come of cardiopulmonary arrest, as measured by survival rates and cerebral performance categories, is worsened when cardiopulmonary resuscitation quality is suboptimal in some way, such as insufficient depth or excessive number of ventilations. Therefore, poor outcomes in out-of-hospital cardiac arrest can be due, at least in part, to suboptimal cardiopulmonary resuscitation quality.[7]

There is evidence that resuscitation and survival also vary with patient sex[3,8-10] and age,[7,11] the presence of bystander cardiopulmonary resuscitation,[8] and early defibrillation after out-of-hospital cardiac arrest.[12] Previous studies examining sex differences in out-of-hospital cardiac arrest have focused on interactions among patient age, incidence of ventricular fibrillation, and survival rate after hospital admission,[3,8-10] reporting that women are more likely to survive these events than men. However, it is unknown whether the female survival advantage is age-specific. In addition, it is currently unclear whether sex also affects neurologic outcomes after cardiac events. Previous studies have typically examined relatively small datasets from small study regions.[5,8-10] The present study analyzed a Japan-wide database involving more than 300,000 out-of-hospital cardiac arrest cases. The purpose of the present study was to describe the incidence, characteristics, and outcomes of out-of-hospital cardiac arrest in men and women. We compared male and female cases, divided into 10-year age groups, and examined age-adjusted and age-specific differences in outcomes between sexes.

CLINICAL SIGNIFICANCE

- Significant sex differences in out-of-hospital cardiac arrest outcomes were observed.
- Men exhibited a higher 1-month survival rate after out-of-hospital cardiac arrests because of a higher frequency of ventricular fibrillation/ventricular tachycardia compared with women.
- Of patients aged 40 to 59 years who presented with ventricular fibrillation/ventricular tachycardia, women were more likely than men to survive with favorable neurologic outcomes.
- Among the witnessed cases, the rate of receiving bystander cardiopulmonary resuscitation was lower for young women than young men.

MATERIALS AND METHODS

Study Design and Data Source

The present study was an observational study of out-of-hospital cardiac arrest cases from January 2005 to December 2007 in Japan. The Fire and Disaster Management Agency (FDMA) of Japan administers emergency medical services, providing the only ambulance service system in Japan. This service can be accessed by anybody in the country. The database in the present study thus encompassed all recorded out-of-hospital cardiac arrest cases transported to hospitals by the emergency medical service in Japan.

The data were gathered by emergency medical service personnel, and the database belonged to local fire departments in Japan. All data were verified and anonymized at the local fire department, and then transferred and stored in the national-level out-of-hospital cardiac arrest database developed by FDMA for public use. We analyzed this database with the permission of the FDMA. This research can therefore be considered a nationwide, population-based observational study covering all recorded cases of out-of-hospital cardiac arrest in Japan over a 3-year period. This study was approved by the Ethical Committee of Nara Medical University (Authorization Code: 260).

Items and Outcome of the Database

The entry form of the out-of-hospital cardiac arrest data was largely based on the Utstein form,[13] extended to include details of out-of-hospital cardiac arrest of non-cardiac origin and non-witnessed cases. Thus, the database included out-of-hospital cardiac arrest of cardiac and non-cardiac origin, such as stroke, asphyxia, and trauma. In addition, the data included witnessed and non-witnessed cases.

The main items of the database were as follows: patient information, including age and sex; the type of bystanders who witnessed the out-of-hospital cardiac arrest (if it was witnessed); the cause of out-of-hospital cardiac arrest (cardiac or non-cardiac); the initially identified cardiac rhythm; whether the collapse was witnessed or not; whether bystander cardiopulmonary resuscitation was performed; bystander category (ie, if there was a bystander, whether the bystander was a layperson or emergency medical service personnel); the interval from call to arrival of emergency medical service on scene (minutes); and the outcome in terms of survival and cerebral performance categories level 1 month after the out-of-hospital cardiac arrest occurred. The initial cardiac rhythm data were sorted by emergency medical service personnel into a range of categories, including ventricular fibrillation, pulseless ventricular tachycardia, pulseless electrical activity, and asystole. The types of witnesses counted as "laypersons" included family members, friends, colleagues, passersby, and others. "Bystander cardiopulmonary resuscitation" was defined as chest compression-only cardiopulmonary resuscitation, conventional cardiopulmonary resuscitation (both chest compression and rescue breathing), or rescue breathing only in the present study. One-month survival and neurologic status data were collected by emergency medical service personnel from the hospitals that received the patients, in cooperation with the physicians in charge of the patients.[14] The cause of cardiac arrest was determined clinically by the physician in charge, in collaboration with emergency medical service personnel.

Subjects

During the 3-year study period, 318,123 patients with out-of-hospital cardiac arrest were enrolled in the database. We selected patients aged 20 to 89 years with out-of-hospital cardiac arrest. This wide age range was selected to allow the examination of women within the reproductive age range and women who had undergone menopause. This enabled us to assess whether endogenous estrogen status affects outcomes after out-of-hospital cardiac arrest events. Six patients for whom a 1-month follow-up was not successfully conducted were excluded. In total, data from 276,590 cases were analyzed. Figure 1 shows a flow diagram depicting the inclusion/exclusion criteria used in the present study.

Data Analysis

To assess sex differences in out-of-hospital cardiac arrest outcome, we focused on the proportion of cases for each sex that were witnessed, where bystander-cardiopulmonary resuscitation was performed, where an initial ventricular fibrillation/ventricular tachycardia cardiac rhythm was exhibited, and whether the cause of cardiopulmonary arrest was cardiac or non-cardiac in origin. We measured outcomes in terms of 1-month survival and favorable neurologic outcome at 1-month between men and women. "Favorable neurologic outcome" was defined as category 1 (good cerebral performance) or 2 (moderate cerebral disability) of the cerebral performance categories.[15] Data were presented to allow these characteristics to be compared by sex and age group (sorted into 10-year categories).

Statistical analyses were conducted to examine the sex differences of factors mentioned above using a *t* test for age and the interval from call to arrival. Chi-square analysis was used for factors other than age and the interval from call to arrival. Logistic regression analyses were performed to identify the effects of sex both on the overall outcomes (1-month survival and favorable neurologic status) and on the outcomes among each age group, using men as a reference. Potential confounding factors included witness status, cause of cardiac arrest, presence of bystander cardiopulmonary resuscitation, use of a public-access automated external defibrillator, administration of first shock by emergency medical services, use of airway devices, and administration of epinephrine. Statistical significance was defined as a *P* value less than .05. All statistical analyses were conducted using PASW ver. 18 (SPSS, Inc, Chicago, Ill).

RESULTS

Baseline Characteristics

Women made up 37.8% of the patients aged 20 to 89 years with out-of hospital cardiac arrests. The mean age of men (67.9 years) was significantly less than that of women (72.7 years). Tables 1 and 2 show the baseline demographic factors and results of the basic analyses between sexes.

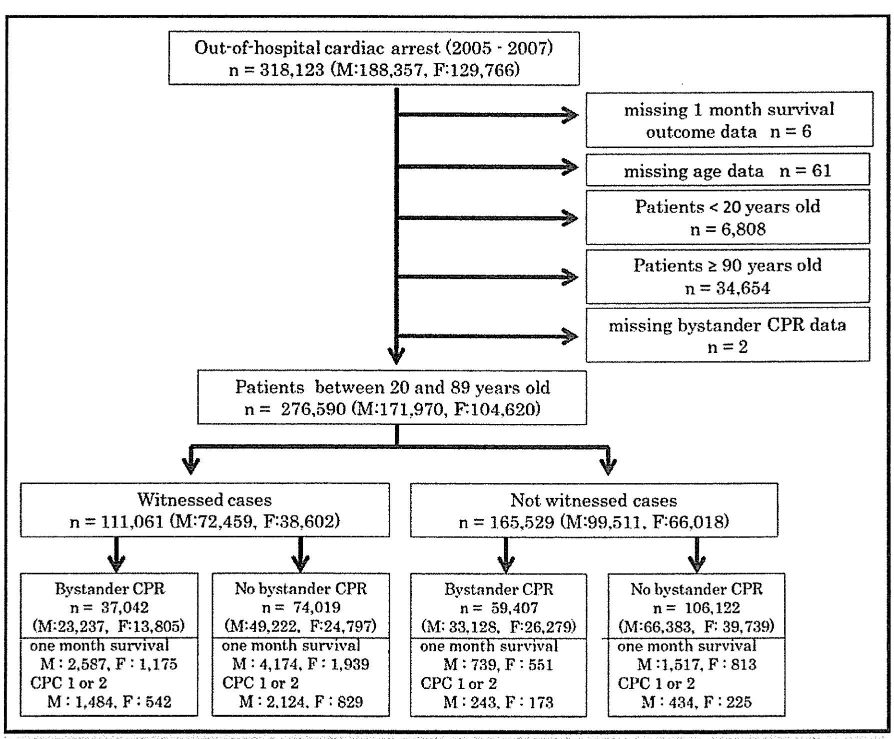

Figure 1 Flow diagram of inclusion/exclusion criteria. M = male; F = female.

Table 1 Sex Differences in Baseline Characteristics

	Male (n = 171,970)	Female (n = 104,620)	*P* Value
No. of cases			
2005	56,153	33,833	
2006	57,531	34,765	
2007	58,286	36,022	
Age mean (SD)	67.9 (15.2)	72.7 (14.9)	
Witnessed cases (%)	72,459 (42.1%)	38,602 (36.9%)	<.001
Bystander CPR attempted (%)	56,365 (32.8%)	40,084 (38.3%)	<.001
VF/VT as initial rhythm (%)	17,417 (10.1%)	4,872 (4.7%)	<.001
1-mo survival (%)			
Overall	9,017 (5.2%)	4,478 (4.3%)	<.001
Cardiac	5,912 (6.4%)	2,381 (4.2%)	<.001
Noncardiac	3,105 (3.9%)	2,097 (4.4%)	<.001
VF/VT as initial rhythm	3,547 (20.4%)	1,030 (21.1%)	.24
Favorable neurologic outcome (%)			
Overall	4,285 (2.5%)	1,769 (1.7%)	<.001
Cardiac	3,293 (3.5%)	1,143 (2.0%)	<.001
Noncardiac	992 (1.3%)	626 (1.3%)	.44
VF/VT as initial rhythm	2,185 (12.5%)	584 (12.0%)	.30
Call-EMS on scene (min, SD)	7.29 (4.34)	7.10 (3.94)	<.001

VF = ventricular fibrillation; VT = ventricular tachycardia; CPR = cardiopulmonary resuscitation; EMS = emergency medical service; SD = standard deviation.

Incidence Rates of Out-of-Hospital Cardiac Arrest

The overall incidence of out-of-hospital cardiac arrest in the general population during the study year was higher for men (0.12%) than women (0.07%). The proportion of patients with witnessed out-of-hospital cardiac arrest in each age group indicates that the ratio of men was higher than that of women in all age groups. In addition, a marked decrease in the proportion of witnessed out-of-hospital cardiac arrest in women aged 20 to 39 years was observed. The interval between call and arrival of emergency medical services on the scene was significantly longer for men than for women (Table 1). Among patients exhibiting ventricular fibrillation/ventricular tachycardia as initial cardiac rhythm, the interval from call to arrival was not significantly different between sexes (male: 6.6 minutes vs female: 6.6 minutes, $P = .35$).

Survival Rates and Favorable Neurologic Outcome

Overall survival rates and favorable neurologic outcomes are shown in Table 1. The unadjusted 1-month survival rates of men and women were 5.2% and 4.3%, respectively (odds ratio [OR] 1.24; 95% confidence interval [CI], 1.20-1.28). The age-adjusted 1-month survival rate was 4.7% for men and 4.3% for women in all out-of-hospital cardiac arrest cases (OR 1.11; 95% CI, 1.06-1.15). However, for witnessed cases, age-adjusted 1-month survival rates between sexes were similar (male: 8.4% vs female: 8.1%, OR 1.04; 95% CI, 0.99-1.09). The unadjusted favorable neurologic outcome rates were 2.5% and 1.7% for men and women, respectively (OR 1.49; 95% CI, 1.41-1.58). The age-adjusted rate was 2.1% for men and 1.7% for women in all out-of-hospital cardiac arrest cases (OR 1.24; 95% CI, 1.17-1.31). Survival rates and rates of favorable neurologic outcome among witnessed cases are shown in Table 2.

Table 3 shows the results of logistic regression analyses for 1-month survival and favorable neurologic status for all cases. Overall, higher rates of survival and favorable neurologic status were significantly associated with younger age, female sex, witnessed events, bystander cardiopulmonary resuscitation, and attempted defibrillation.

Rate of Bystander-Performed Cardiopulmonary Resuscitation

The rate of bystander-performed cardiopulmonary resuscitation in each sex and each age group indicated that women were more likely to receive bystander cardiopulmonary resuscitation than men in all age groups. In contrast, the rate of bystander-performed cardiopulmonary resuscitation decreased slightly for witnessed cases. This noticeable decrease was observed in women aged 20 to 29 years. Consequently, men are more likely to receive bystander cardiopulmonary resuscitation than women in cases in which the collapse was witnessed in the group aged 20 to 49 years, particularly for patients aged 20 to 29 years (Figure 2).

Ventricular Fibrillation/Ventricular Tachycardia as Initial Rhythm

Overall, the rate of initial ventricular fibrillation/ventricular tachycardia rhythm was higher in men (10.1%) than women (4.7%). The proportion of men showing ventricular fibril-

Table 2 Sex Differences in Baseline Characteristics Among Witnessed Cases

	Male (n = 72,459)	Female (n = 38,602)	*P* Value
Bystander CPR attempted			
No. of cases (%)	23,237 (32.1%)	13,805 (35.8%)	
Mean age (SD)	68.5 (14.8)	74.7 (13.5)	
VF/VT as initial rhythm (%)	5,424 (23.3%)	1,401 (10.1%)	<.001
1-mo survival			
Overall	2,587 (11.1%)	1175 (8.5%)	<.001
Cardiac	1,867 (13.1%)	627 (8.2%)	<.001
Noncardiac	720 (8.0%)	548 (8.8%)	.07
VF/VT as initial rhythm	1,372 (25.3%)	357 (25.5%)	.89
Favorable neurologic outcome (%)			
Overall	1,484 (6.4%)	542 (3.9%)	<.001
Cardiac	1,203 (8.4%)	345 (4.5%)	<.001
Noncardiac	281 (3.1%)	197 (3.2%)	.85
VF/VT as initial rhythm	917 (16.9%)	211 (15.1%)	.10
Call-EMS on scene (min, SD)	7.87 (4.73)	7.56 (4.21)	<.001
No bystander CPR attempted			
No. of cases (%)	49,222 (67.9%)	24,797 (64.2%)	
Mean age (SD)	67.9 (14.8)	72.1 (14.6)	
VF/VT as initial rhythm (%)	7,079 (14.4%)	1,855 (7.5%)	<.001
1-mo survival (%)			
Overall	4,174 (8.5%)	1,939 (7.8%)	.002
Cardiac	2,788 (10.5%)	1,092 (8.4%)	<.001
Noncardiac	1,386 (6.1%)	847 (7.2%)	<.001
VF/VT as initial rhythm	1,593 (22.5%)	471 (25.4%)	.009
Favorable neurologic outcome (%)			
Overall	2,124 (4.3%)	829 (3.3%)	<.001
Cardiac	1,655 (6.2%)	582 (4.5%)	<.001
Noncardiac	469 (2.1%)	247 (2.1%)	.86
VF/VT as initial rhythm	1,013 (14.3%)	284 (15.3%)	.28
Call-EMS on scene (min, SD)	7.07 (4.21)	6.91 (3.76)	<.001

VF = ventricular fibrillation; VT = ventricular tachycardia; CPR = cardiopulmonary resuscitation; EMS = emergency medical service; SD = standard deviation.

lation/ventricular tachycardia remained higher than that of women (8.3% vs 4.7%) after adjusting for age. A similar tendency was observed when witnessed cases of out-of-hospital cardiac arrest were examined separately (male: 14.5% vs female: 8.4% after age adjustment), indicating that men had a substantially increased rate of presentation with initial ventricular fibrillation/ventricular tachycardia rhythm. Notably, when initial rhythm was examined by age group, men showed a higher ventricular fibrillation/ventricular tachycardia rate than women in every age group (Figure 3). Although both men and women presenting with ventricular fibrillation/ventricular tachycardia as the initial cardiac rhythm showed relatively high 1-month survival rates, no sex difference in survival rate was observed, as shown in Table 1.

Survival Rate and Favorable Neurologic Outcomes by Age Group

Figure 4 illustrates the 1-month survival rate of each age group. Although the survival rate of men was lower in the group aged 30 to 39 years than in women, the rate in the group aged 50 to 69 years was higher for men. However, out-of-hospital cardiac arrest cases that were not ventricular fibrillation/ventricular tachycardia cases showed a lower survival rate for men aged 30 to 49 years than for women in the same age range (Figure 5). The rate was similar between sexes in the other age groups. In other words, the higher 1-month survival in men aged 50 to 69 years disappeared when ventricular fibrillation/ventricular tachycardia cases were excluded.

Examination of the rates of favorable neurologic outcomes in each age group revealed that the rate of favorable neurologic outcomes was higher in women aged 30 to 49 years, compared with men in this age range (Table 4). Among patients with out-of-hospital cardiac arrest initially presenting with ventricular fibrillation/ventricular tachycardia rhythms, women aged 30 to 79 years showed a higher 1-month survival rate than men in the same age range. The rate of favorable neurologic outcomes also was higher in women aged 40 to 59 years compared with men within this age range (Table 5).

Table 3 Logistic Regression Analyses for 1-Month Outcomes for All of Out-of-Hospital Cardiac Arrests

	1-Mo Survival		Favorable Neurologic Status	
	OR	95% CI	OR	95% CI
Age (10-y increase)	0.91*	0.90-0.92	0.82*	0.80-0.83
Sex				
Male	Reference		Reference	
Female	1.06*	1.02-1.10	1.03	0.97-1.09
Cause of arrest				
Noncardiac	Reference		Reference	
Cardiac	1.01	0.97-1.05	1.66*	1.55-1.77
Witness status				
Not witnessed	Reference		Reference	
Witnessed	3.46*	3.32-3.61	4.96*	4.63-5.32
Bystander CPR				
Not performed	Reference		Reference	
Performed	1.09*	1.05-1.13	1.19*	1.12-1.25
Defibrillation by EMS				
Not attempted	Reference		Reference	
Attempted	4.16*	3.99-4.33	5.47*	5.15-5.80
AED by layperson				
Not used	Reference		Reference	
Used	3.95*	3.30-4.72	5.18*	4.23-6.35
Airway device				
Not used	Reference		Reference	
Used	0.68*	0.65-0.70	0.31*	0.29-0.33
Epinephrine				
Not administered	Reference		Reference	
Administered	0.87*	0.78-0.98	0.47*	0.37-0.59

OR = odds ratio; CI = confidence interval; EMS = emergency medical service; CPR = cardiopulmonary resuscitation; AED = automated external defibrillator.

*Statistical significance ($P < .05$).

DISCUSSION

Principal Findings

The present results revealed that the frequency of out-of-hospital cardiac arrest was higher in men than in women. In addition, men were witnessed significantly more often while out-of-hospital cardiac arrest was occurring, were significantly more likely to present with ventricular fibrillation/ventricular tachycardia as the initial rhythm, and exhibited a significantly higher overall 1-month survival rate. Overall, men were significantly more likely than women to survive out-of-hospital cardiac arrest even after age adjustment, because of the high proportion of presentation with ventricular fibrillation/ventricular tachycardia. However, when sex effects were examined by age group, the survival rates of women aged 20 to 49 years were significantly higher than those in men in the same age range. The rate of favorable neurologic outcomes at 1 month also was significantly higher in women aged 30 to 49 years than in men within this age range.

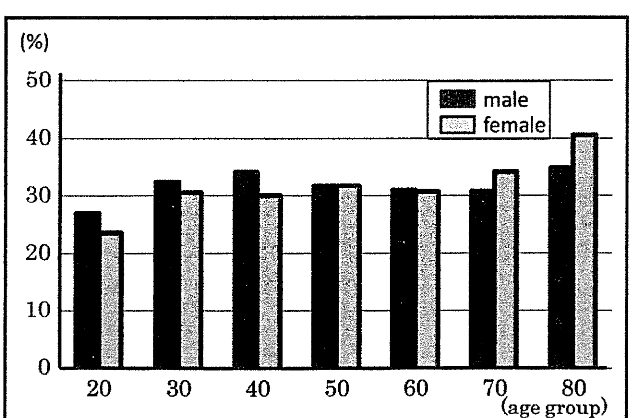

Figure 2 Rate of bystander-performed cardiopulmonary resuscitation in witnessed out-of-hospital cardiac arrest cases in each age group. A marked decrease in the rate relative to men was observed in women in the group aged 20 to 29 years.

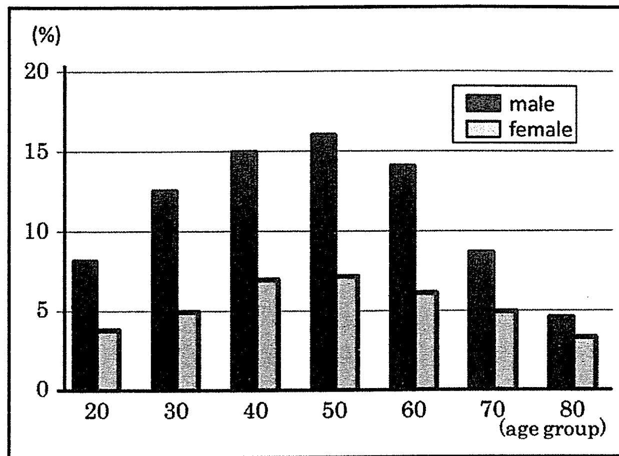

Figure 3 The proportion of cases showing ventricular fibrillation/ventricular tachycardia as the initial cardiac rhythm. Men showed a higher rate of ventricular fibrillation/ventricular tachycardia than women in each age group. VF = ventricular fibrillation; VT = ventricular tachycardia.

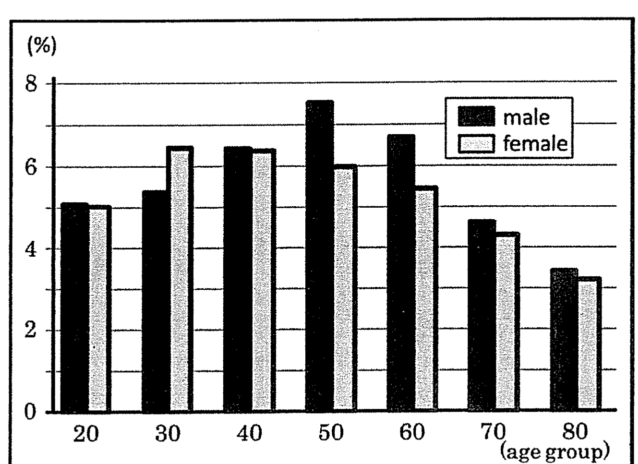

Figure 4 The 1-month survival rate of each age group in overall out-of-hospital cardiac arrest cases. The survival rate in the group aged 50 to 69 years was higher for men than women.

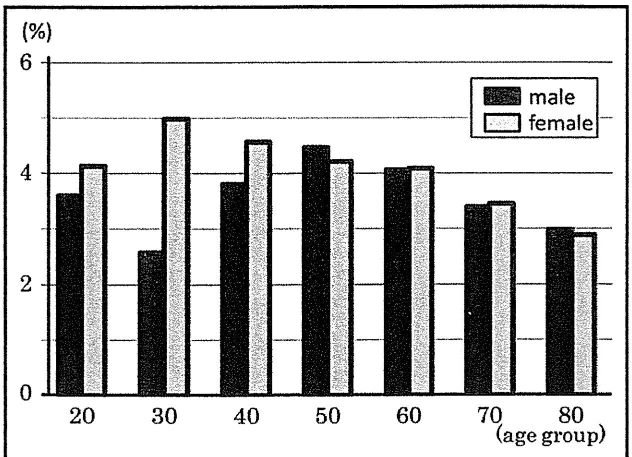

Figure 5 The 1-month survival rate of each age group in out-of-hospital cardiac arrest cases in which ventricular fibrillation/ventricular tachycardia was not presented as the initial rhythm. A lower rate was observed for men than women for patients aged 20 to 50 years. VF = ventricular fibrillation; VT = ventricular tachycardia.

Sex Differences in the Incidence Rates of Out-of-Hospital Cardiac Arrest

Several previous studies examined the effects of sex on out-of-hospital cardiac arrest outcomes.[5,8-10,16] A study examining 681 cases of out-of-hospital cardiac arrest from an urban population reported that the lower unadjusted survival rates observed in women were primarily due to a lower incidence of ventricular fibrillation, and that women had a higher resuscitation rate but similar rates of survival after adjusting for ventricular fibrillation and other factors.[5] Another study that examined 10,139 cases occurring in a metropolitan area and surrounding suburbs reported that the incidence of out-of-hospital cardiac arrest in the general population was approximately 0.13% in men and 0.09% in women.[11] This study also reported that the 1-year survival rate after out-of-hospital cardiac arrest decreased with increasing age in both men and women, but did not differ significantly between sexes.[11]

Sex Differences in Survival and Neurologic Outcomes

A previous study examining 26,940 cases reported that women in the reproductive age range had a lower incidence and a better outcome of out-of-hospital cardiac arrest than women of other ages and men by sorting patients into 3 categories based on the mean age of menarche and menopause, and concluded that endogenous estrogen might have a cardioprotective effect on out-of-hospital cardiac arrest occurrence and outcome.[9] In contrast, we sorted the patients aged 20 to 89 years into seven 10-year categories to assess the sex effect in detail. The number of subjects in the present study was approximately 10 times greater than in the previous study. Therefore, we were able to reveal differences in the effect of sex on outcomes in different age ranges.

Experimental studies have demonstrated that central nervous system and cardiac cells react differently to ischemia and hypoxia in men and women.[17-20] Sex steroids, such as endogenous estrogen, may play a protective role under conditions of cardiopulmonary arrest. A recent animal study revealed that female mice had less brain injury when the insult of hypoxia-ischemia was moderate.[21] Although there is currently no evidence that a similar phenomenon occurs in humans, these findings suggest a possible explanation for the sex difference found in the present study, whereby women were more likely to survive with a favorable neurologic outcome.

Table 4 Logistic Regression Analyses for 1-Month Outcomes by Age Groups

Age Groups	20-29 y	30-39 y	40-49 y	50-59 y	60-69 y	70-79 y	80-89 y
Male, n	4,417	6,726	10,209	22,386	33,263	51,733	43,236
Female, n	2,217	3,077	4,045	8,220	13,943	28,986	44,132
1-mo survival							
Male	224	360	655	1,685	2,223	2,388	1,482
n, %	5.1%	5.4%	6.4%	7.5%	6.7%	4.6%	3.4%
Female	111	198	257	491	758	1,249	1,414
n, %	5.0%	6.4%	6.4%	6.0%	5.4%	4.3%	3.2%
Adjusted OR (95% CI)	1.30* (1.01-1.67)	2.12* (1.73-2.59)	1.48* (1.25-1.74)	1.11 (0.99-1.24)	1.07 (0.98-1.17)	1.08* (1.00-1.16)	1.01 (0.94-1.09)
Favorable neurologic status							
Male	120	238	395	976	1,143	933	480
n, %	2.7%	3.5%	3.9%	4.4%	3.4%	1.8%	1.1%
Female	56	97	125	228	330	473	460
n, %	2.5%	3.2%	3.1%	2.8%	2.4%	1.6%	1.0%
Adjusted OR (95% CI)	1.38 (0.97-1.97)	1.72* (1.31-2.25)	1.36* (1.08-1.71)	1.01 (0.86-1.19)	1.04 (0.91-1.19)	1.10 (0.98-1.24)	0.98 (0.86-1.12)

CI = confidence interval; OR = odds ratio (OR is for female vs male).

Potential confounding factors include sex, cause of cardiac arrest, witnessed status, bystander CPR performed, defibrillation by emergency medical service, automated external defibrillator used, airway device used, and epinephrine administered.

*Statistical significance ($P < .05$).

Table 5 Logistic Regression Analyses for 1-Month Outcomes by Age Groups Among Cases Presenting with Ventricular Fibrillation/Ventricular Tachycardia as the Initial Rhythm

Age Groups	20-29 y	30-39 y	40-49 y	50-59 y	60-69 y	70-79 y	80-89 y
Male, n	360	841	1,523	3,581	4,669	4,470	1,973
Female, n	84	153	282	590	849	1,437	1,477
1-mo survival							
Male	78	208	325	844	1,062	784	246
n, %	21.7%	24.7%	21.3%	23.6%	22.7%	17.5%	12.5%
Female	23	52	85	169	222	297	182
n, %	27.4%	34.0%	30.1%	28.6%	26.1%	20.7%	12.3%
Adjusted OR (95% CI)	1.55 (0.87-2.78)	1.83* (1.23-2.73)	1.92* (1.42-2.61)	1.46* (1.18-1.79)	1.28* (1.07-1.53)	1.29* (1.10-1.50)	1.01 (0.82-1.25)
Favorable neurologic status							
Male	56	161	235	551	658	414	110
n, %	15.6%	19.1%	15.4%	15.4%	14.1%	9.3%	5.6%
Female	16	36	61	105	134	153	79
n, %	19.0%	23.5%	21.6%	17.8%	15.8%	10.6%	5.3%
Adjusted OR (95% CI)	1.48 (0.75-2.91)	1.51 (0.96-2.35)	1.82* (1.29-2.57)	1.39* (1.08-1.78)	1.22 (0.98-1.51)	1.21 (0.99-1.49)	0.97 (0.71-1.32)

CI = confidence interval; OR = odds ratio (OR is for female vs male).

Potential confounding factors include sex, cause of cardiac arrest, witnessed status, bystander CPR performed, defibrillation by emergency medical service, automated external defibrillator used, airway device used, and epinephrine administered.

*Statistical significance ($P < .05$).

The Effect of Witnesses and Ventricular Fibrillation/Ventricular Tachycardia

A previous study reported that the site of arrest differed significantly between sexes. Men collapsed more frequently outside their home and were thus witnessed more frequently and found in ventricular fibrillation more frequently.[11] The sex difference in overall 1-month survival rate we observed might be affected by a slower discovery of women relative to men in cases of out-of-hospital cardiac arrest. A significant difference in overall survival rate between sexes was observed even after adjusting for age. The difference was still marked in witnessed out-of-hospital cardiac arrest cases analyzed separately; however, the difference became smaller after age adjustment. This indicates that the difference may have arisen from a difference in age distribution rather than the ratio of witnessing in men and women.

Presentation with ventricular fibrillation rhythm is believed to be a predictor of survival from out-of-hospital cardiac arrest.[22-24] The interval between the emergency call and the arrival of emergency medical services on the scene might affect the proportion of cases presenting with ventricular fibrillation/ventricular tachycardia as the initial rhythm. However, the interval for men was significantly longer than for women in the current results. Thus, our data suggest that there was a sex difference in the ventricular fibrillation/ventricular tachycardia proportion that was not due to the response interval of the emergency medical service. The present examination of survival rate when ventricular fibrillation/ventricular tachycardia cases were excluded indicates that high ventricular fibrillation/ventricular tachycardia rates may contribute to a higher survival rate in men in older age groups, and that the relative decrease in survival rate in men aged 30 to 49 years was affected by other causes, such as non-cardiac arrest related to suicide.

Frequency of Bystander Cardiopulmonary Resuscitation

Bystander-administered cardiopulmonary resuscitation is one of the most important factors in successful resuscitation. Thus, in the present study, the lower rate of bystander cardiopulmonary resuscitation in young women may have caused a reduced survival rate in women of those ages. However, despite this, the survival rates for women in those age groups were high compared with those for men. Taken together, our results demonstrated that women were more likely to survive with favorable neurologic outcomes than men in out-of-hospital cardiac arrest cases. Although the present study suggests that endogenous estrogen status may affect outcomes, further study is required for the mechanisms underlying the effect of sex on the outcomes to be understood in detail. This will aid the development of effective treatment strategies for out-of-hospital cardiac arrest.

STUDY STRENGTHS AND LIMITATIONS

The database used in the present study included more than 300,000 out-of-hospital cardiac arrest cases. To our knowledge, the sample size in the present study was larger than in any previous studies of the effects of sex on out-of-hospital cardiac arrest outcomes. In addition, the present study examined cases from both urban and rural areas, because all consecutive out-of-hospital cardiac arrest cases occurring in Japan were included.

However, there are several limitations that must be taken into account. First, the survival rate of our study may change if the follow-up period is extended to 1 year after the out-of-hospital cardiac arrest event. Second, the database we analyzed did not involve the medical history of each patient; thus, we are unable to provide a conclusive explanation for why men were more likely to exhibit ventricular fibrillation/ventricular tachycardia or why women were more likely to survive with favorable neurologic outcomes. Third, the generalizability of our findings to other ethnicities remains unclear, because the data were solely derived from a national database in Japan. Similar studies will be required to confirm the present findings using large datasets, such as nationwide population-based studies in other countries.

CONCLUSIONS

The frequency of out-of-hospital cardiac arrest in men was higher than in women. Men were more likely to survive even after age adjustment because of the high proportion presenting with ventricular fibrillation/ventricular tachycardia as the initial rhythm. Although patients of both sexes with out-of-hospital cardiac arrest initially presenting with ventricular fibrillation/ventricular tachycardia had similar overall survival rates, the rate of survival with favorable neurologic outcome was higher for women than men within the group aged 40 to 59 years.

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RESEARCH Open Access

Population density, call-response interval, and survival of out-of-hospital cardiac arrest

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Abstract

Background: Little is known about the effects of geographic variation on outcomes of out-of-hospital cardiac arrest (OHCA). The present study investigated the relationship between population density, time between emergency call and ambulance arrival, and survival of OHCA, using the All-Japan Utstein-style registry database, coupled with geographic information system (GIS) data.

Methods: We examined data from 101,287 bystander-witnessed OHCA patients who received emergency medical services (EMS) through 4,729 ambulatory centers in Japan between 2005 and 2007. Latitudes and longitudes of each center were determined with address-match geocoding, and linked with the Population Census data using GIS. The endpoints were 1-month survival and neurologically favorable 1-month survival defined as Glasgow-Pittsburgh cerebral performance categories 1 or 2.

Results: Overall 1-month survival was 7.8%. Neurologically favorable 1-month survival was 3.6%. In very low-density (<250/km^2) and very high-density (≥10,000/km^2) areas, the mean call-response intervals were 9.3 and 6.2 minutes, 1-month survival rates were 5.4% and 9.1%, and neurologically favorable 1-month survival rates were 2.7% and 4.3%, respectively. After adjustment for age, sex, cause of arrest, first aid by bystander and the proportion of neighborhood elderly people ≥65 yrs, patients in very high-density areas had a significantly higher survival rate (odds ratio (OR), 1.64; 95% confidence interval (CI), 1.44 - 1.87; p < 0.001) and neurologically favorable 1-month survival rate (OR, 1.47; 95%CI, 1.22 - 1.77; p < 0.001) compared with those in very low-density areas.

Conclusion: Living in a low-density area was associated with an independent risk of delay in ambulance response, and a low survival rate in cases of OHCA. Distribution of EMS centers according to population size may lead to inequality in health outcomes between urban and rural areas.

Introduction

Numerous studies have indicated that early initial cardiopulmonary resuscitation (CPR) by laypersons [1,2] and rapid prehospital care by emergency medical service (EMS) providers [3,4] can both substantially increase the survival of out-of-hospital cardiac arrest (OHCA) patients. Over the past several decades, the deployment of trained personnel functioning in an organized EMS system [5] and community-based strategies focusing on early defibrillation with automated external defibrillators (AED) have enhanced the likelihood of successful rescue of OHCA patients [1].

The likelihood of survival of OHCA patients may depend on sociodemographic factors as well as biological and clinical characteristics. One possible social factor that may impede a rapid delivery of EMS is living in a rural area. Geographical barriers in a rural setting, including distance and transportation time, could be crucial factors in the availability of EMS.

With regard to trauma care, increased EMS response time in rural areas has been shown to be a contributing factor to higher mortality rates of critically injured patients from motor vehicle crashes [6]. Several previous studies have suggested a relationship between low population density and low survival rates in cases of OHCA [7-11]. However, these studies were conducted in limited geographic areas or situations.

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To make rational decisions about improving the allocation of EMS resources in a whole nation, health policy makers should ideally take into consideration how population density might influence the overall benefit of such implementations. That is, advanced knowledge of the effects of geographic variation on outcomes of OHCA could guide better identification of effective interventions, including equitable access to EMS, and initiatives in the performance of CPR by members of the public. However, such data are not fully available at present.

The aim of the present study was to investigate the relationship between population density, time between emergency call and ambulance arrival, and the survival of OHCA patients in a nationwide setting, using the All-Japan Utstein-style registry database coupled with geographical information system (GIS) data.

Methods

Japanese EMS system

The Fire and Disaster Management Agency (FDMA) of Japan supervises the EMS system nationwide. The designated universal emergency call number is 119. This number is directly connected to the neighboring dispatch center with a computerized dispatch system. On receipt of an emergency call, the nearest available ambulance is sent to the incident location. All expenses for EMS are covered by taxes, and patients are not charged.

Generally, an ambulance crew includes three EMS staff members, including at least one emergency life-saving technician, who has undergone extensive training to provide prehospital EMS [1,2,12]. All EMS providers perform CPR in accord with the Japanese CPR guidelines, which are based on the American Heart Association and the International Liaison Committee on Resuscitation guidelines [13,14]. Emergency life-saving technicians are allowed to use several methods, including semiautomated external defibrillators, the insertion of an adjunct airway (esophageal obturator airway or laryngeal mask airway), the insertion of a peripheral intravenous line, and the administration of lactate Ringer solution and epinephrine. Only specially trained emergency life-saving technicians are permitted to insert tracheal tubes [1,2,12].

EMS personnel in Japan are legally prohibited from withholding or terminating resuscitation out of hospital, similar to the case in many countries. Most OHCA patients undergo CPR by EMS providers and are transported to hospitals, except in cases where fatality is clear (e.g. rigor mortis, incineration or decomposition) [1].

Data source

In January 2005, the FDMA launched a prospective, nationwide, population-based, observational study involving all OHCA patients who received EMS in Japan [1]. EMS personnel in each center recorded the data of OHCA patients with an Utstein-style form [15,16] in cooperation with the physicians in charge of the patients. These anonymous data were electronically sent to the FDMA database server.

The database included the following data: address of the responding EMS center, patients' sex, age, causes of arrest (cardiac or non-cardiac origin), bystander witness status, presence of bystander CPR with or without AED use, the times of the receipt of an emergency call and vehicle arrival at the scene, 1-month survival and neurological outcome 1 month after cardiac arrest defined in terms of the Glasgow-Pittsburgh cerebral performance categories (CPC: good performance, CPC1; moderate disability, CPC2; severe cerebral disability, CPC3; vegetative state, CPC4; or brain death, CPC5) [15,16]. In Utstein-style format, a de facto "brain death" case is considered to be still "alive" if the patient has not been diagnosed with the standard diagnostic criteria for brain death, but is coded as CPC5. The physicians in charge made a diagnosis of cause in collaboration with EMS staff. We defined 'call-response interval' as the interval between emergency call to vehicle arrival at the scene.

The FDMA provided all the anonymous data to our research group. This study was approved by the Institutional Review Board of the Nara Medical University.

Population and distribution of EMS centers

As of 2005, the population of Japan was approximately 127 million, with several densely populated areas including the Tokyo metropolitan area and the cities of Osaka, Nagoya, Yokohama, Sendai, Fukuoka and Sapporo [17]. The area of the Japanese archipelago is approximately 378,000 km^2, about two-thirds (257,000 km^2) of which is uninhabited mountainous terrain.

To assess the relationship between population and distribution of EMS centers, the area of Japan was divided into 359 medical jurisdictions determined according to the Medical Service Law in Japan. The population (variable X) and the number of EMS centers (variable Y) in each jurisdiction were identified, and the values were plotted on an X-Y plane. The Pearson's correlation coefficient between populations and the numbers of EMS centers in the 359 jurisdictions was calculated.

Geographical information

Geographical information system (GIS) is a computer-based approach to the integration and analysis of geographical data [18-21]. Address-match geocoding, one GIS method, is a process that converts full address information to digital spatial data [19].

In the present study, a text-based address of each EMS center was converted to latitude and longitude coordinates.

For this procedure, we utilized a website of Japanese address match-geocoding (http://www.geocoding.jp/) established with Google Maps Application Program Interface, powered by Google (Mountain View, CA, US). An address (number and street name) and zone (a town name or zip code) of each responding EMS center derived from the OHCA registry database was compared against the full array of addresses in the foundation database of Google Maps, and a 'match' occurred when the two agreed.

The spatial data were linked with the Population Census data [17], using ArcGIS version 9.3.1. (Environmental Systems Research Institute Inc., Redlands, CA, US). In assessing neighborhood sociodemographic characteristics through the use of ArcGIS, the area of Japan was divided into about 378 thousand squares, each square being 1 km^2. The population census data were identified for each 1-km^2 square area where each EMS center was located, including population density (/km^2) and the proportion of elderly people aged ≥ 65 years.

Data Analyses

In the present study, we included OHCA patients whose cardiac arrests were witnessed by bystanders and who received prehospital EMS between Jan 1, 2005 and Dec 31, 2007. Outcome data included overall 1-month survival and neurologically favorable 1-month survival as defined by the Glasgow-Pittsburgh CPC1 or 2. This categorization was determined by a follow-up interview of the physicians in charge by the EMS providers.

Two categories of variables were utilized in the analyses: (i) variables relating to individual patient characteristics and (ii) variables associated with the patients' neighborhood environment. Individual-level patient characteristics included age, sex, causes of arrest (cardiac or non-cardiac origin), presence of bystander CPR with or without AED use, and call-response interval. We also identified the dates of OHCA incidence and divided them into four seasons including spring (Mar-May), summer (Jun-Aug), autumn (Sep-Nov) and winter (Dec-Feb). Variables associated with patients' neighborhood environment were population density, and the proportion of elderly people (aged ≥ 65 years) in each area. Patients were stratified into six population-density groups: very low (<250/km^2), low (250-999/km^2), middle-low (1,000-2,999/km^2), middle-high (3,000-5,999/km^2), high (6,000-9,999/km^2), and very high (≥10,000/km^2) density groups.

Patient characteristics and the neighborhood proportion of elderly people ≥ 65 years were compared between the six population-density groups. We calculated the survival outcomes in each subcategory divided by patient characteristics and patient's neighborhood environment. We performed univariate comparisons of variables using a chi-square test or an analysis of variance (ANOVA) as appropriate. Logistic regression analyses were performed to model the concurrent effects of multiple variables on the outcomes. We first used fixed effect models for logistic regression analyses. Then, we tried to develop hierarchical logistic regression models including site effect. These models included random intercepts for EMS centers in addition to the above-mentioned variables. The threshold for significance was a p-value < 0.05. All statistical analyses were conducted using PASW Statistics version 18.0 (SPSS Inc., Chicago, IL, US).

Results

We enrolled 101,287 consecutive OHCA patients who had been witnessed by bystanders and who received EMS from 4,729 dispatch centers in Japan between 2005 and 2007. All the addresses of 4,729 centers were successfully geocoded.

Figure 1 shows the relationship between population and the number of EMS dispatch centers in 359 jurisdictions. The Pearson's correlation coefficient was 0.841 ($p < 0.001$), indicating that the distribution of EMS centers was almost in proportion to the size of the population.

Figure 2 shows a map of EMS centers in Japan, and Figure 3 focuses on EMS centers in the Tokyo metropolitan area and surrounding areas coupled with population information.

Table 1 shows the patient background and neighborhood environment. An ANOVA showed that the average age of patients in lower-density areas was significantly higher than those in higher-density areas ($p < 0.001$). A chi-square test showed a significant difference in the proportion of elderly people (aged ≥65 years)

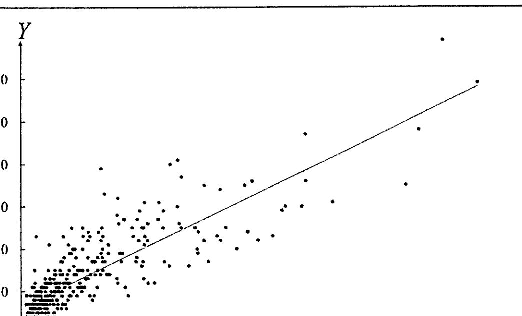

Figure 1 The correlation between size of population and the number of emergency medical service centers in 359 jurisdictions. Variable X denotes population (million persons), while variable Y denotes the number of emergency medical service centers in 359 jurisdictions. $Y = 19.71X+6.16$, $R^2 = 0.708$.

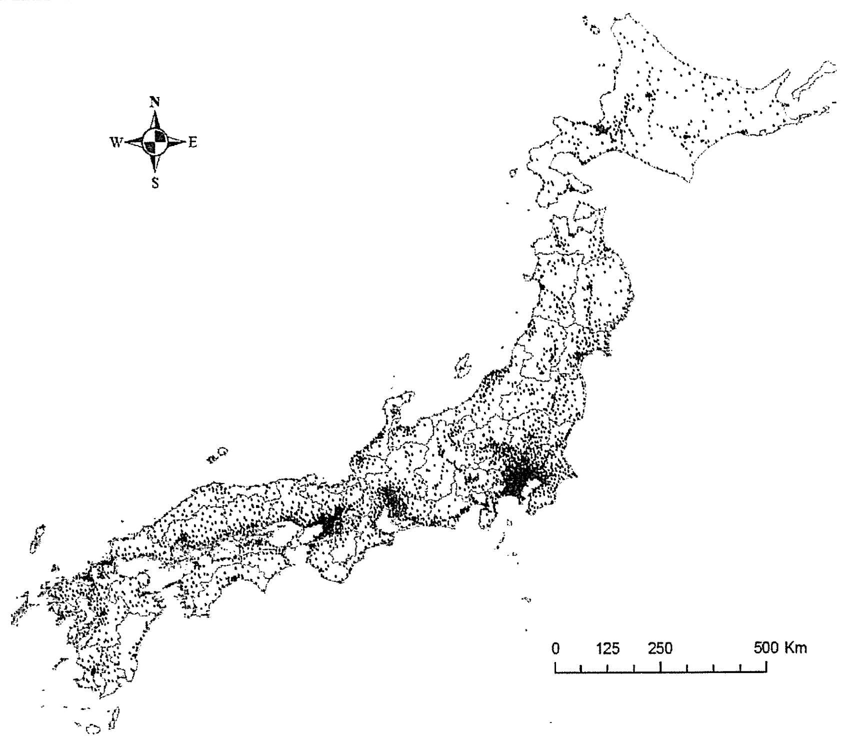

Figure 2 A map of emergency medical service centers in Japan (47 prefectures). Dots indicate locations of emergency medical service centers.

between the groups; 25.6% in very low-density areas against 18.1% in very high-density areas ($p < 0.001$).

Table 2 shows the survival outcomes in each subcategory. Seasonal data for 8 patients were missing. Overall, 1-month survival and neurologically favorable 1-month survival occurred in 7,915 (7.8%) and 3,639 (3.6%) cases, respectively. Fewer cases of survival were observed in females ($p < 0.001$) and higher age groups ($p < 0.001$). Bystander CPR coupled with AED use showed greater improvements of survival likelihood compared with bystander CPR alone ($p < 0.001$), but AED was used in only 572 (0.56%) cases. Cases of arrest with cardiac origin showed higher rates of survival than those with non-cardiac origin ($p < 0.001$). With regard to call-response intervals, 1-month survival rates were 13.2% and 3.6% in the subgroups of ≤ 2 min and ≥11 min, respectively ($p < 0.001$). Neurologically favorable 1-month survival rates were 8.4% and 1.6% the subgroups of ≤ 2 min and ≥11 min, respectively ($p < 0.001$). Neighborhoods with a higher proportion of elderly people (≥65 years) were significantly associated with lower 1-month survival ($p < 0.001$) and neurologically favorable 1-month survival ($p < 0.001$).

Table 3 shows the average and 95% confidence intervals (CIs) of call-response interval and outcomes in each population-density group. Comparing between very low- and very high-density areas, call-response intervals were 9.3 [9.1-9.4] min vs. 6.2 [6.1-6.3] min ($p < 0.001$), 1-month survival rates were 5.4% [4.8-6.0%] vs. 9.1% [8.7-9.5%] ($p < 0.001$), and neurologically favorable 1-month survival rates were 2.7% [2.3-3.1%] vs. 4.3% [4.0-4.6%] ($p < 0.001$), respectively.

The hierarchical logistic regression models including random intercepts for EMS centers did not converge. Table 4 shows the results of logistic regressions fitted with fixed effect models for 1-month survival and neurologically favorable 1-month survival. The odds of being alive at 1 month are lower for females, older patients, cases of arrest of non-cardiac origin and cases in winter or spring. The odds of being alive at 1 month are 5.79 times higher for patients receiving first aid with CPR and AED than for those receiving no first aid. Patients in very high-density areas were significantly more likely to exhibit a better 1-month survival (OR, 1.64; 95%CI, 1.44 -1.87; $p < 0.001$) and neurologically favorable 1-month survival (OR, 1.47; 95% CI, 1.22 - 1.77; $p < 0.001$) compared with those in very low-density areas. Even after being adjusted for various factors including individual patient ages, the outcomes

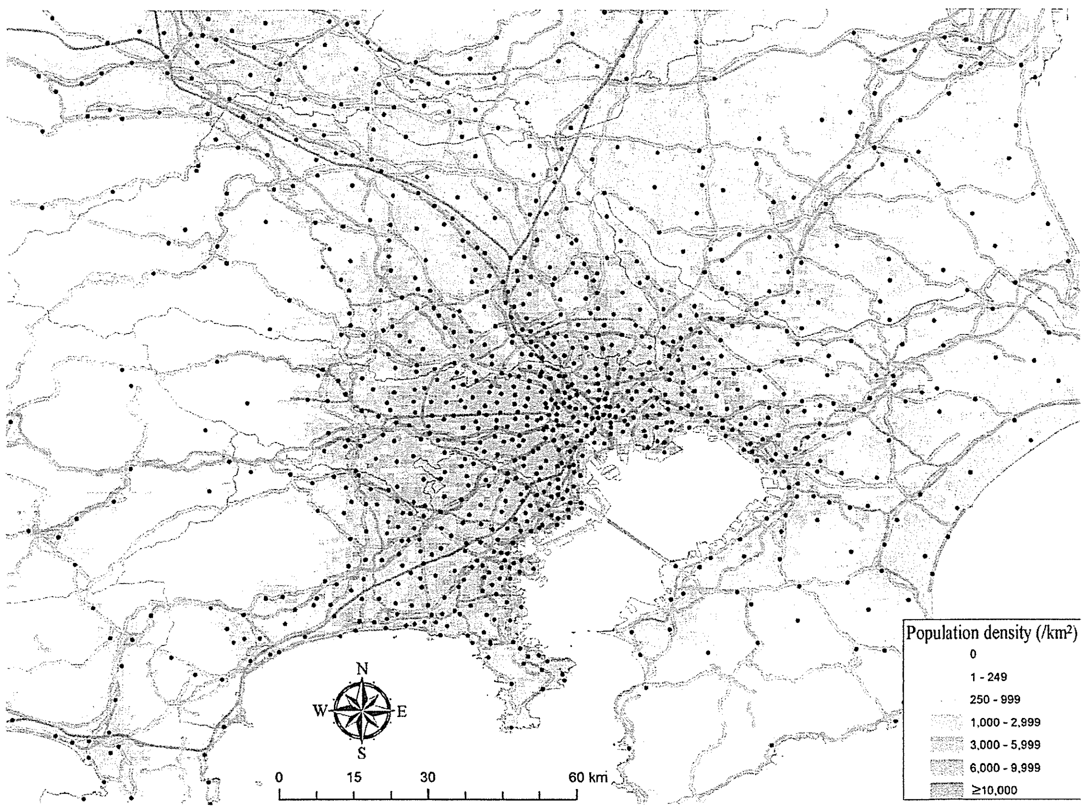

Figure 3 A map of emergency medical service centers in the Tokyo metropolitan area and surrounding areas coupled with population information. Dots indicate locations of emergency medical service centers. Green shading indicates population density. White areas are uninhabited. Lines are highways and national roads. Drawn with ArcGIS.

were significantly affected by the proportion of neighborhood elderly people (aged ≥65 yrs). That is, patients living in areas where ≥ 25% of people were aged ≥65 yrs had a significantly lower probability of 1-month survival (OR, 0.86; 95%CI, 0.79 - 0.93; $p < 0.001$) and neurologically favorable 1-month survival (OR, 0.88; 95%CI, 0.78 - 0.98; $p = 0.021$), compared with those residing in areas where < 15% of people were aged ≥65 yrs.

Discussion

Some previous data have suggested an association between population density and survival following

Table 1 Patient characteristics and neighborhood environment in each population-density area

Population density (/km2)	Very low (<250)	Low (250-999)	Middle-low (1,000-2,999)	Middle-high (3,000-5,999)	High (6,000-9,999)	Very high (≥10,000)	p
No. of patients	5,605	14,870	23,057	21,702	16,193	19,860	
Sex (males)	62.6%	61.9%	61.6%	61.7%	61.6%	61.3%	0.587*
Age (Average ± SD, yrs)	73.2 ± 17.0	72.9 ± 17.6	72.2 ± 17.7	71.6 ± 17.8	70.8 ± 18.1	70.5 ± 18.1	<0.001**
Cardiac origin (%)	53.6%	53.6%	54.0%	55.2%	57.2%	58.0%	<0.001*
Occurrence of bystander-initiated CPR	46.4%	45.3%	44.2%	42.8%	41.4%	36.3%	<0.001*
Occurrence of AED use	0.55%	0.35%	0.52%	0.48%	0.59%	0.85%	<0.001*
The proportion of neighborhood elderly people aged ≥65 yrs	25.6%	24.6%	21.9%	20.5%	18.6%	18.1%	<0.001*

CPR: cardiopulmonary resuscitation, AED: automated external defibrillators, SD: standard deviation. *Chi-square tests **Analysis of variance.

Table 2 1-month survival rates and neurologically favorable 1-month survival rates in each subgroup

	N	1-month survival		Neurologically favorable 1-month survival	
Total	101,287	7,915	(7.8%)	3,639	(3.6%)
Sex					
Male	62,445	5,297	(8.5%)	2,611	(4.2%)
Female	38,842	2,618	(6.7%)	1,028	(2.6%)
Age (yrs)					
≤ 59	20,457	2,473	(12.1%)	1,493	(7.3%)
60 - 69	15,530	1,612	(10.4%)	808	(5.2%)
70 - 79	26,010	1,888	(7.3%)	733	(2.8%)
80 - 89	27,497	1,521	(5.5%)	476	(1.7%)
≥ 90	11,775	419	(3.6%)	128	(1.1%)
First aid by bystander					
None	58,525	3,868	(6.6%)	1,498	(2.6%)
CPR without AED	42,190	3,851	(9.1%)	1,976	(4.7%)
CPR with AED	572	196	(34.3%)	165	(28.8%)
Cause of arrest					
Cardiac	56,188	4,829	(8.6%)	2,640	(4.7%)
Non-cardiac	45,099	3,086	(6.8%)	999	(2.2%)
Seasons					
Summer (June-August)	20,899	1,856	(8.9%)	895	(4.3%)
Autumn (September-November)	23,811	1,966	(8.3%)	929	(3.9%)
Winter (December-February)	30,900	2,188	(7.1%)	973	(3.1%)
Spring (March-May)	25,669	1,904	(7.4%)	842	(3.3%)
Call-response interval (min)					
≤ 2	2,736	361	(13.2%)	229	(8.4%)
3 - 4	17,074	1,899	(11.1%)	931	(5.5%)
5 - 6	30,515	2,770	(9.1%)	1,254	(4.1%)
7 - 8	23,683	1,656	(7.0%)	694	(2.9%)
9 - 10	13,004	707	(5.4%)	301	(2.3%)
≥ 11	14,234	516	(3.6%)	228	(1.6%)
The proportion of neighborhood elderly people ≥65 yrs (%)					
< 15	17,912	1,571	(8.8%)	718	(4.0%)
15 - 25	59,422	4,792	(8.1%)	2,221	(3.7%)
> 25	23,953	1,552	(6.5%)	700	(2.9%)

CPR: cardiopulmonary resuscitation, AED: automated external defibrillators.

OHCA [7-11]. In a previous study of 311 OHCA cases in Kentucky, USA, population density ≥100/square mile was associated with higher survival of OHCA [7]. In one study of 793 OHCA patients in Pennsylvania, USA, survival rates were 9%, 14% and 23% in rural, suburban and urban areas, respectively [9]. Another study of 1,956 patients in Scotland showed no significant difference in survival to discharge between areas with different median response times [11]. However, these studies were conducted in limited geographical areas with relatively

Table 3 Population density, call-response interval and survival of out-of-hospital cardiac arrest

Population density (/km2)	Call-response interval, average [95% CI] (min)		1-month survival, average [95% CI] (%)		Neurologically favorable 1-month survival, average [95% CI] (%)	
Very low (<250)	9.3	[9.1-9.4]	5.4	[4.8-6.0]	2.7	[2.3-3.1]
Low (250-999)	8.4	[8.3-8.5]	6.0	[5.6-6.4]	2.7	[2.4-3.0]
Middle-low (1,000-2,999)	7.7	[7.7-7.8]	7.2	[6.9-7.6]	3.5	[3.3-3.7]
Middle-high (3,000-5,999)	7.2	[7.2-7.3]	8.3	[7.9-8.7]	3.6	[3.3-3.8]
High (6,000-9,999)	6.7	[6.7-6.8]	9.0	[8.5-9.4]	4.0	[3.7-4.3]
Very high (≥10,000)	6.2	[6.2-6.3]	9.1	[8.7-9.5]	4.3	[4.0-4.6]

CI: confidence interval.

Table 4 Logistic regressions for 1-month survival rates and neurologically favorable 1-month survival rates

	1-month survival					Neurologically favorable 1-month survival				
	OR	95%CI			p	OR	95%CI			p
Sex										
Male	1.00					1.00				
Female	0.95	0.90	-	1.00	0.040	0.87	0.80	-	0.93	<0.001
Age (yrs)										
≤59	1.00					1.00				
60 - 69	0.83	0.72	-	0.96	0.011	0.65	0.54	-	0.80	<0.001
70 - 79	0.57	0.49	-	0.65	<0.001	0.32	0.26	-	0.40	<0.001
80 - 89	0.37	0.32	-	0.43	<0.001	0.23	0.18	-	0.29	<0.001
≥90	0.27	0.21	-	0.34	<0.001	0.15	0.10	-	0.22	<0.001
Cause of arrest										
Cardiac	1.00					1.00				
Non-cardiac	0.81	0.78	-	0.85	<0.001	0.49	0.45	-	0.53	<0.001
First aid by bystander										
None	1.00					1.00				
CPR without AED use	1.52	1.45	-	1.60	<0.001	1.99	1.85	-	2.13	<0.001
CPR with AED use	5.73	4.80	-	6.84	<0.001	9.60	7.89	-	11.7	<0.001
Seasons										
Summer (June-August)	1.00					1.00				
Autumn (September-November)	0.95	0.88	-	1.01	0.103	0.94	0.86	-	1.04	0.224
Winter (December-February)	0.84	0.78	-	0.89	<0.001	0.81	0.74	-	0.90	<0.001
Spring (March-May)	0.85	0.80	-	0.91	<0.001	0.80	0.73	-	0.88	<0.001
Population density (/km^2)										
Very low (<250)	1.00					1.00				
Low (250-999)	1.14	0.99	-	1.30	0.067	1.03	0.85	-	1.25	0.776
Middle-low (1,000-2,999)	1.34	1.18	-	1.53	<0.001	1.29	1.08	-	1.55	0.006
Middle-high (3,000-5,999)	1.53	1.35	-	1.74	<0.001	1.29	1.08	-	1.55	0.006
High (6,000-9,999)	1.63	1.42	-	1.85	<0.001	1.39	1.15	-	1.67	0.001
Very high (≥10,000)	1.64	1.44	-	1.87	<0.001	1.47	1.22	-	1.77	<0.001
The proportion of neighborhood elderly people (aged ≥65 yrs; %)										
<15	1.00					1.00				
15 - 25	0.89	0.80	-	0.98	0.025	0.94	0.82	-	1.08	0.384
>25	0.82	0.72	-	0.94	0.005	0.81	0.68	-	0.96	0.017

CPR: cardiopulmonary resuscitation, AED: automated external defibrillators, OR: odds ratio, CI: confidence interval.

small sample sizes. Our study of 101,287 OHCA cases in Japan showed that 1-month survival rates were 5.4% and 9.1% in very low-density (<250/km^2) and very high-density (≥10,000/km^2) areas, respectively. To our knowledge, the present study is the first to demonstrate the relationship between population density and survival of OHCA in a nationwide setting. The very large sample size allowed more robust multivariate analyses of survival correlates and precise estimates of odds ratios. In the present study, population density was a consistent independent correlate of 1-month survival and neurologically favorable 1-month survival.

The distribution of EMS centers in different regions of Japan is almost in proportion to population density. The low survival of OHCA in low-density areas is likely to be due primarily to greater call-response intervals in these areas. These findings have important health policy implications for nations that wish to improve survival in cases of OHCA; EMS resource allocation according to population size may cause disparities in response times and subsequent health benefit inequalities between urban and rural areas. Compared to their urban counterparts, rural EMS personnel travel longer distances to provide prehospital EMS, contributing to poor survival outcomes.

Minimizing call-response interval could enhance survival rates. Increasing the number of ambulances could decrease call-response intervals across large, sparsely populated areas, but may not be practical because of costs and a need for cost-effective measures. Nevertheless, health policy makers should make every effort to minimize disparities in EMS availability, and maximize the overall effectiveness of a national EMS system by optimizing the allocation of EMS resources under budget constraints. For example, it may be worth considering helicopter transportation in rural EMS systems [22], though the applicability and effectiveness of implementing this approach would require further investigation [23,24]. The use of other existing resources should also be taken into consideration to optimize call-response intervals. For example, a police first-responder program may be beneficial in regions where ambulance response times are longer [25].

At the same time, other more cost-effective strategies should also be explored. Our study revealed that bystander CPR occurred in only approximately 42% of OHCA cases. While this figure is relatively high compared with many countries [5,26], there is much room for improvement. There is evidence that people may be unwilling to perform this distressing psychomotor task because of fear of doing harm or an aversion to mouth-to-mouth breathing [27].

The present study further corroborated the importance of bystander CPR. Emergency medical professionals should make further efforts to enable the general public to provide CPR when necessary. Although public access defibrillation with AED significantly improved survival, its use was extremely rare. Despite the nationwide dissemination of AED in Japan [6], there was a benefit of AED use in only 0.56% cases of bystander-witnessed OHCA; an analysis of the cost-effectiveness of AED implementation will be essential to evaluate this measure.

Another significant finding in this study was the lower survival rate of OHCA cases in areas with a higher proportion of elderly people. Patients' individual age is a biological factor that definitely influences mortality. Living in an aged society is a social factor that is independent from individual age. Even after adjusting for various factors including individual patients' age and presence of bystander CPR, patients living in aged-population areas had a lower probability of survival following OHCA. This may also be attributed to older patients having greater degree of disease or multiple co-morbidities. However, it could be hypothesized that OHCA patients in aged-population areas may be more likely to receive CPR from elderly bystanders, and the quality of their CPR may be relatively poor, resulting in lower success rates.

Increasing the quality of bystander CPR is a common public health problem worldwide. School-based training programs could be an effective way of training younger populations [28]. New driver's license applicants in Japan are now obliged to undergo CPR training program at driver's school [12]. However, the problem of training the elderly population in CPR remains, especially in rural areas. A previous report showed that the elderly perceived themselves as able to perform and interested in receiving training [29]. Although public health programs that teach CPR to large numbers of the public are expensive, additional emphasis on widespread CPR training for elderly people for improving CPR quality could be worthwhile.

Several limitations of the current study should be acknowledged. First, in common with all registry-based surveys, the validity and integrity of the data are potential limitations, although their effects were likely to be minimized by the large sample size collected with our population-based design. Second, the categories for the population groups were arbitrarily made, and such division could not be generalized to other countries. Third, generalizability of our results could be limited because Japanese geographic characteristics (two-thirds of the country being uninhabitable and a majority of people living in urban areas) could be different compared to other countries. Lastly, our database lacked detailed data to make further risk adjustments for survival; e.g. comorbid conditions of patients or severity of cardiac arrest based on clinical markers, experiences of EMS personnel [30], the existence of specialists of emergency care or cardiologists or treatments available at the receiving hospitals [31].

Conclusion

Our study is the first to demonstrate in a nationwide setting that population density is a consistent factor independently affecting the likelihood of survival following OHCA events. Appropriate strategies should be implemented to minimize the current disparity in EMS availability and subsequent inequality of health benefits between urban and rural areas.

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Authors' contributions

HY conceived the study concept and study design and wrote the draft. HY and HM carried out statistical analyses HH performed compilation, synthesis and analyses of data on the geographic information system. TI obtained the Utstein data from the Fire and Disaster Management Agency of Japan on behalf of our research team, and supervised the research project. HY, HM, HH, MA, TO, ST, SK, and TI participated in interpretation of the results and writing of the report. All authors approved the final version.

Competing interests

The authors declare that they have no competing interests.

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