14%; RD, 9%; 95% CI, 7−11), or TTM (33% vs 40%; RD, 7%; 95% CI, 4−10). In the unadjusted comparison, women had decreased survival to hospital discharge (33% vs 40%; RD, 7%; 95% CI, 4−10) and a lower proportion survived with good neurological outcome (16% vs 24%; RD, 8%; 95% CI, 6−10).

Among patients with a witnessed cardiac arrest with an initial shockable rhythm shown in Table 2, of whom there were 974 males and 390 females, sex differences were similar, with a few exceptions. The reduced use of TTM among females was not statistically significant in this group. In addition, survival to hospital discharge was the same as compared to men. However, survival with good neurological outcome among women remained lower (38% vs 45%; RD, 7%; 95% CI, 1−13).

Tables 3 and 4 show the results of the regression analyses. With adjustment for age and arrest characteristics, there is a borderline statistically significant association between female sex and worse neurological outcome (OR, 0.8; 95% CI, 0.7−1.0; Table 3). However, after adjustment for age, arrest characteristics (initial rhythm, witness, and bystander CPR), and interventions (coronary angiography, PCI, and TTM), female sex was not associated with decreased survival with good neurological outcome (OR, 0.9; 95% CI, 0.8−1.1; Table 4). The sensitivity analysis, shown in Table 5, including the interaction terms between sex and TTM and between sex and catheterization, demonstrated similar results with a wider confidence interval (OR, 1.0; 95% CI, 0.7−1.4). That is, taking into account the potential differing effects of hospital interventions in males and females, when coronary angiography and TTM are performed, there is no association of sex on outcome. In both models, the Hosmer–Lemeshow test demonstrated adequate model fit.

Discussion

In this contemporary cohort of consecutive patients treated in a large, regional care system, we found significant sex differences in OHCA. Overall, men were more likely to present with favorable arrest characteristics (initial shockable rhythm) and more likely to receive interventions (emergent coronary angiography and TTM). However, there was no association

Table 2. Characteristics, Treatment, and Outcome by Sex for Patients With Witnessed Arrest and Initial Shockable Rhythm (N=1364)

	Male		Female		Risk Difference (95% CI)	
	N	%	N	%		
Age, median/IQR, y	62	53–72	67	55–77	4%	(2, 6)
Race/ethnicity						
Black	102	10	69	18	8%	(4, 12)
Asian	105	11	28	7	−4%	(−7, −1)
Hispanic	198	20	76	19	−1%	(−6, 4)
White	500	51	194	50	−1%	(−7, 5)
Pacific Islander/Hawaiian	8	1	5	1	0%	(−1, 1)
Other/unknown	61	6	18	5	−1%	(−4, 2)
Bystander CPR	476	49	175	45	−4%	(−10, 2)
STEMI	473	49	147	38	−11%	(−17, −5)
Coronary angiography	474	49	122	31	−18%	(−24, −12)
PCI (% of catheterizations)	279	59	72	59	0%	(−6, 6)
TTM	484	50	185	47	−3%	(−9, 3)
Survival to hospital discharge	581	60	234	60	0%	(−6, 6)
Length of stay*, median/IQR	7	4–12	7	4–12	0.6	(−0.7, 0.8)
CPC 1 to 2	439	45	150	38	−7%	(−13, −1)

CPC indicates cerebral performance category; CPR, cardiopulmonary resuscitation; IQR, interquartile range; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TTM, targeted temperature management.
*Among survivors.

with sex and neurologically intact survival after adjustment for these factors. Our data support underlying differences in the presentation and management of cardiac arrest between men and women as the cause for noted outcome disparities.

These results add to the past literature. Kim et al evaluated sex's modification of the effect of therapeutic hypothermia on neurological outcome and reported an overall lower mortality in men. The researchers noted that the favorable arrest characteristics, including increased frequency of initial

shockable rhythm, witnessed arrest, and bystander CPR, were a potential reason.[4] A large study in Japan reported better unadjusted survival in men compared to women and attributed this to a higher proportion of initial shockable rhythm and witnessed arrest.[3] The differences in arrest

Table 3. Odds Ratios for Survival to Hospital Discharge With Good Neurological Outcome Adjusting for Age and Arrest Characteristics and Accounting for Clustering by Hospital (N=4504)

	Adjusted OR (95% CI)	
Sex	0.8	0.7 to 1.0
Age, per y	0.97	0.97 to 0.98
Initial shockable rhythm	6.0	5.1 to 7.1
Witnessed arrest	2.5	1.7 to 3.6
Bystander CPR	1.1	0.9 to 1.2

CPR indicates cardiopulmonary resuscitation; OR, odds ratio.
*Hosmer-Lemeshow goodness-of-fit statistics $P=0.05$, Akaike Information Criterion=3800.8.

Table 4. Odds Ratios for Survival to Hospital Discharge With Good Neurological Outcome Adjusting for Age, Arrest Characteristics and Interventions, and Accounting for Clustering by Hospital (N=4477)

	Adjusted OR (95% CI)	
Sex	0.9	0.8–1.1
Age, per y	0.98	0.97–0.98
Initial shockable rhythm	4.8	3.9–5.9
Witnessed arrest	2.4	1.6–3.6
Bystander CPR	1.1	0.9–1.2
Coronary angiography	2.2	1.6–3.2
PCI	1.1	0.8–1.4
TTM	0.9	0.8–1.1

CPR indicates cardiopulmonary resuscitation; OR, odds ratio; PCI, percutaneous coronary intervention; TTM, targeted temperature management.
*Hosmer-Lemeshow goodness-of-fit statistics $P=0.5$, Akaike Information Criterion=3703.8.

Table 5. Odds Ratios for Survival to Hospital Discharge With Good Neurological Outcome Adjusting for Age, Arrest Characteristics, and Interventions Including Sex-Treatment Interaction Terms and Accounting for Clustering by Hospital (N=4477)

	Adjusted OR (95% CI)	
Sex*	1.0	0.7–1.4
Age, per y	0.97	0.97–0.98
Initial shockable rhythm	4.8	3.9–5.9
Witnessed arrest	2.4	1.6–3.6
Bystander CPR	1.1	0.9–1.2
Coronary angiography†	1.8	1.1–3.0
PCI	1.0	0.8–1.4
TTM†	1.2	1.0–1.6

CPR indicates cardiopulmonary resuscitation; OR, odds ratio; PCI, percutaneous coronary intervention; TTM, targeted temperature management.

*At coronary angiography and TTM=yes.

†At sex=female.

‡Hosmer-Lemeshow goodness-of-fit statistics *P*=0.3 , Akaike Information Criterion=3700.3.

characteristics were also noted in a subsequent analysis of the Lucas in Cardiac Arrest trial. Similar to our study, women were older and less frequently presented with an initial shockable rhythm, although there was no difference in the frequency of bystander witness arrests or CPR. With adjustment for these factors, there was no association between sex and survival to hospital discharge or at 6 months.[5]

Our study differs from much of the past literature in the population and setting. The majority of past studies included in the recent meta-analysis by Bougouin et al, which noted improved survival in women, spanned a time frame when current postresuscitation management was not available.[10] In addition, much of the more recent studies are from cohorts in Asia and Scandinavia and inclusive of all OHCA resuscitations.[3,4,14,17,18] Our US study population, with racial and ethnic diversity, is limited to those patients with ROSC, regardless of whether sustained, because that is the entry criteria into the data registry. Despite these dissimilarities, the differences in arrest characteristics between men and women are consistent across these various populations.

Interestingly, earlier studies suggested protective benefits of female sex,[2,6,7] whereas in later studies that account for the current standards of patient care the results are less clear.[9,14,17,18] Several population studies have continued to find a survival advantage to female sex within strata of shockable and/or nonshockable rhythm; however, these studies have not reported frequency of interventions in postresuscitation care.[19,20]

Changes in resuscitation care may differentially affect men and women. In LA County, advanced postresuscitation care capabilities, including PCI and TTM, are required at the cardiac arrest receiving centers. In addition to the differences in arrest characteristics, we found differences in frequency of these interventions between men and women. In our cohort, women were less likely to receive interventions, including emergent coronary angiography and TTM, even among those most likely to have good neurological outcome, with witnessed arrest and initial shockable rhythm. Yet, the sensitivity analysis accounting for effect modification between sex and interventions, further confirmed that female sex was not associated with differences in neurological outcome. Other studies have noted similar sex disparities in interventions.[8,14–16] Given the retrospective nature of this study, the reason for this difference is not known. It is likely attributable, in part, to a higher frequency of STEMI on the ECG and initial shockable rhythm for men. Aggressive postresuscitation care, including early coronary angiography, is more likely in patients with favorable arrest characteristics. As such, men may preferentially benefit from the advancements in resuscitation care. It is notable that, among those patients who received early coronary angiography, men and women had a similar proportion of PCI. Furthermore, although both crude analysis and initial adjustment for patient and arrest characteristics alone showed worse outcomes for women, once accounting for interventions in the regression model, we did not find a difference in survival with good neurological outcome between men and women. These results raise the possibility of an effect of disparities in treatment shifting outcomes from OHCA.

This study is limited to LA County. The generalizability is thereby limited, given that results may differ in other regions. Compared to national surveillance data of OHCA, women make up a similar proportion of our cohort (40% vs 39%), but LA County data have a much higher proportion of Hispanics (22% vs 5%).[1] There was also a higher proportion of witnessed arrest (84% vs 47%), bystander CPR (41% vs 33%), and initial shockable rhythm (32% vs 24%) in these patients transported to specialty centers. Similarly, in comparison to the study population evaluated by Daya et al, representing 139 different EMS Agencies across the United States, our population had a similar median age, proportion of women, and bystander CPR rate but a higher proportion of witnessed arrest (84% vs 49%) and initial shockable rhythm (32% vs 22%).[21]

This study has several additional limitations. This is a retrospective cohort. As such, we cannot determine causality, and the frequency of interventions is subject to selection bias. Our analysis is not inclusive of all patients with cardiac arrest in LA County; the registry includes patients with OHCA who achieve ROSC, at least transiently, and are treated at a cardiac arrest receiving center. This likely explains the higher proportion of witnessed arrests and initial shockable rhythm

compared with national studies. Patients who were not transported (met termination of resuscitation criteria) and those transported to a hospital other than a cardiac arrest receiving center were not included in this analysis. We were unable to include adjustment for downtime, which is known to affect outcomes, because this was missing in the majority of patients and is likely to be inaccurate when reported.[22,23] By limiting analysis to complete subjects, we make the assumption that data are missing completely at random, which, if untrue, can lead to bias or incomplete control of confounders. However, because values were missing less than 10% of the time, we believe that imputation or other means of adjusting for missing values would not make a substantive difference in the results. In addition, given the retrospective methodology, there are other potential confounders that remain unmeasured. Specifically, the database does not include information on comorbid conditions, arrest etiology, and other risk factors that may differ between men and women presenting with OHCA. These factors could not be accounted for in this analysis and causality cannot be determined.

Conclusion

Sex-related differences in OHCA characteristics and treatment are predictors of outcome disparities. After adjustment for these factors, sex was not associated with outcome after OHCA.

Acknowledgments

Disclosures

None.

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