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Clinical paper

Sex-related disparities in the in-hospital management of patients with out-of-hospital cardiac arrest

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Abstract

Aim: We investigated sex-related differences in the in-hospital management of patients with out-of-hospital cardiac arrest (OHCA).

Methods: We retrospectively analyzed prospectively collected data from the Korean Cardiac Arrest Resuscitation Consortium (KoCARC) registry, a prospective, multicenter OHCA registry. We enrolled adult patients with OHCA between October 2015 and June 2020. The primary outcomes were coronary angiography (CAG), percutaneous coronary intervention (PCI), targeted temperature management (TTM), and extracorporeal membrane oxygenation (ECMO) performed in the hospital. Propensity score matching (PSM) was performed to minimize differences in baseline demographics and characteristics.

Results: Among 12,321 patients in the KoCARC registry, we analyzed 8,177 with OHCA. PSM yielded 5,564 matched patients (2,782 women and men, respectively). In the unmatched cohort, women were less likely to undergo CAG, PCI, TTM, and ECMO. In the PSM cohort, women were less likely to undergo CAG and PCI (6.4% *vs.* 9.1%, $p < 0.001$ and 1.9% *vs.* 3.7%, $p < 0.001$). The duration of cardiopulmonary resuscitation was shorter in women (19 *vs.* 20 min, $p < 0.001$). TTM, ECMO use, and survival outcomes did not differ significantly between sexes. The subgroup analysis according to age showed that among patients aged < 65 years, women were less likely than men to undergo CAG and PCI (12.7% vs. 19.2%, $p < 0.001$ and 2.3% vs. 8.1%, $p < 0.001$).

Conclusions: In the PSM cohort, women with OHCA underwent CAG and PCI less frequently than men, regardless of the initial rhythm. However, these sex-related differences narrowed with increasing age. Further studies are needed to confirm the sex-related disparities in the in-hospital management of patients with OHCA.

Keywords: Out-of-hospital cardiac arrest, Sex, In-hospital management, Survival

Introduction

Annually, approximately 300,000 individuals in the United States and 275,000 in Europe experience out-of-hospital cardiac arrest (OHCA).[1,2] Although the survival rate of patients with OHCA has increased, the mortality rate remains high.[3–5]

In the past decade, sex disparities in health care systems have been reported, particularly in OHCA characteristics and survival.[6–16] While men have a higher OHCA incidence than women,[1–5] women are less likely to experience witnessed cardiac arrest,[6–9] as its occurrence in public places is more common in men.[10,11] Women experiencing cardiac arrest are less likely to receive bystander cardiopulmonary resuscitation (CPR)[5,12–14] and less frequently present with a shockable rhythm.[15,16] Conflicting results regarding sex disparities in survival and prognosis after OHCA were noted.[16–28] However, the extent of sex disparities in OHCA remains unclear.

Conflicting sex-related differences in the in-hospital management of OHCA patients have been reported.[7,21–25,29–33] While some stud-

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ies reported that women with OHCA were less likely to undergo early coronary angiography (CAG),[17,23,24,30,31] Lindgren et al. did not observe this tendency.[32] The findings on sex-related differences in performing percutaneous coronary intervention (PCI) are also conflicting.[17,21–25,30,33] Targeted temperature management (TTM) was less frequently performed in women in older studies,[17,23] whereas more recent studies showed no sex-related differences.[22,24,25,30]

Providing better resuscitation care for both men and women with OHCA and improving survival outcomes require an evaluation of sex-related differences in multiple in-hospital procedures performed in patients with OHCA. Therefore, we investigated sex-related differences in the in-hospital management of patients with OHCA through propensity score matching (PSM) analysis to adjust for covariate imbalance. We hypothesized that women were less likely to undergo procedures related to in-hospital management of OHCA, such as CAG, PCI, TTM, and extracorporeal membrane oxygenation (ECMO).

Methods

Study design and setting

We retrospectively analyzed data prospectively collected between October 2015 and June 2020 from the Korean Cardiac Arrest Resuscitation Consortium (KoCARC) registry, a prospective, multicenter OHCA registry based on a university-affiliated hospital-based research network.[34]

The KoCARC registry was designed to enroll patients with OHCA with resuscitation attempts and presumed medical etiology who were transported by emergency medical services (EMS) to the emergency departments (EDs) of the participating hospitals. The KoCARC investigators have prospectively collected predetermined data from OHCA patients since 2015. The exclusion criteria are patients with OHCA due to non-cardiac etiology, under hospice care, with a terminal illness, pregnant, and with a documented 'Do Not Attempt Resuscitation' order. The collected data were entered into a web-based registry using a standardized form for uniform reporting of OHCA. The case report form consisted of more than 200 variables, including patient demographics, past medical history, etiology of arrest, prehospital management, laboratory test results, in-hospital management, and clinical outcomes. Research coordinators at each participating ED gathered data via a medical record review. Among survivors, the prognosis 6 months after the event was assessed through telephone interviews with the survivors or their family members. The KoCARC registry was registered with ClinicalTrials.gov (NCT03222999) and approved by the institutional review board of the participating hospitals.

The Korean EMS system, which is operated by the government, has local headquarters at the National Fire Agency. Ambulances were dispatched for each OHCA case from regional EMS agencies belonging to fire departments. A partially dual-dispatch response system (BLS-fire engine, ACLS-ambulances) was operated for suspected OHCA cases. The prehospital EMS provider consists of trained emergency medical technicians (EMTs) or nurses belonging to the fire department. A typical responding ambulance crew consists of 2–3 persons, including one level-1 EMT (equivalent to EMT-intermediate in the North American EMS) and one level-2 EMT (equivalent to EMT-basic). EMTs in Korea provide basic to intermediate levels of service. Advanced airway management and the administration of resuscitation medications at the scene are allowed for level-1 EMTs only under direct medical supervision. Direct medical supervision refers to online medical direction, which is carried out under the direct order by telephone of an EMS physician on duty at a dispatch center. The declaration of death at the scene is prohibited unless the patient has obvious signs of death. Most patients with OHCA are transported to a hospital for continuing CPR.

Study population and data extraction

This study included patients aged $\geq$ 18 years who experienced OHCA, regardless of the return of spontaneous circulation (ROSC), between October 2015 and June 2020. Patients with missing or unknown study outcomes and covariate values were excluded. We extracted the following information from the KoCARC registry: age, sex, witness status, place of arrest, bystander CPR, initial cardiac arrest rhythm, prehospital defibrillation, prehospital advanced airway, total epinephrine dose during CPR, in-hospital CPR duration, CAG, time of CAG, PCI, TTM, ECMO, survival to admission, survival to discharge, and neurological outcome at discharge. Good neurological outcome was defined as a cerebral performance category score of 1 or 2.

Outcome variables and subgroup analysis

The primary outcome was in-hospital management such as CAG, PCI, TTM, and ECMO. The secondary outcomes were survival to admission, survival to discharge, good neurological outcome at discharge, total epinephrine dose during CPR, total CPR duration, time from ED arrival to CAG, and proportion of early CAG (performed within 24 h). Subgroup analysis of outcomes by sex according to age (<65 or $\geq$ 65 years) was also performed. Additionally, CPR duration and total epinephrine dose were evaluated in patients who died in the ED to evaluate the physicians' efforts to resuscitate depending on the sex of the patient.

Statistical analysis

Continuous variables were expressed as means and standard deviations or medians and interquartile ranges, depending on the data distribution; they were compared using Student's t- or Mann–Whitney U tests, as appropriate. Categorical variables were expressed as numbers and percentages and were compared using chi-square or Fisher's exact tests.

PSM was performed to balance the variables between the sexes. Age, witness status, place of arrest, bystander CPR, initial cardiac arrest rhythm, prehospital defibrillation, and prehospital advanced airway management were incorporated into the logistic regression model to calculate propensity scores for the variables of interest. The distributions and overlaps of the propensity scores were evaluated before matching (Supplementary Fig. 1). A 1:1 nearest-neighbor matching using a caliper width of 0.1, without replacement, was performed. The standardized difference was used to assess the balance of the variables before and after PSM. The variables were considered balanced if the standardized difference was < 0.1. In the matched cohorts, differences in variables were analyzed using statistical tests for paired data.

We conducted multivariable logistic regression analyses for both the matched and unmatched (full) cohorts to identify independent associations between sex and outcomes (in-hospital management and survival). Risk factors were directly selected based on previous literature and included the same variables used for PSM.

To investigate the non-linear relationship between age and in-hospital management, additional restricted cubic spline analysis of in-hospital management by sex according to age was performed. A restricted cubic spline curve with five knots was used after adjusting for the abovementioned variables by multivariable logistic regression. The predicted probabilities were calculated using separate multivariable logistic regressions for each subgroup as the regression equation, and degrees of associations between each variable and outcomes might vary by sex. We also performed a subgroup analysis of sex and outcomes according to age (65 years) in the matched cohort and sensitivity analysis according to the initial cardiac arrest rhythm. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Demographics of all eligible patients

A total of 12,321 patients with OHCA were registered in the KoCARC. Among these, 4,144 patients were excluded due to age < 18 years, unknown covariate data, and missing primary outcomes. Finally, the analysis included 8,177 patients (Fig. 1). The mean age of the total population was 68.1 ± 15.6 years (median age, 71.0 [57.0–80.0] years; 65.8% male, 34.2% female). Of the patients, 60.2% had witnessed arrest, 19.7% experienced cardiac arrest in public places, and 19.9% had a shockable rhythm. Bystander CPR was performed in 54.1% of the patients, defibrillation in 25.2%, and prehospital advanced airway management in 82.6%. CAG, PCI, TTM, and ECMO were performed in 13.3%, 4.9%, 10.2%, and 2.8% of the patients, respectively. Among the patients, 28.8% survived to admission, 13.4% survived to discharge, and 9.2% were discharged with good neurological outcomes (Table 1).

Before and after PSM

Before matching, the women were older than men. Witnessed arrest, arrest in public places, shockable rhythm, and prehospital defibrillation were less common in women than in men (Table 2). CAG, PCI, TTM, and ECMO were less frequently performed in women than in men (all $p < 0.001$). The time interval from ED arrival to CAG and the proportion of early CAG did not differ significantly between the sexes. The rates of survival to admission, survival to discharge, and good neurological outcome were lower in women than in men (all $p < 0.001$) (Table 2).

After PSM, 2,782 men and 2,782 women were matched. All variables were well-balanced (all standardized differences were < 0.1). CAG and PCI were less frequently performed in women than in men (6.4% vs. 9.1%, $p < 0.001$ and 1.9% vs. 3.7%, $p < 0.001$). The proportion of TTM and ECMO use did not differ significantly between the sexes (8.2% vs. 8.2%, $p = 0.961$ and 1.8% vs. 1.8%, $p = 1.000$). The total epinephrine dose was lower and the CPR duration shorter in women than in men (5 vs. 6 mg, $p = 0.002$ and 19 vs. 20 min, $p < 0.001$). The time interval from ED arrival to CAG and the proportion of early CAG did not differ significantly between the sexes. The rates of survival to admission, survival to discharge, and good neurological outcome did not differ significantly between the sexes (Table 2).

Multivariable logistic analysis of sex and outcomes in the matched and full cohorts

Compared to men, women were less likely to undergo CAG (adjusted odds ratio [aOR] 0.63, 95% confidence interval [CI] 0.50–0.79, $p < 0.001$) and PCI (aOR 0.49, 95% CI 0.35–0.70, $p < 0.001$) after adjusting for age, witness status, place of arrest, bystander CPR, initial cardiac arrest rhythm, prehospital defibrilla-

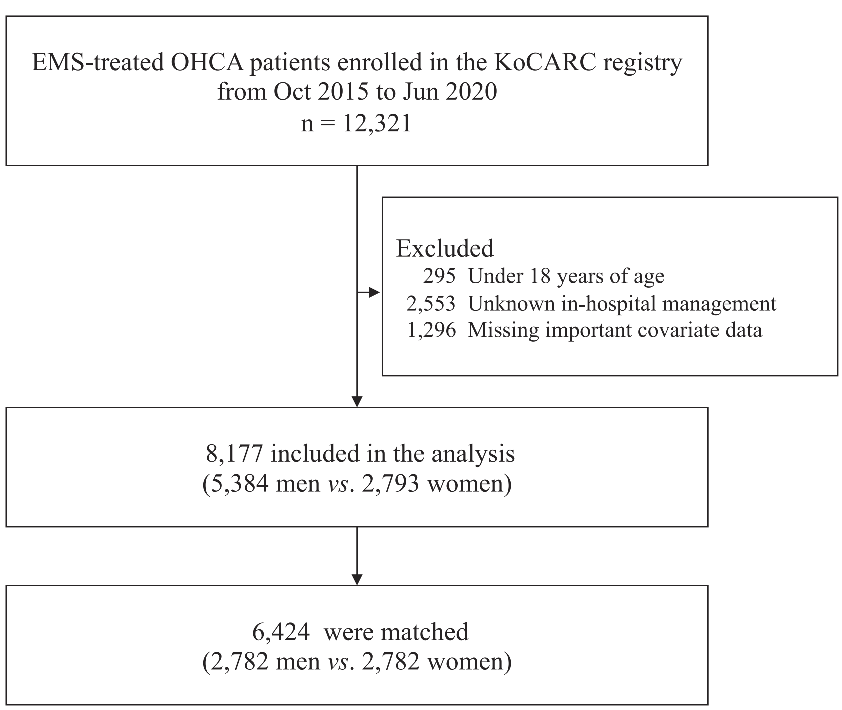

Fig. 1 – Flow diagram of the derivation of the study population. EMS, emergency medical services; OHCA, out-of-hospital cardiac arrest; KoCARC, Korean Cardiac Arrest Resuscitation Consortium.

Table 1 – Demographics and clinical characteristics of all eligible patients with out-of-hospital cardiac arrest.

Variables	Total (n = 8177)
Age, years, mean ± SD	68.1 ± 15.6
Median age, years, IQR	71 [57–80]
Sex	
Men, n (%)	5384 (65.8%)
Women, n (%)	2793 (34.2%)
Witnessed arrest, n (%)	4925 (60.2%)
Public location, n (%)	1613 (19.7%)
Bystander CPR, n (%)	4422 (54.1%)
Initial shockable rhythm, n (%)	1625 (19.9%)
Prehospital defibrillation, n (%)	2059 (25.2%)
Advanced airway insertion, n (%)	6752 (82.6%)
ROSC on arrival in the ED, n (%)	1135 (13.9%)
Survival to admission, n (%)	2358 (28.8%)
Survival to discharge, n (%)	1095 (13.4%)
Good neurological outcome, n (%)	753 (9.2%)
In-hospital management	
CAG, n (%)	1086 (13.3%)
PCI, n (%)	403 (4.9%)
TTM, n (%)	834 (10.2%)
ECMO, n (%)	230 (2.8%)
CPR time* (min) (median [IQR])	20 [10–30]
Epinephrine total dose** (mg) (median [IQR])	6 [3–9]

* n = 7184, ** n = 7528.

CPR, cardiopulmonary resuscitation; CAG, coronary angiography; PCI, percutaneous coronary intervention; TTM, targeted temperature management; ECMO, extracorporeal membrane oxygenation; ROSC, return of spontaneous circulation; IQR, interquartile range.

tion, and prehospital advanced airway management in the multivariable logistic regression model of the matched cohort (n = 5,564). Sex was not independently associated with TTM and ECMO use, survival to admission, survival to discharge, or good neurological outcomes (Fig. 2). In the full cohort (n = 8,177), the logistic regression analysis also showed similar results to those in the matched cohort (Supplementary Fig. 2).

Restricted cubic spline analysis of study outcomes by sex according to age in the matched and full cohorts

In the restricted cubic spline analysis of the matched cohort to show a non-linear relationship between age and in-hospital management, the gap in the predicted probability of undergoing CAG by sex was wider in the younger age group than that in the older age group (Fig. 3A). This gap between sexes decreased with increasing age. Fig. 3B-D shows the predicted probabilities of performing PCI, TTM, and ECMO by sex. The restricted cubic spline of the full cohort also showed a similar CAG trend to that of the matched cohort (Supplementary Fig. 3).

Subgroup analysis on sex and outcomes according to age in the matched cohort

The subgroup analysis according to age (65 years) showed that among patients aged < 65 years, women were less likely than men to undergo CAG and PCI (12.7% vs. 19.2%, $p < 0.001$ and 2.3% vs. 8.1%, $p < 0.001$) (Table 3). The total epinephrine dose was lower and CPR duration was shorter in women than in men (5 vs. 6 mg, $p < 0.001$ and 19 vs. 21 min, $p = 0.001$). Among patients aged $\geq$ 65 years, the outcomes did not differ significantly between the sexes.

Subgroup analysis of patients in the matched cohort who died in the ED

The CPR duration was shorter, and the total epinephrine dose was lower in women than in men (20 vs. 21 min, $p = 0.001$ and 6 vs. 7 mg, $p = 0.002$) (Supplementary Table 1).

Sensitivity analysis of the matched cohort

The proportions of patients undergoing CAG and PCI were statistically lower in women than in men among patients with and without shockable rhythm. However, the proportions of TTM and ECMO use did not differ significantly between the sexes in patients with and without shockable rhythm. Moreover, survival to admission, survival to discharge, and good neurological outcomes did not differ significantly between the sexes (Supplementary Tables 2 and 3).

Discussion

Our PSM analysis of patients from a prospective OHCA registry showed that women with OHCA were less likely to undergo CAG and PCI; however, we observed no sex-related differences in TTM and ECMO use. Although the proportion of women undergoing CAG and PCI was lower, these differences decreased with increasing age in the restricted cubic spline curve. Additionally, we did not observe differences in survival outcomes between sexes after adjusting for prehospital variables. Our findings provide insight into the sex disparities in OHCA and better inform resuscitation care to improve survival for both men and women.

Our study evaluated sex-related disparities in in-hospital management by investigating multiple procedures performed in patients

Table 2 – Patient characteristics, survival, and in-hospital management according to sex in pre- and post-propensity score matching.†

variables	Pre-matching				Post-matching			
	Men (n = 5384)	Women (n = 2793)	Standardized difference	p-value	Men (n = 2782)	Women (n = 2782)	Standardized difference	p-value§
Age	68 [56–78]	76 [63–83]	0.400		76 [63–82]	76 [63–83]	0.036	
Witnessed arrest, n (%)	3285 (61.0%)	1640 (58.7%)	0.047		1642 (59.0%)	1629 (58.6%)	0.009	
Public location, n (%)	1290 (24.0%)	323 (11.6%)	0.329		329 (11.8%)	323 (11.6%)	0.007	
Bystander CPR, n (%)	2904 (53.9%)	1518 (54.4%)	0.008		1489 (53.5%)	1510 (54.3%)	0.015	
Initial shockable rhythm, n (%)	1336 (24.8%)	289 (10.3%)	0.387		288 (10.4%)	289 (10.4%)	0.001	
Prehospital defibrillation, n (%)	1634 (30.3%)	425 (15.2%)	0.367		391 (14.1%)	425 (15.3%)	0.035	
Advanced airway insertion, n (%)	4461 (82.9%)	2291 (82.0%)	0.022		2302 (82.7%)	2283 (82.1%)	0.018	
ROSC on arrival in the ED	874 (16.2%)	261 (9.3%)		<0.001	253 (9.1%)	260 (9.3%)		0.781
Survival to admission	1709 (31.7%)	649 (23.2%)		<0.001	685 (24.6%)	647 (23.3%)		0.245
Survival to discharge	850 (15.8%)	245 (8.8%)		<0.001	270 (9.7%)	244 (8.8%)		0.247
Good neurological outcome	605 (11.2%)	148 (5.3%)		<0.001	158 (5.7%)	148 (5.3%)		0.597
In-hospital management								
CAG, n (%)	907 (16.8%)	179 (6.4%)		<0.001	252 (9.1%)	179 (6.4%)		<0.001
CAG time* (hr)	1.9 [1.2–4.6]	1.8 [1.2–4.0]		0.620	1.8 [1.2–3.6]	1.8 [1.2–4.0]		0.810
CAG within 24 hr*, n (%)	766 (86.4%)	151 (87.8%)		0.702	214 (87.7%)	151 (87.8%)		1.000
PCI, n (%)	349 (6.5%)	54 (1.9%)		<0.001	104 (3.7%)	54 (1.9%)		<0.001
TTM, n (%)	605 (11.2%)	229 (8.2%)		<0.001	227 (8.2%)	229 (8.2%)		0.961
ECMO, n (%)	180 (3.3%)	50 (1.8%)		<0.001	51 (1.8%)	50 (1.8%)		1.000
CPR time** (min)	20 [11–30]	19 [9–28]		<0.001	20 [10.0–29]	19 [9–28]		0.001
Epinephrine total dose*** (mg)	6 [3–9]	5 [3–8]		<0.001	6 [3–9]	5 [3–8]		0.002

Data are presented as median [interquartile range] or number (percentage), unless otherwise specified.

*n = 1059 in the pre-matching cohort, n = 416 in the post-matching cohort; **n = 7184 in the pre-matching cohort, n = 5102 in the post-matching cohort; *** n = 7528 in the pre-matching cohort, n = 5256 in the post-matching cohort.

†PSM was performed to balance variables such as age, witnessed status, place of arrest, bystander CPR, initial cardiac arrest rhythm, prehospital defibrillation, and prehospital advanced airway management. A 1:1 nearest-neighbor matching using a caliper width of 0.1, without replacement, was performed.

§The dataset after propensity score matching was analyzed using statistical tests for paired data.

CPR, cardiopulmonary resuscitation; CAG, coronary angiography; PCI, percutaneous coronary intervention; TTM, targeted temperature management; ECMO, extracorporeal membrane oxygenation; ROSC, return of spontaneous circulation; ED, emergency department.

with OHCA. To our knowledge, few studies have conducted this analysis. The other strength of this study lies in the nationwide, multicenter prospective registry and the adjustment for prehospital variables using PSM analysis. Similar results to the main findings were observed in the multivariable logistic regression analysis of the matched cohort.

Previous studies also reported sex-related disparities in performing CAG.[17,23,24,31] As expected, a larger proportion of patients in the younger group received CAG than in the older group. Our study revealed that the sex-related difference in CAG was observed in the group of patients under 65 years of age but not in the older group. Interestingly, the difference decreased with increasing patient age.

While previous studies[23,30,31,35] reported that women were less likely to undergo early CAG (performed within 24 h), we did not observe this tendency. These previous studies focused on patients who were expected to have better outcomes, such as those who survived to admission[30] or underwent TTM.[31,35] The broad inclusion criteria in our study were more similar to real-world clinical practice than previous studies. Most (approximately 87%) of both men and women received early CAG in our study. In real-world clinical practice, the sex-related difference in CAG might be more relevant in deciding whether CAG should be performed than in deciding when to perform CAG.

Our results showed that women were less likely to undergo PCI, consistent with previous reports.[17,22–24,31,33] Studies that evaluated CAG results revealed that culprit vessels were less frequently identified in women than in men.[24] Moreover, significant and severe coronary artery diseases were less frequently observed in women than in men.[22] Furthermore, women were less likely to have more severe one-, two-, and three-vessel diseases than men.[22] Among those who underwent CAG in the PSM cohort, 54 (30.2%) women and 104 (41.3%) men underwent PCI (p = 0.018). The sex-related difference in performing PCI might be more relevant due to the higher difference in culprit vessels than in performing CAG. Our subgroup analysis revealed a sex-related difference in PCI in patients aged < 65 years. The restricted cubic spline curve revealed a widening of sex-related differences between 40 and 60 years of age. The difference in culprit vessels might be more prominent in the 40 s to 60 s age group.

John et al.[25] and Bougouin et al.[30] reported no sex differences in performing PCI. However, the former did not adjust for other variables for performing PCI,[25] while the latter analyzed sex differences only in immediate PCI after early CAG.[30] Therefore, the generalizability of their findings is limited.

In older studies, TTM was less frequently performed in women.[17,23] However, more recent studies have reported that there is insufficient evidence to conclude the presence of sex disparities in TTM use.[14,22,25,30] Our results were consistent with those of these recent studies[14,22,25,30]. As TTM is commonly used nowadays, the

Outcomes	aOR	95% CI	P-value
CAG	0.63	0.50-0.79	<0.001
PCI	0.49	0.35-0.70	<0.001
TTM	1.01	0.83-1.24	0.888
ECMO	0.97	0.65-1.46	0.900
Survival to admission	0.93	0.81-1.06	0.265
Survival to discharge	0.88	0.72-1.08	0.208
Good neurologic outcome	0.93	0.70-1.22	0.591

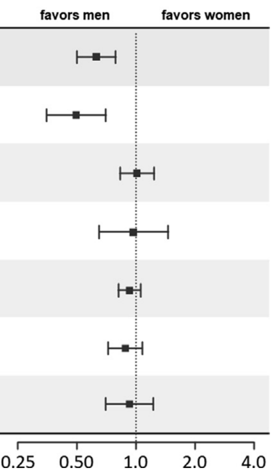

Fig. 2 – Multivariable logistic analysis of sex and outcomes in the matched cohort. Multivariable logistic regression modeling was performed after adjusting for age, witnessed status, place of arrest, bystander CPR, initial cardiac arrest rhythm, prehospital defibrillation, and prehospital advanced airway management. Odds ratio values > 1 indicate better outcomes in women. CPR, cardiopulmonary resuscitation; aOR, adjusted odds ratio; CI, confidence interval; CAG, coronary angiography; PCI, percutaneous coronary intervention; TTM, targeted temperature management; ECMO, extracorporeal membrane oxygenation.

existence of standardized indications for TTM might contribute to our results and those of other recent studies.[14,22,25,30]

ECMO can be applied during or after CPR to provide mechanical, pulmonary, and circulatory support.[36] ECMO is beneficial for selected patients.[36] Men have been identified as predominant candidates for ECMO during CPR; however, a recent large multicenter study reported that this trend is diminishing.[36] Meanwhile, similar to our findings, John et al.[25] also reported low proportions of patients of both sexes undergoing ECMO and showed no sex-related disparity. However, these previous studies did not adjust for prehospital

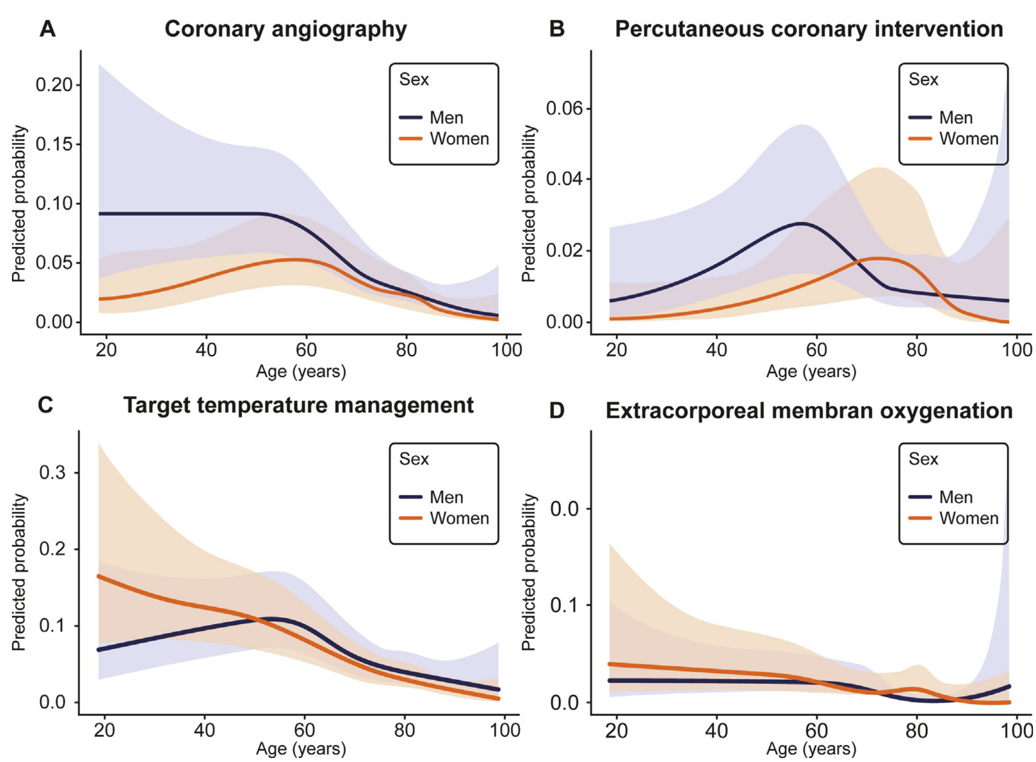

Fig. 3 – Association of men versus women regarding in-hospital management across the age spectrum. The restricted cubic spline curve shows the adjusted association between age and the probability of men (navy) vs. women (orange) receiving in-hospital management. The shaded area shows the 95% confidence interval of the predicted probability point estimate. The model was adjusted for age, witnessed status, place of arrest, bystander CPR, initial cardiac arrest rhythm, prehospital defibrillation, and prehospital advanced airway management.

Table 3 – Subgroup analysis of the matched cohort based on age.

	< 65 years			≥ 65 years		
Outcomes	Men (n = 769)	Women (n = 740)	p-value†	Men (n = 2,013)	Women (n = 2,042)	p-value†
In-hospital management						
CAG, n (%)	148 (19.2%)	94 (12.7%)	0.001	104 (5.2%)	85 (4.2%)	0.149
CAG time* (hr)	1.9 [1.2–5.0]	1.8 [1.2–10.6]	0.986	1.8 [1.0–2.7]	1.9 [1.2–2.9]	0.567
CAG within 24 hr*, n (%)	124 (84.9%)	76 (82.6%)	0.768	90 (91.8%)	75 (93.8%)	0.843
PCI, n (%)	62 (8.1%)	17 (2.3%)	<0.001	42 (2.1%)	37 (1.8%)	0.604
TTM, n (%)	113 (14.7%)	128 (17.3%)	0.190	114 (5.7%)	101 (4.9%)	0.343
ECMO, n (%)	34 (4.4%)	29 (3.9%)	0.720	17 (0.8%)	21 (1.0%)	0.657
CPR time** (min)	21 [11–30]	19 [7–30]	0.001	19 [10–28]	19.0 [10–27]	0.106
Epinephrine total dose*** (mg)	6 [3–10]	5 [2–9]	<0.001	6 [3–8]	6.0 [3–8]	0.264
Survival						
Survival to admission	309 (40.2%)	306 (41.4%)	0.682	376 (18.7%)	341 (16.7%)	0.107
Survival to discharge	143 (18.6%)	143 (19.3%)	0.768	127 (6.3%)	101 (4.9%)	0.069
Good neurological outcome	113 (14.7%)	100 (13.5%)	0.559	45 (2.2%)	48 (2.4%)	0.889

Data are presented as median [interquartile range] or number (percentage), unless otherwise specified.

†The dataset after propensity score matching was analyzed using statistical tests for paired data.

*n = 238 in < 65, n = 1364 in ≥ 65; **n = 1278 in < 65, n = 3824 in ≥ 65; *** n = 1365 in < 65, n = 3890 in ≥ 65.

CPR, cardiopulmonary resuscitation; CAG, coronary angiography; PCI, percutaneous coronary intervention; TTM, targeted temperature management; ECMO, extracorporeal membrane oxygenation; ROSC, return of spontaneous circulation.

variables in ECMO use.[25,36] In our study, the adjustment for prehospital variables might have contributed to the lack of significant sex difference in ECMO use.

Women received a shorter duration of CPR and lower epinephrine doses than men in the PSM cohort. Although almost 75% of the patients in our cohort died and failed to survive to admission, those who achieved early ROSC might have contributed to the shorter CPR duration. Therefore, we evaluated the subgroup of patients who failed to survive to admission. The sex-related differences were maintained in this subgroup. Stankovic et al. reported a shorter duration of resuscitation in women than in men among patients with in-hospital cardiac arrest without ROSC.[37] Moreover, in previous studies, more women than men had established a do-not-resuscitate order.[38,39] The differences in resuscitation efforts by physicians depending on patient sex might contribute to shorter CPR duration.

Despite considerable debate, the reasons for these sex-related differences in OHCA remain largely unknown. Potential explanations include epidemiological differences, differences in eligibility for treatment, unmeasured illness severity, unmeasured physician implicit bias, and confounding by other clinical factors. Overall, our study results showed that women with OHCA underwent CAG and PCI less frequently than men and that the differences decreased with increasing age. However, we observed no sex-related differences in survival outcomes. Our findings provide insight into the sex disparities in patients with OHCA. Further studies on physician judgment in performing in-hospital management according to sex are warranted.

Our study should be interpreted in the context of the following limitations: First, owing to the observational nature of the study, unmeasured confounders may exist. PSM and multivariable logistic regression analyses were used to balance the baseline characteristics between the sexes. However, comorbidities and lifestyle factors (e.g., alcohol consumption and smoking) were not analyzed. Smoking, diabetes, dyslipidemia, and obesity are major risk factors for coronary artery disease.[40] Therefore, studies are needed to evaluate sex-related differences in the in-hospital management of patients with OHCA after adjusting for risk factors for coronary artery disease. Second, more than 30% of cases were excluded for missing data. Missing data can reduce the statistical power of a study and cause bias in the estimation, leading to invalid conclusions. For this reason, we performed sensitivity analysis using worst case scenario of adult OHCA patients enrolled in the registry. The sensitivity analysis showed similar results to our main results (Supplementary Table 4). Third, PSM has been challenged. The target population for generalization could be restricted, as the statistical analysis after PSM only included a portion of the original study population. As a result, the statistical power may decrease. Matching based on propensity score can also yield imbalanced unit pairs that aggravate the bias. However, logistic regression analysis using an unmatched cohort showed similar results to the main findings in our study (Supplementary Fig. 2). Fourth, as survival outcomes can be affected by in-hospital management, the results should be interpreted with caution. Further studies are needed to evaluate sex-related differences in survival outcomes after adjusting for in-hospital management. Fifth, information on whether the patients had a do-not-resuscitate order after hospital admission was not collected. These orders may affect in-hospital management and survival outcomes. Despite these limitations, our findings provide insight into the sex disparities in OHCA.

Conclusions

In the PSM cohort, women with OHCA underwent CAG and PCI less frequently than men, regardless of the initial rhythm. However, the sex-related differences narrowed with increasing age. Moreover, no significant sex-related differences were observed in TTM use, ECMO use, and survival outcomes.

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Appendix A. Supplementary data

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