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Major interventions are associated with survival of out of hospital cardiac arrest patients - a population based survey

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ABSTRACT

Background. The overall survival rate of out-of-hospital cardiac arrest (OHCA) in Taiwan or even in the whole of Asia is relatively low. Major interventions, such as target temperature management (TTM), coronary artery angiography, and extracorporeal membrane oxygenation (ECMO), have been associated with better patient outcome. However, studies in Taiwan revealing evidence of the benefits of these interventions are limited.
Methods. A population-based study used an 8-year database to analyze overall survival and risk factors ″among OHCA patients. All adult non-trauma OHCA patients were identified through diagnostic and procedure codes. Hospital survival and return of spontaneous circulation (ROSC) were primary and secondary outcomes. Logistic regression and Cox regression analyses were conducted.
Results. There was a relationship between major interventions (including TTM, coronary artery angiography, and ECMO) and better hospital survival. Age, income, major interventions, and acute myocardial infarction history were associated with hospital survival. The adjusted hazard ratios (HRs) were 0.406 (95% CI, 0.295 to 0.558), 1.109 (95% CI, 1.027 to 1.197), 1.075 (95% CI, 1.002 to 1.154), 1.097 (95% CI, 1.02 to 1.181) and 0.799(95% CI, 0.677 to 0.942) for patients with major interventions, age≥50, medium low and low income, middle income, and acute myocardial infarction history, respectively.
Conclusion. This population-based study in Taiwan revealed that older age (≥50), medium low and low income were associated with a lower rate of survival. Major interventions, including TTM, coronary angiography, and ECMO, were related to better survival.

Key words: OHCA, ROSC, out-of-hospital cardiac arrest, target temperature management, ECMO

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) remains a leading cause of mortality and a substantial issue for public health worldwide. According to a statistical update from the American Heart Association, the incidence of OHCA in the United States is approximately 359,400 each year with an overall survival rate of 9.5%. (1) Overall survival to hospital discharge rates are lower in the Asian population with rates ranging from 0.5% to 8.5%. (2-4) The overall survival to hospital discharge in Taiwan ranges from 1.4% to 6%. (5-7) To overcome the low survival rate, the concept of an out-of-hospital chain of survival has been established, including 1) early recognition of cardiac arrest and activation of the emergency medical service (EMS) system, 2) early cardiopulmonary resuscitation (CPR) with highlight on high quality chest compressions, 3) early defibrillation, 4) basic and advanced EMS, 5) advanced life support (ALS) and post-cardiac arrest care. (8)
Several interventions, such as extracorporeal membrane oxygenation (ECMO), (9,10) target temperature management (TTM), (11,12) and percutaneous coronary intervention, (13,14) have been associated with favorable patient outcomes. In Taiwan, there is limited data on major interventions (TTM, coronary artery angiography, ECMO) and their influence on patient outcomes. The aim of our study was to assess the impact of patient demographic features, hospital characteristics, and major interventions on prognoses of OHCA.

METHODS

Data Sources

The National Health Insurance (NHI) program was conducted in Taiwan in 1995 and provides compulsory universal health insurance. It enrolls about 99% of the Taiwanese population and contracts with 97% of all the country's health care services. (15) For research purposes, a random sample of 1,000,000 people who received

health services from the NHI program was selected based on calendar-year 2005 reimbursement data. According to the Taiwan National Health Research Institute (NHRI), the random sample group is considered representative of the entire population since the group did not differ statistically from the whole cohort in age, sex, or health care costs. This random sample of 1,000,000 people was used as our study cohort. Information about admissions and outpatient visits, both of which included information on patient characteristics (sex, date of birth, date of admission, date of discharge, dates of visits) and up to five discharge diagnoses or three out-patient visit diagnoses (based on the International Classification of Diseases, Ninth Revision [ICD-9]), was collected. (16) We also gained information on patient prescriptions, including the names of prescribed drugs, dosage, duration, and total expenditure. Previously used for epidemiologic research, the NHRI database provided high quality information on prescription use, diagnoses, and hospitalizations (17) and this database had been previously used for OHCA research. (18,19) The NHRI strictly followed confidentiality guidelines in accordance with personal electronic data protection regulations, making the NHI reimbursement data suitable for research. (15) In addition, this study was approved by Chang Gung Medical Foundation Institutional Review Board.

Identification of Study Sample

We carried out a population-based cohort study in which we identified all alive patients older than 18 years who suffered from out-of-hospital cardiac arrest (OHCA) (ICD-9 codes 427.5, 798.9, 798.1, 798.2) and were admitted to the emergency department (ED) between January 1, 2005 and December 31, 2012. Thus, we formed a study cohort with a total number of 6,815 individuals. Individuals with cardiac arrest announced death by EMS at the scene or without transportation to the hospital were not included because EMS records were not available in our NHI database. In Taiwan, prehospital emergency care is provided by emergency medical technicians (EMTs) in different fire bureaus. Most EMTs are EMT-II, but some cities have paramedics (EMT-Ps). Once a patient with cardiac arrest is identified, EMTs or EMT-Ps do not terminate resuscitation even when the patient had signed a do not resuscitate (DNR) consent or has signs of obvious death (rigor, mortis, lividity, decapitation etc.) unless the patient's family understands and requests to discontinue. Complete prehospital advanced life support (ALS) is performed only in some urban areas since the number of EMT-Ps is limited. On the basis of an evaluation in urban Taipei, ALS demand accounted for approximately 9–16% of total EMS calls, and the average response time was 4.1–4.9 minutes. In rural areas, the average response time was found to be longer, even exceeding 6.6 minutes. (20)

Two hundred and twenty-four (224) individuals with trauma, intoxication, submersion, and accidents (ICD-9 codes 800-999 and E800-999) were excluded. Those who did not receive any CPR, defibrillation, or endotracheal intubation during ED stay were also excluded (number =1253). All enrolled patients were followed up until December 31, 2013 (Figure1). The primary outcome was hospital survival, which was defined as survival to hospital discharge. The secondary outcome was return of spontaneous circulation (ROSC), which was defined in this study as sustained ROSC with hospital admission.

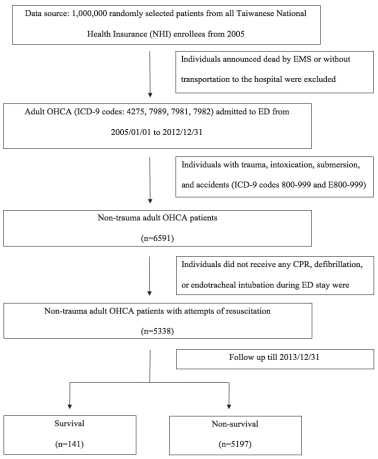

Figure 1. Flow chart of identification of study sample and follow up.

CPR, cardiopulmonary resuscitation; ED, emergency department; EMS, emergency medical system; ICD-9, International Classification of Diseases, Ninth Revision; OHCA, out of hospital cardiac arres.

Potential Covariates and Management

We identified in a systematic way any comorbid conditions as potential confounders, defined by the following diagnoses recorded before January 1, 2005: angina (ICD-9 codes 413.0, 413.1,and 413.9), acute myocardial infarction (ICD-9 codes 410.70, 410.71, 410.72, 410.80, 410.81, 410.82, 410.90, 410.91, 410.92), coronary artery disease (ICD-9 codes 410.x-414.x), diabetes (ICD-9 codes250.0-250.3, 250.8, 250.9), malignancies (ICD-9 codes140.x-172.x, 174.x-195.8, 200.x-208.x, 238.6), heart failure (ICD-9 codes398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428.x), cerebrovascular disease (ICD-9 codes362.34, 430.x-438.x), and the Charlson Comorbidity Index (CCI). The CCI is a scoring system that strengthens important concomitant diseases and has been validated for studies that employ ICD-9 data. (18)

We also considered socio-demographic characteristics (age, sex, level of urbanization, level of hospital, and level of monthly income) in the modeling. Level of hospital is classified as either medical center or non-medical center. (21) Urbanization levels in Taiwan are divided into seven groups according to the Taiwan National Health Research Institute publications. (22) Group 1 is called highly urbanized area, group 2 is moderately urbanized area, group 3 is emerging area, group 4 is general rural area, group 5 is aging area, group 6 is agricultural area, and group 7 is remote area. (22) In our study, groups 4, 5, 6, and 7 are merged into a single group, called general rural area. Thus, urbanization levels in our report are classified as highly urbanized area, moderately urbanized area, emerging area and general rural area. Individual monthly income in New Taiwan dollars (NTD) is divided into four groups: 0,1-15,840,15,841-25000 and ≥25,001. According to the Ministry of Health and Welfare of Taiwan, individual monthly income less than 150 percent of the poverty level amount is defined as low income. (23) Thus, we classified these four groups as follows: no income (0), medium low and low income (1-15,840), middle income (15,841-25000), high income (≥25,001).

For the survey of factors associated with hospital survival, major interventions, which were composed of three managements: TTM, coronary artery angiography, and ECMO, were identified during the hospital stay.

Statistical Analyses

We used the Kaplan–Meier method to analyze the survival of patients with and without major interventions, and the log-rank test was performed to examine the differences in mortality. Cox proportional hazard models were used to compute the hazard ratios (HRs) for mortality of OHCA patients and logistic regression model was

applied for risk analysis of ROSC, accompanying 95% confidence interval (CI) after adjustment for the variables mentioned. Two-tailed P<0.05 was considered significant. All of these analyses were conducted using SAS statistical software (version 9.4; SAS Institute, Cary, NC).

RESULTS

Figure 1 illustrates the selection process of study participants. A total of 5,338 OHCA patients met inclusion and exclusion criteria for this study. Of these patients, 12.2% (652) were admitted to hospital and 2.64% (141) survived to hospital discharge. Table 1 lists the demographic characteristics of all OHCA patients. Twenty-three (0.4%) patients received TTM, 19 (0.36%) received coronary artery angiography, 11 (0.2%) received ECMO, and 48 (0.9%) received major interventions. Cox regression model reveals that age, income, major interventions, and acute myocardial infarction history were associated with hospital survival after adjusting for gender, age, urbanized level, individual income, major interventions, level of hospital, Charlson comorbidity index, angina, acute myocardial infarction, any tumor, cerebrovascular disease, congestive heart failure, coronary artery disease, and diabetes (table 2). A logistic regression model demonstrates factors associated with ROSC, including age, income, and comorbidities with coronary artery disease and cerebrovascular disease after adjusting for every variable in Table 2 (table 3). Figure 2 illustrates the results of the Kaplan-Meier method for the cohort.

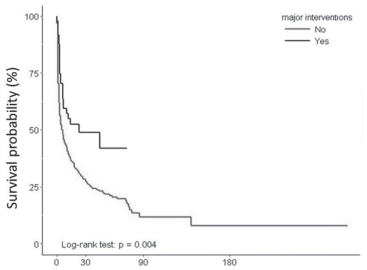

Figure 2. Kaplan–Meier estimates of survival of patients with and without major interventions (p=0.004).

Table 1. Demographic characteristics of OHCA patients

Variables	**OHCA (N= 5338)**	
	n	**%**
Gender		
Female	1989	37.26
Male	3349	62.74
Age		
Age <50	927	17.37
Age ≥50	4411	82.63
Urbanized level		
highly urbanized area	1323	24.78
moderately urbanized area	2506	46.95
emerging area	979	18.34
general rural area	530	9.93
Individual income		
No income	1944	36.42
Medium low and Low		
income	1512	28.33
Middle income	1518	28.44
High income	364	6.82
ROSC		
No	4622	86.59
Yes	716	13.41
OPD follow up	64	1.2
Admission	652	12.2
Major interventions	48	0.9
No major interventions	604	11.3
Survival	141	2.64
Non-survival	5197	97.36
Level of hospital		
Medical center	1373	25.72
Non-medical center	3965	74.28

Covariates		
Charlson comorbidity index		
0	3171	59.4
1	597	11.2
≥2	1570	29.4
Angina	115	2.15
Any tumor	367	6.88
Acute myocardial infarction	176	3.3
Cerebrovascular disease	451	8.45
Congestive heart failure	471	8.82
Coronary artery disease	365	6.84
Diabetes	296	5.55

OHCA, out of hospital cardiac arrest; OPD, outpatient department; ROSC, return of spontaneous circulation.

Table 2. Cox regression analysis for hospital survival of all OHCA patients

Variables	**Crude hazard ratio**				**Adjusted hazard ratio**			
	hazard ratio 95% CI			**P**	**hazard ratio 95% CI**			**P**
Gender								
Female	1				1			
Male	1.017	0.962	1.076	0.5466	1.017	0.96	1.077	0.5748
Age								
<50	1				1			
≥50	1.094	1.018	1.177	0.0149*	1.109	1.027	1.197	0.0082*
Urbanized level								
highly urbanized area	0.919	0.83	1.017	0.1037	0.982	0.882	1.094	0.7418
moderately urbanized area	0.934	0.849	1.026	0.1553	0.972	0.882	1.072	0.5748
emerging area	0.987	0.887	1.098	0.8041	1	0.898	1.112	0.9933
general rural area	1				1			
Individual income								
No income	1				1			
Medium low and Low income	1.073	1.002	1.149	0.0436*	1.075	1.002	1.154	0.0427*
Middle income	1.104	1.031	1.182	0.0046*	1.097	1.02	1.181	0.0125*
High income	1.002	0.894	1.123	0.9704	1.032	0.918	1.16	0.5965
Interventions								
no major interventions	1							
major interventions	0.38	0.277	0.522	<.0001*	0.406	0.295	0.558	<.0001*
Level of hospital								
Non-Medical center	1				1			
Medical center	0.908	0.853	0.966	0.0025*	0.938	0.88	1.001	0.0537
Covariates								
Charlson comorbidity index								
0	1				1			
1	1.019	0.938	1.106	0.6601	0.995	0.916	1.082	0.9139
≥2	1.04	0.98	1.104	0.1942	1.031	0.969	1.098	0.3366
Angina	1.018	0.845	1.227	0.8472	1.093	0.902	1.325	0.3629
Acute myocardial infarction	0.758	0.648	0.886	0.0005*	0.799	0.677	0.942	0.0077*
Any tumor	1.014	0.911	1.127	0.8052	0.991	0.889	1.103	0.8636
Cerebrovascular disease	0.957	0.868	1.054	0.372	0.946	0.857	1.044	0.2682
Congestive heart failure	0.916	0.832	1.008	0.0723	0.936	0.847	1.034	0.1915

Coronary artery disease	0.846	0.758	0.945	0.0029	0.896	0.796	1.008	0.067
Diabetes	0.949	0.841	1.071	0.3988	0.924	0.732	1.167	0.507

OHCA, out of hospital cardiac arrest.

Table 3. Logistic regression analysis for return of spontaneous circulation (ROSC)

Variables	**Crude odds ratio**				**Adjusted odds ratio**			
	odds ratio	**95% CI**		**P**	**odds ratio**	**95% CI**		**P**
Gender								
Female	1				1			
Male	1.195	1.018	1.403	0.0296	1.179	0.996	1.396	0.0559
Age								
<50	1				1			
≥50	1.209	0.991	1.476	0.0614	1.505	1.213	1.867	0.0002*
Urbanized level								
highly urbanized area	0.736	0.544	0.995	0.0466	0.936	0.677	1.294	0.6881
moderately urbanized area	0.868	0.652	1.157	0.3348	1.024	0.758	1.385	0.8757
emerging area	1.055	0.759	1.466	0.7503	1.112	0.796	1.555	0.5325
general rural area	1				1			
Individual income								
No income	1				1			
Medium low and Low income	1.209	0.997	1.466	0.0531	1.199	0.979	1.468	0.079
Middle income	1.489	1.217	1.822	0.0001	1.412	1.134	1.759	0.002*
High income	1.384	0.984	1.946	0.0619	1.466	1.026	2.094	0.0356*
Level of hospital								
Non-Medical center	1				1			
Medical center	0.668	0.564	0.792	<.0001	0.701	0.586	0.838	0.0001
Covariates								
Charlson comorbidity index								
0	1				1			
1	0.975	0.771	1.233	0.8323	0.92	0.723	1.173	0.5024
≥2	1.026	0.862	1.22	0.7736	1.142	0.947	1.378	0.1655
Angina	1.337	0.731	2.443	0.3455	2.139	1.126	4.063	0.0201*
Acute myocardial infarction	0.267	0.194	0.367	<.0001	0.333	0.232	0.478	<.0001*
Any tumor	0.813	0.607	1.089	0.1643	0.759	0.561	1.027	0.0737
Cerebrovascular disease	0.521	0.411	0.662	<.0001	0.496	0.387	0.636	<.0001*
Congestive heart failure	0.522	0.413	0.661	<.0001	0.608	0.47	0.788	0.0002*
Coronary artery disease	0.463	0.359	0.597	<.0001	0.605	0.451	0.812	0.0008*
Diabetes	0.831	0.599	1.154	0.2689	0.949	0.461	1.954	0.8864

DISCUSSION

There were two main findings in this study. First, older age (≥50), medium low and low income were associated with a lower rate of hospital survival. Second, major interventions (including TTM, coronary artery angiography, and ECMO) were associated with a higher rate of in-hospital survival.

Consistent with other reports, (24,25) the incidence of OHCA in men was higher than in women, and men were prone to have a lower rate of ROSC than women in our investigation. The possible reasons might be the effect of estrogen and progesterone on reduction of cardiac arrest risk in women and higher prevalence of lifestyle and cardiovascular risk factors in men. (26) However, the effect of gender on hospital survival of OHCA was not significant, as previous studies have described. (24,25)

According to a recent retrospective survey in Sweden, there was no association between urbanization and outcomes after OHCA, consistent with our discovery. (27) In contrast with urbanization, higher level of hospital care, such as in a medical center, was associated with successful ROSC in our report. Several studies have identified in-hospital factors associated with improved mortality after successful resuscitation from OHCA in patients ad-

mitted to different hospitals with different levels of care. (28,29) Level of hospital care has been suggested as an important factor for the difference in mortality of OHCA patients. One Denmark study demonstrated that a tertiary center had improved survival than other hospitals, and another Australia report declared that hospitals, especially those with 24-h cardiac intervention services, were associated with better outcomes in OHCA setting. (29,30) According to data from the Ministry of Health and Welfare of Taiwan, all medical centers are capable of providing 24-h, 7 days per week emergency cardiac catheterization services for acute ST elevation myocardial infarction patients and cardiac surgeon consultation. (21)

In our study, medium low and low income was associated with a lower rate of hospital survival. Previous studies have revealed that persons of lower socioeconomic status (SES) have been found to have a greater load of risk factors for cardiovascular disease (31) and less knowledge of risk factors for cardiovascular disease. (32) One report, in a Taiwan metropolitan region, showed that areas with low SES were associated with worse patient outcomes following OHCA. (33) Lower rates of witnessed arrest and bystander cardiopulmonary resuscitation and higher incidence of cardiovascular disease were possible contributors to unfavorable outcomes in the low SES group after cardiac arrest. (34)

Several randomized trials have revealed that TTM is effective in the improvement of both neurological function and survival. (11,12,35) Two trials focusing on OHCA with an initial shockable rhythm had demonstrated the association between TTM and good neurologic outcome (11,12) and survival to hospital discharge. (11) Post-arrest coronary artery angiography had influence on the increase of hospital survival and good neurologic function. (36-38) The benefit of emergency cardiac catheterization, compared with catheterization later during hospital stay or no intervention, has been documented among post-arrest patients, either with evidence of ST elevation on electrocardiography (ECG) (36,37) or with no ST elevation on ECG. (38,39)

The benefit of ECMO on survival and neurological function in a selected patient group following OHCA had also been documented. (9,10) Though there was a relatively small number of major interventions in our study, patients with TTM, or coronary artery angiography, or ECMO had higher hospital survival, in agreement with the results of many reports.

Limitations

There were several potential limitations of this study. First, the data was obtained from an administrative database, which has been shown in the past to have inaccuracies when used for cardiac arrest research. (40) To overcome this, procedures and drugs administrated during resuscitation were another key element in data selection in addition to ICD-9 diagnosis code. Only those with attempts in resuscitation were enrolled in the analysis.

Second, several unmeasured confounders, which were related to pre-hospital factors and the emergency medical service(EMS) system, including place of occurrence, witnessed collapse, bystander-initiated CPR, EMS response time, initial arrest rhythm, prehospital defibrillation, airway management, and drug administration, were not available in our database. Third, we were unable to document non-sustained ROSC but merely those sustained ROCS with survival to hospital admission or survival to outpatient follow up. Fourth, neurologic functional status was not available in our database; hence, the effect of major interventions on neurologic outcome could not be evaluated. Another concern of our report was that the numbers of patients treated with TTM and angiography were very low. One probable explanation is the treating physician's selection bias for who would receive the treatments. Another probable explanation is that some materials for TTM and angiography were not covered by NHI and were relatively expensive, decreasing patients' willingness to receive the interventions.

CONCLUSION

This population-based study in Taiwan revealed that older age (≥50), medium low and low income were associated with a lower rate of survival. Major interventions, including TTM, coronary angiography, and ECMO were related to better survival.

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