

Original Research

Sex Differences in “Do Not Attempt Resuscitation” Orders After Out-of-Hospital Cardiac Arrest and the Relationship to Critical Hospital Interventions



Sarah M. Perman, MD, MSCE¹; Bonnie J. Siry, MS¹; Adit A. Ginde, MD, MPH¹; Anne V. Grossestreuer, PhD²; Benjamin S. Abella, MD, MPhil³; Stacie L. Daugherty, MD, MSPH⁴; and Edward P. Havranek, MD⁵

¹Department of Emergency Medicine, University of Colorado School of Medicine, Aurora, CO, USA; ²Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA; ³Department of Emergency Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA; ⁴Division of Cardiology, University of Colorado School of Medicine, Aurora, CO, USA; and ⁵Department of Medicine, Denver Health Medical Center, Denver, CO, USA

ABSTRACT

Purpose: Women who experience out-of-hospital cardiac arrest have similar rates of survival to hospital admission as men; however, women are less likely to survive to hospital discharge. We hypothesized that women would have higher rates of “do not attempt resuscitation” (DNAR) orders and that this order would be associated with lower use of aggressive interventions.

Methods: We identified adult hospital admissions with a diagnosis of cardiac arrest (ICD-9 427.5) from the 2010 California State Inpatient Dataset. Multivariable logistic regression was used to test the association between patient sex and a DNAR order within the first 24 h of admission, adjusting for patient demographic characteristics and comorbid medical conditions. In secondary analysis, procedures performed after establishment of DNAR order and survival to hospital discharge were compared by sex.

Findings: We analyzed 6562 patients (44% women, 56% men) who experienced out-of-hospital cardiac arrest and survived to hospital admission. In unadjusted analysis, more women than men had establishment of a DNAR order during the first 24 h of admission (23.4% versus 19.3%; $P < 0.01$). After adjusting for age, race, and comorbid conditions, women remained significantly more likely to have a DNAR order established during the first 24 h of their hospital admission after cardiac

arrest compared with men (odds ratio = 1.23; 95% CI, 1.09–1.40). No sex difference was found in procedures used after DNAR order was established.

Implications: Female survivors of cardiac arrest are significantly more likely than men to have a DNAR order established within the first 24 h of in-hospital treatment. The establishment of a DNAR order is associated with patients undergoing fewer procedures than individuals who do not have a DNAR order established. Given that patients who have a DNAR order receive less-aggressive intervention after arrest, it is possible that an early DNAR order may contribute to sex differences in survival to hospital discharge. (*Clin Ther.* 2019;41:1029–1037) © 2019 Published by Elsevier Inc.

Key words: cardiac arrest, DNR, outcomes, sex differences.

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) affects >350,000 individuals annually in the United States, and women account for approximately one-third of

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this number.^{1,2} Overall survival from cardiac arrest is poor, with rates varying between 7% and 10%.³ Women on average have worse initial arrest characteristics, including older age at the time of arrest, less bystander cardiopulmonary resuscitation (CPR), and a higher frequency of non-shockable initial rhythms.^{4–9} Despite these characteristics, women survive to hospital admission at similar rates to men. However, women do not fare as well in regard to survival at hospital discharge, with lower rates than men.^{4,9} Reasons for these sex differences in hospital discharge survival are not known.

The literature had described that survivors of cardiac arrest who are given a poor prognosis have early discontinuation of life-sustaining therapy and subsequent death, thereby reinforcing the initial prognosis.^{10,11} The American Heart Association recommends delaying neuro-prognostication for at least 72 h after achievement of return of spontaneous circulation, or 72 h after arrival at normothermia in patients who receive targeted temperature management. These evidence-based guidelines allow patients the necessary time to awaken after cardiac arrest, metabolize sedating drugs, and recover from the neurologic dysfunction associated with postcardiac arrest syndrome.¹² This is also the time when neurologic testing becomes accurate, and multimodal algorithms can be applied. Despite evidence suggesting that early prognostication is unreliable, patients continue to have premature predictions of poor prognosis that precede establishment of “Do Not Attempt Resuscitation” (DNAR) orders and withdrawal of life-sustaining therapy.¹³ A DNAR order is placed to limit aggressive life-restoring measures, such as CPR. Whether the timing of DNAR orders vary by sex has not been addressed in patients after OHCA.

The objective of this study was to explore sex differences in early establishment of a DNAR order (defined as within the first 24 h of admission) and the resultant association with critical hospital interventions that contribute to improved outcomes from cardiac arrest. We hypothesized that women would have a higher incidence of early DNAR order, defined as establishment of DNAR order in the first 24 h after hospital admission from OHCA, compared with men. Our secondary objective was to assess for an association between early establishment of a DNAR order and the critical care treatments received

by patients and to see if this differed by sex. We hypothesized that an early DNAR order would be associated with lower use of procedures thought to improve outcomes. Higher incidence of an early DNAR order in women and the association with lower use of interventions after establishment of the DNAR order could potentially contribute to the differences observed between men and women in survival to hospital discharge. Therefore, understanding first and foremost the difference in DNAR use is the first step in exploring sex differences in cardiac arrest outcomes.

METHODS

Study Design and Setting

This was a cross-sectional analysis of a large administrative dataset that was recorded for 12 months, between 2010 and 2011. The California State Inpatient Dataset (SID) from the Healthcare Cost and Utilization Project, Agency for Healthcare Research, consists of patient-level hospital discharge data for all patients irrespective of payer status. The state of California was selected to investigate the questions proposed because this state presents a large diverse patient population and collects the variable of interest, DNAR order. Not all states capture this data element. The DNAR variable is defined as a DNAR order established *within 24 h of hospital admission*. Studies have found that testing for the purposes of neuro-prognostication before 72 h after resuscitation from cardiac arrest is unreliable¹⁰; therefore, guidelines recommend delaying prognostication until 72 h after return of spontaneous circulation.¹² The Colorado Multiple Institutional Review Board approved this study as “not human subjects” research.

Study Patients

Study patients were identified by an admitting *International Classification of Disease, Ninth Revision* (ICD-9) hospital discharge code for “cardiac arrest” (427.5).¹⁴ This ICD-9 code has been validated in prior work and captures patients with OHCA with a sensitivity of 86.5% and a specificity of 99.4%.¹⁴ Patients were excluded if they were <18 years of age or not admitted through the emergency department. Patient demographic characteristics, including age, sex, and race/ethnicity, were collected for each patient. Comorbid medical conditions were identified a priori and evaluated for their incidence in this

cohort of patients after cardiac arrest stratified by sex and DNAR status. These comorbid medical conditions included chronic lung disease, congestive heart failure, diabetes, hypertension, liver disease, metastatic disease, neurologic disease, renal failure, and solid tumor disease without metastasis.

Primary and Secondary Outcomes

Our primary outcome was establishment of a DNAR order within the first 24 h of hospitalization by sex. Our secondary outcomes were the use of critical care procedures potentially integral to the care of a patient after cardiac arrest, including coronary angiography (CAG), percutaneous coronary intervention (PCI), implantable cardioverter-defibrillator (AICD), hemodialysis (HD), echocardiography (Echo), and EEG by sex and DNAR status. These procedures were selected because they were found to be associated with improved outcomes from cardiac arrest¹⁵ or are frequently used in postcardiac arrest care bundles.¹⁶ ICD-9 procedure codes were used to identify these procedures such as CAG: 88.54, 88.55, 88.56, 88.57, 00.24, 00.59, 37.22, 37.23; PCI: 00.66, 17.55, 36.01, 36.02, 36.05; AICD: 00.50, 00.51, 00.53, 00.54, 37.67, 37.8, 37.94, 37.96; HD: 38.95, 39.95; Echo: 00.24, 88.72; and EEG: 89.14.^{17–19} Survival to hospital discharge was also captured as a secondary outcome.

Statistical Analysis

Descriptive statistics were used to describe the cohort stratified by sex and DNAR status. We tested differences by group with the use of χ^2 test or a Fisher's exact test if the number of observations in each cell was <5. Multivariable logistic regression was used to explore the association between sex and DNAR status. We included age, race, and chronic medical conditions in the multivariable model to evaluate how the association between sex and DNAR status was affected by these variables.²⁰ We also measured the association between female sex and survival to hospital discharge, accounting for DNAR status, age, race, and medical comorbidities. A *P* value of 0.05 was statistically significant. All hospitalizations in California were included; therefore, sample weighting was not necessary. All analyses were completed with the use of STATA 14.1 (StataCorp, College Station, TX).

RESULTS

The SID contained 7703 individuals with an admitting ICD-9 code diagnosis of 427.5. There were 214 patients excluded for being <18 years of age and 916 were excluded for not being admitted from the emergency department. An additional 11 patients were excluded for having missing data for age (*n* = 3) and sex (*n* = 8). Our final cohort therefore consisted of 6562 adult hospitalizations for individuals who experienced an OHCA in 2010. Women comprised 44% of the total cohort (*n* = 2887). In total, 21% (*n* = 1385) of patients hospitalized after cardiac arrest had a DNAR order placed in their chart within 24 h of hospital admission. Women were more likely to have an early DNAR order (within 24 h of admission) than men (23.4% versus 19.3%, *P* < 0.01).

Women who had an early DNAR order established were older than men with early DNAR order established and those who had no DNAR order documented in the first 24 h (Table I). Caucasian patients were more likely to have a DNAR order in this dataset. Interestingly, the incidence of comorbid conditions was variable, because women with DNAR orders had a higher incidence of hypertension and chronic lung disease, whereas men with DNAR orders had the highest proportion of liver disease, metastatic disease, neurologic disease, renal failure, and solid tumor without metastatic disease.

Individuals with a DNAR order placed within the first 24 h had lower rates of procedures after cardiac arrest, including CAG, PCI, AICD, HD, Echo, and EEG (Table II). Women overall had much lower use of cardiac interventions, including CAG, PCI, and AICD; however, when it came to patients with DNAR orders, men and women were comparable.

In multivariable analysis that controlled for age, race, and comorbid conditions, women had a greater chance of having a DNAR order established during the first 24 h of their hospital admission after cardiac arrest (odds ratio = 1.23; 95% CI, 1.09–1.40; *P* = 0.001) in comparison with men (Table III). When controlling for age, DNAR order, race, and comorbid conditions, female sex was slightly associated with greater in-hospital mortality (odds ratio = 1.16; 95% CI, 1.04–1.29; *P* = 0.001) (Table IV).

Table I. Patient demographic characteristics and comorbid conditions stratified by sex and DNAR order.

Variable	Without DNAR Order			With DNAR Order		
	Women (n = 2211)	Men (n = 2966)	<i>P</i>	Women (n = 676)	Men (n = 709)	<i>P</i>
Age, mean [SD], years	65.9 [17.0]	62.9 [16.3]	<0.001	74.1 [14.0]	70.3 [15.2]	<0.001
Race, % (n)*			<0.001			<0.001
Caucasian	51.9 (1096)	55.3 (1551)		60.8 (399)	63.9 (430)	
African-American	14.5 (305)	10.0 (279)		7.3 (48)	4.9 (33)	
Hispanic	22.1 (466)	22.5 (631)		19.4 (127)	19.0 (128)	
Asian/Pacific Islander	9.2 (195)	9.1 (255)		9.9 (65)	9.8 (66)	
Other	2.3 (49)	3.1 (88)		2.6 (17)	2.4 (16)	
Chronic conditions, % (n)						
Congestive heart failure	22.8 (503)	18.2 (541)	0.240	20.0 (135)	18.3 (130)	0.759
Chronic lung disease	25.7 (569)	22.3 (660)	0.009	26.2 (177)	22.7 (161)	0.384
Diabetes	29.4 (649)	25.5 (757)	0.004	29.6 (200)	28.9 (201)	0.960
Hypertension	59.8 (1323)	56.0 (1661)	<0.001	61.2 (414)	56.7 (402)	0.027
Liver disease	5.1 (112)	6.4 (189)	<0.001	4.6 (31)	7.2 (51)	0.674
Metastatic disease	2.4 (53)	1.9 (56)	0.774	4.3 (29)	6.1 (43)	0.099
Neurologic disease	18.7 (413)	16.4 (487)	0.014	19.8 (134)	20.7 (147)	0.438
Renal failure	26.0 (575)	27.7 (822)	<0.001	26.0 (176)	29.5 (209)	0.093
Solid tumor without metastasis	2.3 (50)	2.7 (18)	0.002	2.7 (18)	6.5 (46)	<0.001

DNAR = do not attempt resuscitation.

* Race is calculated with n = 6244.

DISCUSSION

Previous studies reported variable outcomes with regard to the association between sex and survival from OHCA, with the predominance of studies exhibiting a worse outcome for women in comparison with other studies that found no difference.⁴⁻⁹ The literature indicates that women who experience cardiac arrest are older in age and receive less bystander CPR than men. Women also tend to arrest from initial non-shockable rhythms at a greater proportion than men.^{4,5,8,21} These characteristics have been identified as poor prognostic indicators for survival from cardiac arrest, yet women's survival to hospital admission is equal if not better than rates for men.^{6,9} With a similar survival to hospital admission but reduced survival to hospital discharge, we theorize that factors associated with the in-hospital care after arrest contribute to the reduced survival to hospital discharge for women.

This study explores the use of DNAR orders in a large state administrative dataset that accounts for all hospitalizations in the state of California in the year 2010. We found that more women have DNAR orders established in the first 24 h of admission after OHCA than men (23.4% versus 19.3%; $P < 0.01$). The association between female sex and establishment of DNAR order persisted when accounting for age, race, and comorbid conditions. Patients with a DNAR order had less procedures performed, and women had more early DNAR orders. In our cohort of patients with OHCA, in adjusted analysis that accounted for age and premorbid conditions, we found that female sex was associated with less survival to hospital discharge.

Our study found there to be an association between female sex and early establishment of DNAR order that might contribute to the variability that has been observed in outcomes for women who experience

Table II. Use of advanced procedures/diagnostic tests, hospital length of stay, and survival stratified by sex and DNAR order.

Variable	Without DNAR Order			With DNAR Order		
	Women (n = 2211)	Men (n = 2966)	<i>P</i>	Women (n = 676)	Men (n = 709)	<i>P</i>
Coronary angiography, % (n)	11.3 (249)	21.4 (636)	<0.001	3.0 (20)	4.4 (31)	0.16
Percutaneous coronary intervention, % (n)	4.6 (102)	11.2 (332)	<0.001	1.3 (9)	2.3 (16)	0.20
Automated implantable cardioverter-defibrillator, % (n)*	3.1 (69)	5.2 (153)	<0.001	0.2 (1)	0.7 (5)	0.11
Hemodialysis, % (n)	12.9 (285)	13.0 (386)	0.90	6.8 (46)	5.9 (42)	0.50
Echocardiography, % (n)	7.5 (166)	8.4 (248)	0.26	4.9 (33)	4.9 (35)	0.96
EEG, % (n)	3.7 (82)	3.5 (105)	0.75	2.1 (14)	2.4 (17)	0.68
Length of stay, mean [SD], days	7.7 [13.8]	8.2 [14.2]	0.21	4.1 [8.0]	4.1 [7.7]	0.99
Died during hospitalization, % (n)	56.8 (1256)	51.7 (1533)	<0.001	86.2 (583)	88.7 (629)	0.17

DNAR = do not attempt resuscitation.

* Fisher's exact test was used to test the hypothesis, given cells have less than 5 observations.

cardiac arrest. This study reflects findings in prior studies that have found an association between female sex and establishment of DNAR order in other disease processes, most notably intracranial

hemorrhage and acute surgical care.^{22,23} Why women succumb to this phenomenon is unknown. Theories include that women are better at divulging their wishes to family than men,²⁴ women outlive their

Table III. Multivariable logistic regression model of early do not attempt resuscitation order (first 24 h of hospitalization) in hospitalized patients with out-of-hospital cardiac arrest.

Variable	Odds Ratio	95% CI	<i>P</i>
Women	1.23	1.09–1.40	0.001
Age	1.03	1.03–1.04	<0.001
Race			
Caucasian	Reference		
African-American	0.49	0.38–0.62	<0.001
Hispanic	0.84	0.71–0.99	0.042
Asian/Pacific Islander	0.84	0.67–1.04	0.105
Other	0.67	0.44–1.01	0.058
Congestive heart failure	0.85	0.73–1.00	0.056
Chronic lung disease	0.95	0.82–1.10	0.485
Diabetes	1.09	0.95–1.26	0.225
Hypertension	0.88	0.77–1.00	0.058
Liver disease	1.24	0.94–1.63	0.126
Metastatic disease	2.74	1.98–3.80	<0.001
Neurologic disease	1.31	1.11–1.53	0.001
Renal failure	1.09	0.94–1.27	0.246
Solid tumor without metastasis	1.72	1.25–2.37	0.001

Table IV. Multivariable logistic regression model of in-hospital mortality for hospitalized patients with out-of-hospital cardiac arrest.

Variable	Odds Ratio	95% CI	<i>P</i>
Women	1.16	1.04–1.29	0.010
Age	1.01	1.01–1.02	<0.001
DNAR order	5.42	4.55–6.45	<0.001
Race			
Caucasian	Reference		
African-American	1.10	0.92–1.32	0.277
Hispanic	1.21	1.05–1.39	0.008
Asian/Pacific Islander	1.19	0.98–1.44	0.075
Other	1.29	0.91–1.82	0.149
Congestive heart failure	0.81	0.70–0.93	0.002
Chronic lung disease	1.04	0.91–1.18	0.563
Diabetes	0.96	0.85–1.09	0.517
Hypertension	0.67	0.59–0.75	<0.001
Liver disease	1.78	1.40–2.27	<0.001
Metastatic disease	2.18	1.45–3.26	<0.001
Neurologic disease	0.96	0.84–1.11	0.581
Renal failure	1.07	0.94–1.21	0.336
Solid tumor without metastasis	1.41	1.00–1.98	0.049

DNAR = do not attempt resuscitation.

spouses and therefore decisions are often made by a different surrogate decision maker,²⁵ or provider bias contributes to the decisions to establish DNAR orders in women versus men.^{23,26} To fully understand the social implications that lead to greater incidence of early DNAR orders in women, further qualitative exploration is necessary.

Note that women who do not have a DNAR order appear to receive less-aggressive therapies than men, including CAG and PCI (Table II). This trend is similar to previous studies that found similar sex differences⁴; however, our study is unable to fully evaluate this trend because we are unable to account for the initial cardiac arrest rhythm or cause of cardiac arrest. Without knowledge of these aspects of the arrest, we are unable to determine whether either of the aforementioned procedures would be indicated and if a true sex difference exists, or if this difference is predicted by the observation that women more frequently experience cardiac arrest with initial non-shockable rhythms that would not indicate the need for PCI or angiography.

This study indicates a global trend in how patients who experience cardiac arrest are treated. A DNAR order is not an order to limit treatment, but an order to limit aggressive life-restoring measures such as CPR. Our findings indicate that a DNAR order is associated with fewer critical interventions that have been found to impart better outcomes to patients who experience cardiac arrest, such as CAG and EEG in the diagnosis of significant coronary lesions and potential anoxic seizure activity. How DNAR orders are perceived by treating physicians and patient families warrants further exploration, because their intention is to limit unwanted resuscitation, but not necessarily to limit treatment. Previous studies have explored the decline in aggressive care that is observed after the establishment of DNAR orders.^{17,18} Although our analysis does not prove that a DNAR order was causal in the limitations of therapy, our analysis is able to support those previous studies in which those connections were recognized.

This analysis has similar limitations because most retrospective studies of administrative datasets,

mainly disease-specific data are often not abstracted. This is true for exploring cardiac arrest from such datasets, given that vital data such as initial cardiac arrest rhythm, duration of resuscitation, timing/use of defibrillation, and bystander CPR are not reported. A major concern with OHCA outcomes is neurologic recovery. This dataset accounts for the survival of patients to discharge but does not address the neurologic recovery of the patient or their quality of life after discharge from the hospital. Nonetheless, this dataset allows for a large-scale exploration of the use of DNAR orders and critical procedures in men and women who experience OHCA. Given the lack of a time stamp within this dataset, we are not able to determine the exact time of the DNAR order and the studied interventions; however, given the definition of the DNAR variable, we know that this occurred within 24 h of hospitalization. The data used was abstracted from the SID, given that this state specifically captures the predictive variable of interest, DNAR order. This dataset includes numerous institutions for which we cannot measure any variety in the general practices after cardiac arrest of each institution. We have no means of validating the quality of the DNAR variable in this large database; therefore, misclassification is possible. Fortunately, we do not suspect that there would be sex differences in misclassification, if it has occurred in this dataset. The circumstances for which a DNAR order was placed early cannot be ascertained through data available in this dataset, and we were unable to account for patient or family preferences for potential goals of care or end-of-life discussion that includes accounting for spiritual or religious beliefs, level of education, or socioeconomic factors. In addition to patient and family preferences, we were also unable to measure variability at the hospital level. Data from an in-hospital cardiac arrest registry have found that hospital variability has been observed regarding the use of DNAR orders in resuscitated patients,²⁷ which may represent varying culture pertaining to care after cardiac arrest. In addition, there are issues that pertain to generalizability, given a single state registry was used. However, the DNAR variable is not uniformly captured in other state inpatient databases; therefore, we were confined to explore the state database where the variable was collected.

CONCLUSIONS

This study represents a broad exploration of the association between female sex and establishment of DNAR orders in patients with OHCA admitted to the hospital in California. Observations that women survive to hospital admission at equal to greater rates as men, but that this survival benefit does not translate to discharge, whereby women fare worse, has led our group to question if the caliber of care after arrest differs. This study supports the hypothesis that women are assigned DNAR status earlier than men, and patients with DNAR orders receive less-aggressive intervention. With more early DNAR orders in women there are more opportunities for less-aggressive interventions. Overall, this finding warrants further exploration into the reasoning behind these statistical trends and interventions that could potentially limit observed differences in outcome from cardiac arrest.

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Address correspondence to: Sarah M. Perman, MD, MSCE, 12401 E. 17th Street, Aurora, CO, 80045, USA. E-mail: sarah.perman@ucdenver.edu