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ORIGINAL RESEARCH

Comparison of the survival and neurological outcomes in OHCA based on smoking status: investigation of the existence of the smoker's paradox

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Abstract

The smoker's paradox has been reported to reduce mortality following out-of-hospital cardiac arrest (OHCA). However, recent studies on this paradox have reported contradictory findings, with some indicating that it does not exist. Therefore, the purpose of this study was to evaluate the association between smoking status and OHCA outcomes. This retrospective observational study was conducted using multicenter registry data. The associations between smoking status and OHCA outcomes were assessed using multivariable logistic regression analyses and propensity score-adjusted methods. We compared outcomes among current, former, and never-smokers, as well as between current and non-smokers and between ever- and never-smokers. The primary outcome was survival to hospital discharge, and the secondary outcome was favourable neurological outcomes. Among 4443 patients with OHCA, 19.9% were current smokers, 15.2% were former smokers, and 64.9% were never-smokers. Current smokers had significantly better outcomes than former or never-smokers. However, the significant differences observed in univariable analysis or before propensity score matching were not observed after adjustments with multivariable logistic regression or after propensity score matching analysis in both current vs. non-smokers and ever- vs. never-smokers. Other propensity score adjusted models also did not show significant differences, except for the stratification method. This study suggests that smoking is not an independent prognostic factor for OHCA. The statistically significant better outcomes observed in current or ever-smokers were not maintained after adjusting for confounders. Therefore, the smoker's paradox should be investigated in additional prospective studies.

Keywords

Smokers; Ex-smokers; Non-smokers; Cardiac arrest; Propensity score

1. Introduction

Smoking is a known risk factor for cardiovascular disease. However, smokers have a rather low myocardial infarction- and stroke-related mortality rate, and this phenomenon, the so-called smoker's paradox, has also been reported in the case of cardiac arrest. Pollack *et al.* [1] reported that smokers had good neurological outcomes after out-of-hospital cardiac arrest (OHCA). This effect was significant even after adjusting for confounders. Lahmann *et al.* [2] also reported that former smoking was associated with improved survival in patients with OHCA. Further, Gupta *et al.* [3] reported that smokers had a higher rate of survival to discharge and more favorable neurological outcomes following in-hospital cardiac arrest. The mechanism by which smoking improves outcomes after cardiac arrest is not clear but can potentially be explained by the phenomenon of ischemic preconditioning [4].

Recent studies have reported contradictory results regarding the smoker's paradox in several disease entities. According to a systematic review of the smoker's paradox in acute coronary syndrome, the findings of only six studies were consistent with the paradox among the 17 included studies [5]. This paradox has not been demonstrated in more recent studies involving routine early invasive therapeutic strategies. Another systematic review of 18 studies on patients with ischemic stroke indicated that smoking is not a protective factor and that the smoker's paradox is not an actual phenomenon [6]. A recent study of all the incident OHCAs in San Francisco over a 4-year period found no difference in tobacco use rates between survivors and non-survivors [7]. Therefore, the smoker's paradox should also be evaluated in patients with cardiac arrest through additional research.

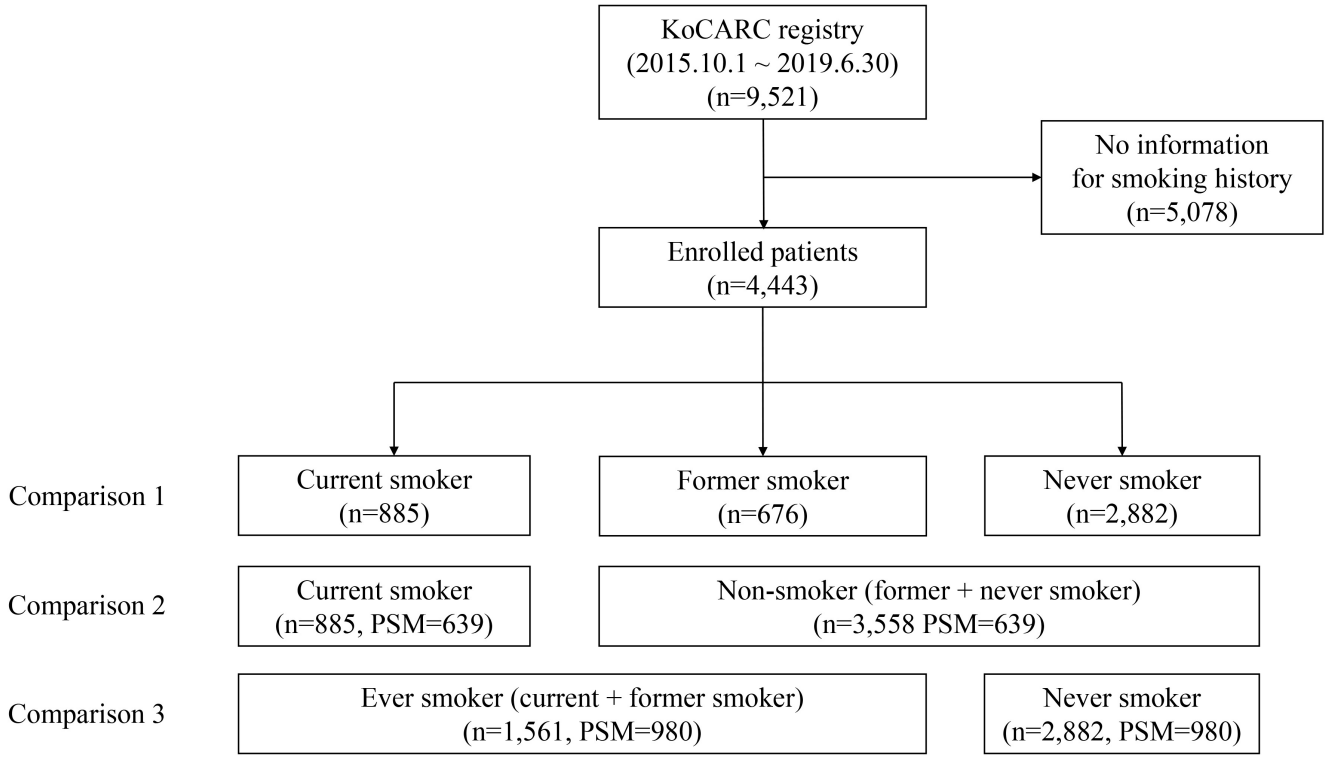

FIGURE 1. Patient flow chart. KoCARC, Korean Cardiac Arrest Research Consortium; PSM, propensity score matching.

The purpose of this study was to evaluate the association between an individual's smoking status and OHCA-related survival and neurological outcomes by analyzing data from a retrospective multicenter registry.

2. Materials and methods

2.1 Study design

A retrospective observational analysis was performed using data from the Korean Cardiac Arrest Research Consortium (KoCARC) registry from October 2015 to June 2019. The KoCARC is a nationwide research registry for OHCA and is based on Utstein templates and a hospital-based collaborative research network [8, 9]. This study was conducted according to the guidelines of the Committee on Publication Ethics (COPE) and the International Committee of Medical Journal Editors (ICMJE) Recommendations.

2.2 Patient population

The KoCARC registry includes patients with OHCA who were transported to the participating emergency departments via emergency medical services (EMS) with resuscitation efforts and who had a presumed medical etiology identified by emergency physicians. The registry excludes patients with a terminal illness documented in medical records, patients under hospice care, pregnant patients, and patients with a previously documented 'Do Not Resuscitate' order. Patients with cardiac arrest due to a definite non-medical etiology, including trauma, drowning, poisoning, burns, asphyxia, or hanging, were also excluded. Additionally, we excluded patients with no information regarding their smoking status.

The patients were classified into three groups according to their smoking status: the current, former, and never-smoker groups. Current smokers (CS) were defined as those who smoked cigarettes, water pipes, or cigars or who used chewing tobacco within 1 month of index admission. Former smokers (FS) were defined as those who quit smoking for at least 1 month. Never smokers (NS) were defined as those who had never smoked during their lifetime.

2.3 Data collection

Information regarding the KoCARC database, data elements, and quality assurance has previously been published [8]. The data were collected via a standardized form and were uploaded into a web-based electronic database registry by research coordinators in the participating institutions. The quality of this registry is controlled by a quality management committee.

The authors extracted data regarding the following variables from the registry: clinical characteristics (age; sex; history of hypertension, diabetes mellitus, and dyslipidemia; and smoking status), cardiopulmonary resuscitation (CPR) (first monitored electrocardiography [ECG] rhythm, witnessed arrest, bystander CPR, bystander use of automated external defibrillator [AED], and prehospital defibrillation or epinephrine use by the EMS), and treatment after return of spontaneous circulation (ROSC) (coronary angiography findings and targeted temperature management [TTM]).

2.4 Outcome variables

The primary outcome was survival to hospital discharge. The secondary outcome was favorable neurological outcomes defined as a cerebral performance category (CPC) of 1 or 2 at

TABLE 1. Baseline characteristics among current smoker, former smoker, and never smoker.

Characteristics	Overall	Current smoker	Former smoker	Never smoker	*p*-value	Post hoc analysis		
	(n = 4443)	(n = 885)	(n = 676)	(n = 2882)		CS vs. FS	CS vs. NS	FS vs. NS
Age, years	64.0 ± 20.4	58.0 ± 13.6	70.6 ± 12.6	64.3 ± 22.9	<0.001***	<0.001***	<0.001***	<0.001***
Male sex	2867 (64.5)	815 (92.1)	626 (92.6)	1426 (49.5)	<0.001***	0.706	<0.001***	<0.001***
Hypertension	1974 (45.3)	348 (40.9)	361 (54.1)	1265 (44.6)	<0.001***	<0.001***	0.056	<0.001***
Diabetes	1207 (27.8)	209 (24.7)	227 (34.1)	771 (27.3)	<0.001***	<0.001***	0.131	<0.001***
Dyslipidemia	258 (6.1)	58 (7.0)	55 (8.6)	145 (5.2)	0.002**	0.257	0.048	0.001***
Witnessed arrest	2830 (64.3)	586 (66.7)	451 (67.2)	1793 (62.9)	0.025*	0.845	0.036	0.035
Bystander CPR	2266 (51.0)	457 (51.6)	343 (50.7)	1461 (50.7)	0.701			
Shockable rhythm	953 (21.4)	315 (35.6)	153 (22.6)	485 (16.8)	<0.001***	<0.001***	<0.001***	0.018
Bystander AED use	75 (1.7)	12 (1.4)	19 (2.9)	44 (1.6)	0.048*	0.046	0.752	0.022
Prehospital defibrillation	1202 (27.6)	377 (43.4)	185 (27.7)	640 (22.7)	<0.001***	<0.001***	<0.001***	0.006**
Prehospital epinephrine	533 (12.0)	111 (12.6)	96 (14.2)	326 (11.4)	0.100			
Prehospital ROSC	801 (18.4)	266 (30.6)	114 (17.1)	421 (14.9)	<0.001***	<0.001***	<0.001***	0.166
Coronary angiography	780 (17.6)	279 (31.5)	129 (19.1)	372 (12.9)	<0.001***	<0.001***	<0.001***	<0.001***
TTM	592 (15.4)	175 (22.6)	85 (14.4)	332 (13.4)	<0.001***	<0.001***	<0.001***	0.530
Survival to discharge	841 (18.9)	269 (30.4)	126 (18.6)	446 (15.5)	<0.001***	<0.001***	<0.001***	0.043
CPC 1 or 2	601 (13.5)	212 (23.9)	87 (12.9)	302 (10.5)	<0.001***	<0.001***	<0.001***	0.073

*CS, current smoker; NS, never smoker; FS, former smoker; CPR, cardiopulmonary resuscitation; AED, automated external defibrillator; ROSC, return of spontaneous circulation; TTM, targeted temperature management; CPC, cerebral performance category. * <0.05, ** <0.01, *** <0.001.*

the time of hospital discharge. Patients had a CPC of 1 if they had good cerebral performance and were conscious, alert, and able to work with a possible mild neurological or psychological deficit. Patients had a CPC of 2 if they had a moderate cerebral disability, were conscious, had sufficient cerebral function in order to perform independent activities of daily life, and were able to work in sheltered environments. This performance scale indicates mortality by a CPC of 5, defined as death or brain death [10].

2.5 Statistical analysis

Three comparisons were performed (Fig. 1). First, the study variables and outcomes were compared among the CS, FS, and NS groups (comparison 1). Second, we compared the CS and non-smoker groups (comparison 2). A non-smoker was defined as a combination of an FS and NS. Third, we compared ever-smokers and NS (comparison 3). An ever-smoker was defined as a combination of a CS and an FS. Descriptive statistics are presented as mean and standard deviation (SD) for continuous variables and as frequency (percentage) for categorical variables. An independent sample *t*-test or analysis of variance (ANOVA) was performed for continuous variables, and a chi-square test or Fisher's exact test, for categorical variables. Bonferroni correction was used for post-hoc comparison, and it was judged to have statistical significance when the *p*-value was 0.0167 or less.

To adjust for baseline differences between the CS and non-smoker groups and between the ever-smoker and NS groups, propensity scores (PS) were estimated using a logistic regression model as a function of all the potential confounders listed in Table 1. The PS of an individual was defined as the probability of being in the exposure group, given all relevant covariates. Based on the PS, the patients in the smoking status-related groups were matched using the greedy matching algorithm at a 1:1 ratio to create a PS-matched population. The balance in baseline characteristics among the PS-matched cohorts was assessed using a paired *t*-test or McNemar's test. Three additional PS-based methods were performed: (i) stratification to divide the sample into five strata based on rank-ordered PS, followed by comparisons between groups within each stratum; (ii) stabilized inverse probability treatment weighting (IPTW) to weight cases by the inverse of the PS; and (iii) regression adjustment to include PS as an additional covariate in a regression model [11, 12].

The association between outcomes and smoking status was assessed using a logistic regression analysis. We first performed univariable logistic regressions on outcome predictors of OHCA, such as age; sex; history of hypertension, diabetes mellitus, or dyslipidemia; initial ECG rhythm; witnessed arrest; bystander CPR; bystander AED use; coronary angiography findings; and TTM. We then built a stepwise multivariable regression model starting with the predictor that had the strongest association with the outcome based on the results of the univariable logistic regression. Collinearity between the

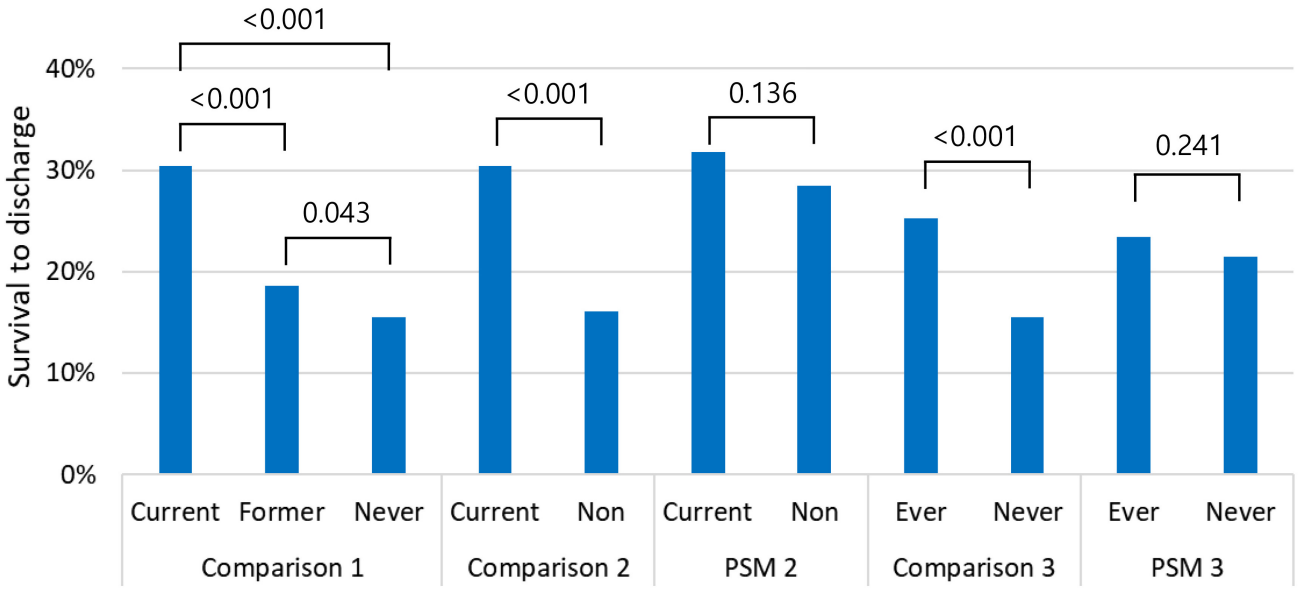

FIGURE 2. Rate of survival to hospital discharge among patients with different smoking status according to the comparisons. PSM, propensity score matching.

TABLE 2. Characteristics of overall population and propensity score matched cohort stratified by current smoker vs. non-smoker.

	Overall population (n = 4443)			PS-matched cohort (n = 1278)		
Characteristics	Current smoker	Non-smoker	*p*-value	Current smoker	Non-smoker	*p*-value
	(n = 885)	(n = 3558)		(n = 639)	(n = 639)	
Age, years	58.0 ± 13.6	65.5 ± 21.5	<0.001***	58.4 ± 13.4	57.8 ± 20.7	0.440
Male sex	815 (92.1)	2052 (57.7)	<0.001***	578 (90.5)	580 (90.8)	0.527
Hypertension	348 (40.9)	1626 (46.4)	0.003**	253 (39.6)	251 (39.3)	0.895
Diabetes	209 (24.7)	998 (28.6)	0.022*	154 (24.1)	146 (22.9)	0.563
Dyslipidemia	58 (7.0)	200 (5.9)	0.207	44 (6.9)	36 (5.6)	0.358
Witnessed arrest	586 (66.7)	2244 (63.7)	0.091	440 (68.9)	465 (72.8)	0.080
Bystander CPR	462 (54.6)	1804 (8.9)	0.366	345 (53.9)	338 (52.9)	0.768
Shockable rhythm	315 (38.0)	638 (19.1)	<0.001***	241 (37.7)	240 (37.5)	0.312
Bystander AED use	12 (1.4)	63 (1.81)	0.421	7 (1.1)	3 (0.5)	0.205
Prehospital defibrillation	377 (43.4)	825 (23.7)	<0.001***	278 (44.3)	263 (41.9)	0.315
Prehospital epinephrine	111 (12.6)	422 (11.9)	0.558	80 (12.6)	74 (11.6)	0.606
Prehospital ROSC	266 (30.6)	535 (15.4)	<0.001***	194 (30.9)	163 (26.0)	0.020*
Coronary angiography	279 (35.8)	501 (16.1)	<0.001***	219 (34.3)	180 (28.2)	0.027*
TTM	175 (22.6)	417 (13.6)	<0.001***	137 (21.4)	123 (19.3)	0.274
Survival to discharge	269 (30.4)	572 (16.1)	<0.001***	203 (31.8)	182 (28.5)	0.136
CPC 1 or 2	212 (23.9)	389 (10.9)	<0.001***	162 (25.4)	145 (22.7)	0.172

*PS, propensity score; CPR, cardiopulmonary resuscitation; AED, automated external defibrillator; ROSC, return of spontaneous circulation; TTM, targeted temperature management; CPC, cerebral performance category. * <0.05, ** <0.01, ***<0.001.*

predictors was assessed by calculating the variance inflation factor (VIF) for each predictor and excluding variables with a VIF greater than 5. No predictor met this criterion, and therefore none were removed from the analysis based on collinearity. Adjusted odds ratios (AOR) and 95% confidence intervals (CI), obtained from the multivariable logistic regression after controlling for potential confounders, were used to interpret associations between variables and outcomes.

Data analyses and visualization were performed using Excel (Microsoft, Redmond, WA, USA) and the SAS program (version 9.4, SAS Institute Inc., Cary, NC, USA). A *p*-value of <0.05 was considered statistically significant.

TABLE 3. Characteristics of overall population and propensity score matched cohort stratified by ever smoker vs. never smoker.

	Overall population (n = 4443)			PS-matched cohort (n = 1960)		
Characteristics	Ever smoker (n = 1561)	Never smoker (n = 2882)	*p*-value	Ever smoker (n = 980)	Never smoker (n = 980)	*p*-value
Age, years	63.5 ± 14.6	64.3 ± 22.9	0.123	64.4 ± 14.8	65.3 ± 17.8	0.152
Male sex	1441 (92.3)	1426 (49.5)	<0.001***	885 (90.3)	885 (90.3)	0.999
Hypertension	709 (46.7)	1265 (44.6)	0.181	448 (45.7)	455 (46.4)	0.707
Diabetes	436 (28.8)	771 (27.3)	0.285	273 (27.9)	276 (28.2)	0.866
Dyslipidemia	113 (7.7)	145 (5.2)	0.001**	63 (6.4)	52 (5.3)	0.248
Witnessed arrest	1037 (66.9)	1793 (62.9)	0.007**	669 (68.3)	667 (68.1)	0.909
Bystander CPR	805 (53.3)	1461 (52.0)	0.702	494 (50.4)	501 (51.1)	0.282
Shockable rhythm	468 (31.8)	485 (17.9)	<0.001***	272 (27.7)	280 (28.5)	0.267
Bystander AED use	31 (2.05)	44 (1.6)	0.239	13 (1.3)	15 (1.5)	0.683
Prehospital defibrillation	562 (36.6)	640 (22.7)	<0.001***	322 (33.5)	322 (33.5)	0.999
Prehospital epinephrine	207 (13.3)	326 (11.4)	0.055	131 (13.4)	123 (12.6)	0.594
Prehospital ROSC	380 (24.7)	421 (14.9)	<0.001***	214 (22.3)	189 (19.7)	0.073
Coronary angiography	408 (29.7)	372 (14.8)	<0.001***	244 (24.9)	215 (21.9)	0.196
TTM	260 (19.0)	332 (13.4)	<0.001***	162 (16.5)	161 (16.4)	0.945
Survival to discharge	395 (25.3)	446 (15.5)	<0.001***	229 (23.4)	211 (21.5)	0.241
CPC 1 or 2	299 (19.2)	302 (10.5)	<0.001***	168 (17.1)	154 (15.7)	0.294

*PS, propensity score; CPR, cardiopulmonary resuscitation; AED, automated external defibrillator; ROSC, return of spontaneous circulation; TTM, targeted temperature management; CPC, cerebral performance category. * <0.05, ** <0.01, ***<0.001.*

3. Results

Of the 9521 OHCA patients listed in the KoCARC registry from October 2015 to June 2019, we enrolled 4443 patients in the final analysis after excluding patients whose smoking history could not be obtained. The overall survival rate to discharge was 18.9%, and the proportion of patients with good neurological outcomes was 13.5%. Among these patients, 885 (19.9%) were CS, 676 (15.2%) were FS, and 2882 (64.9%) were NS (Fig. 1).

The baseline characteristics of the overall population and the three groups according to the smoking status are presented in Table 1. CS had a significantly better survival to discharge rate (30.4% vs. 18.6% vs. 15.5%, $p < 0.001$) and more favorable neurological outcomes (23.9% vs. 12.9% vs. 10.5%, $p < 0.001$) than FS or NS. However, the baseline characteristics, apart from bystander CPR and prehospital epinephrine use, were also significantly different among the groups. After the PS matching procedure, 639 matched pairs were selected between the CS and non-smokers, and 980 matched pairs were selected between the ever-smokers and NS. The differences in baseline characteristics were well balanced between the PS-matched cohorts, but significant differences in resuscitation outcomes were not observed after PS-matching between CS and non-smokers (survival to discharge: 31.8% vs. 28.5%, $p = 0.136$; favorable neurological outcomes: 25.4% vs. 22.7%, $p = 0.172$, Table 2) and between ever-smokers and NS (survival to discharge: 23.4% vs. 21.5%, $p = 0.241$; favorable neurological outcomes: 17.1% vs. 15.7%, $p = 0.294$, Table 3). The survival to discharge rate among the groups with various smoking statuses is presented in Fig. 2.

In the unadjusted logistic regression model, CS had significantly higher chances of survival to discharge (OR, 2.28; 95% CI, 1.925–2.699; $p < 0.001$) and better neurological outcomes (OR, 2.566; 95% CI, 2.129–3.094; $p < 0.001$) than non-smokers. Ever-smokers also had significantly higher chances of survival to discharge (OR, 1.85; 95% CI, 1.589–2.155; $p < 0.001$) and better neurological outcomes (OR, 2.024; 95% CI, 1.702–2.408; $p < 0.001$) than NS. However, significant improvements in outcomes were not observed in the multivariable adjusted models in both CS vs. non-smokers and ever-smokers vs. NS (Table 4).

A sensitivity analysis was performed using different statistical methods with PS. There were no significant differences in outcomes between ever-smokers and NS on constructing PS-adjusted models by stratification, regression adjustment, and IPTW. When comparing CS and NS, regression adjustment with PS and IPTW did not reveal statistically significant findings; however, the neurological outcomes of CS were more favorable than those of non-smokers when using the stratification method (Table 4).

4. Discussion

The results of this study suggest that the smoker's paradox may be a pseudo-paradox in OHCA patients. Although current smoking and ever-smoking were associated with improved survival and favorable neurological outcomes following OHCA,

TABLE 4. Adjusted odds ratios of survival to discharge and good neurological outcome with different statistical methods according to smoking status.

Statistical methods	N	Current smoker vs. non-smoker (ref)				N	Ever smoker vs. never smoker (ref)			
		Survival to discharge		Good neurological outcome			Survival to discharge		Good neurological outcome	
	Current/Non	OR	*p*-value	OR	*p*-value	Ever/Never	OR	*p*-value	OR	*p*-value
		(95% CI)		(95% CI)			(95% CI)		(95% CI)	
Logistic regression model										
Unadjusted model	885/3558	2.28	<0.001***	2.566	<0.001***	1561/2882	1.85	<0.001***	2.024	<0.001***
		(1.925–2.699)		(2.129–3.094)			(1.589–2.155)		(1.702–2.408)	
Multivariable-adjusted model	657/2693	1.018	0.900	1.236	0.197	1179/2171	1.12	0.396	1.221	0.212
		(0.768–1.350)		(0.895–1.708)			(0.862–1.456)		(0.892–1.670)	
Propensity score adjusted model										
Matching 1:1 (paired)	639/639	1.236	0.137	1.246	0.173	980/980	1.165	0.241	1.171	0.294
		(0.935–1.634)		(0.908–1.711)			(0.902–1.505)		(0.872–1.572)	
Matching 1:1 (independent)	639/639	1.169	0.200	1.157	0.265	980/980	1.111	0.329	1.11	0.393
		(0.920–1.485)		(0.895–1.496)			(0.899–1.374)		(0.874–1.410)	
Weighting (IPTW)	657/2693	1.048	0.613	1.169	0.129	1179/2171	1.066	0.423	1.17	0.082
		(0.875–1.255)		(0.955–1.431)			(0.911–1.247)		(0.980–1.397)	
Regression adjustment by PS	657/2693	1.075	0.520	1.193	0.156	1179/2171	1.072	0.469	1.097	0.393
		(0.863–1.338)		(0.934–1.523)			(0.888–1.293)		(0.887–1.356)	
Stratification (quintile)	657/2693	1.194	0.127	1.348	0.019*	1179/2171	1.161	0.178	1.205	0.135
		(0.951–1.498)		(1.050–1.731)			(0.934–1.444)		(0.943–1.539)	

OR, odds ratio; CI, confidence interval; IPTW, inverse probability treatment weighting; PS, propensity score.

the protective effects of smoking often disappeared after various statistical adjustments, including multivariable logistic regression or PS-based adjustments.

A previous study that investigated the smoker's paradox in OHCA revealed better outcomes in smokers than in non-smokers, even after adjusting for confounders [11]. However, the sample size of the study was relatively small, comprising of 95 smokers and 86 non-smokers. A study of patients with in-hospital cardiac arrest, which analyzed a large nationwide dataset, showed that smokers had a higher rate of survival to hospital discharge and more favorable neurological outcomes than non-smokers [3]. There is a possibility of systematic error owing to the finding that smokers who experience an acute cardiac event could have a greater case fatality before hospital admission than non-smokers [13, 14]. Those admitted alive to the hospital would already represent the survivors.

These two studies, which investigated the smoker's paradox in cardiac arrest, only compared ever-smokers with NS, but we added a comparison between CS and current non-smokers, including FS. If smoking exerts a protective effect in OHCA patients through the mechanism of ischemic preconditioning, a dose-response relationship may be possible among CS, FS, and NS. However, the FS group had the oldest patients and the largest proportion of patients with histories of hypertension or diabetes. CS had a higher survival rate and more favorable neurological outcomes than non-smokers, and both these outcomes were the same between ever-smokers and NS. However, these differences were not statistically significant after PS matching.

This was also the case in the logistic regression analysis. As a result of multivariable logistic regression, the statistical differences observed in the unadjusted model for survival or neurological outcomes in both CS and ever-smokers compared with in non-smokers or NS were no longer observed. We performed additional PS-adjusted analyses, such as independent 1:1 PS matching, IPTW, and regression adjustment, all of which showed the same results. However, in the case of the stratification method, it was found that the neurological outcomes were significantly better in CS than in non-smokers (OR, 1.348; 95% CI, 1.050–1.731; $p = 0.019$). This implies that the results may vary depending on the statistical adjustment method used.

The smoker's paradox was first described in 1968 by Weinblatt *et al.* [15] who stated that smokers had lower mortality after myocardial infarction compared to non-smokers. Some studies have supported the existence of this phenomenon, whereas others have refuted its existence. This phenomenon, which has more unfavorable outcomes after cardiac arrest in non-smokers than in smokers, explains that frequent hypoxic injury due to smoking can diminish the effect of reperfusion injury during post-cardiac arrest period. The concept of "ischemic preconditioning of smoking" is that mortality rate of myocardial infarction is lower in smokers, although smoking increases the prevalence of acute coronary syndromes [16, 17]. The apparent smoker's paradox has usually been disproved in many studies on acute coronary syndrome after the adjustment for measured risk factors [5]. For example, among myocardial infarction patients undergoing percutaneous coronary interventions, FS and CS had a decreased unadjusted hazard ratio for both 30-day and 1-year mortality when compared with NS. However, this protective effect of smoking was not observed after adjusting for potential confounding factors [18]. Similar controversial findings exist in the case of patients with ischemic stroke. Smokers may exhibit better recovery and thrombolytic responses than non-smokers.

The smoker's paradox has also been reported in patients with conditions other than myocardial infarction, such as stroke [19], trauma [20] and heart failure [21]. However, this paradox has also been denied in recent studies on such patients. A systematic review of ischemic stroke reported that smoking was not a protective factor and that the smoker's paradox was not an actual phenomenon [6]. Among adolescent trauma patients, smokers had an increased rate of pneumonia, a longer length of hospital stay, and no difference in overall mortality compared to non-smokers [22]. There was no survival advantage of smoking in patients hospitalized with heart failure, and the smoker's paradox is likely to be a result of residual confounding [23].

In this study, statistical adjustment was attempted using various methods, and the smoker's paradox was not observed with most of these methods except for with the stratification method using PS. The neurological outcomes were more favorable in CS than in non-smokers when statistical significance was maintained even after the adjustment by stratification with PS. We divided the data into five strata, and the neurological outcomes in CS were better in the first and last quintiles. Therefore, the results indicating whether the smoker's paradox occurred are likely to differ depending on the statistical adjustment method, and it is necessary to conduct a thorough adjustment for various confounders.

This study has several limitations. First, as a retrospective study using a registry, there are inherent limitations, including reporting bias, coding errors, and missing data. More than half of the patients were excluded due to the lack of information regarding their smoking history. Second, smoking status was usually reported by family members who may have incorrectly recorded individuals as non-smokers. Ideally, an objective test, such as urinary nicotine or cotinine tests, could have been used; however, this is impractical in the OHCA setting. Third, the duration and amount of smoking was not reported and dose-dependent effects of smoking were not considered. Even among smokers, the prognosis according to smoking period might be different. Lastly, we recommend applying caution in extrapolating these findings to Caucasian and/or other populations because this study was based on the Korean population.

5. Conclusions

This study suggests that smoking is not an independent prognostic factor in OHCA. The statistically significant better outcomes observed in CS or ever-smokers were not maintained after adjusting for confounders. Therefore, the smoker's paradox should be investigated through additional prospective studies on OHCA and should not be interpreted as a benefit of or justification for smoking.

ABBREVIATIONS

OHCA, out-of-hospital cardiac arrest; CS, current smoker; FS, former smoker; NS, never-smoker; KoCARC, Korean Cardiac Arrest Research Consortium; CPR, cardiopulmonary resuscitation; ECG, electrocardiography; AED, automated external defibrillator; ROSC, return of spontaneous circulation; TTM, targeted temperature management; CPC, cerebral performance category; IPTW, inverse probability treatment weighting; PS, propensity score; OR, odds ratio; CI, confidence interval.

AUTHOR CONTRIBUTIONS

Conceptualization—SPC, GY. Data curation—HSL, GY. Formal analysis—SPC, HSL. Investigation—SPC, GY. Methodology—TK, JSY. Software—HSL, GY. Validation—YSP. Visualization—SPC. Writing — original draft—SPC, GY. Writing — review & editing—SPC, TK, HSL, YSP, JSY.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was reviewed and approved by the institutional review boards (IRB) of the 62 participating hospitals in the KoCARC OHCA registry. The need for informed consent was waived by the IRB. This research project was registered at ClinicalTrials.gov (identifier: NCT03222999). Patient consent was waived due to observational nature of the study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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