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Non-Linear Relationship Between Alcohol Consumption and Neurological Outcomes in Patients With Out-of-Hospital Cardiac Arrest Presenting to the Emergency Department

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ABSTRACT

Background: Out-of-hospital cardiac arrest (OHCA) is a major public health issue associated with low survival rates and poor neurological outcomes. Comorbidities and various triggers are associated with OHCA incidence and outcomes. However, the association between alcohol consumption and the neurological prognosis in patients with OHCA remains unknown. Therefore, this study aimed to examine the potential association between the frequency of alcohol consumption and neurological outcomes in patients with OHCA.
Methods: This retrospective observational study used data from the Korean Cardiac Arrest Research Consortium registry, encompassing 62 hospitals in Korea. Patients aged > 18 years who experienced OHCA and were transported by the public emergency medical service system were included. Alcohol consumption was categorized into four groups: never drinkers, light drinkers, moderate drinkers, and heavy drinkers. The primary outcome measured was a favorable neurological outcome at hospital discharge (cerebral performance category score 1 or 2).
Results: Among the 6,671 enrolled patients, 14.7% had favorable neurological outcomes. The odd ratio of achieving a good neurologic outcome was reduced by 0.597 (95% confidence interval [CI], 0.444–0.802; $P < 0.001$), 0.650 (95% CI, 0.431–0.983; $P = 0.041$), and 0.666-fold (95% CI, 0.448–0.989; $P = 0.044$) for never, light, and heavy drinkers, respectively, compared to moderate drinkers.
Conclusion: This study revealed a nonlinear association between the frequency of alcohol consumption and neurological prognosis in patients with OHCA. Therefore, future studies should focus on investigating the mechanism underlying the potential brain-protective effects of alcohol to further understand its impact on neurological recovery following OHCA.

Trial Registration: ClinicalTrials.gov Identifier: NCT03222999

Keywords: Out-of-Hospital Cardiac Arrest; Alcohol Consumption; Neurological Outcome; Korea

Disclosure
The authors have no potential conflicts of interest to disclose.

Data Sharing Statement
Data sharing statement is provided in **Supplementary Data 1**.

Author Contributions
Conceptualization: Choi A, Park I, Chung SP, Park YS. Data curation: Park I, Park YS. Formal analysis: Choi A, You JS, Chung SP. Methodology: Choi A, Chung SP. Supervision: Park YS. Writing - original draft: Choi A, Park I, Park YS. Writing - review & editing: Choi A, You JS, Park YS.

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is an important global public health issue characterized by an overall poor clinical outcome, typically with a low survival rate of < 10%.[1] Although the precise etiology of OHCA remains unknown, certain comorbidities such as cardiovascular disease, diabetes mellitus, chronic kidney disease, and liver cirrhosis have been identified as factors associated with increased OHCA incidence and poor patient outcomes.[2-4] Furthermore, various triggers have been recognized as potential factors influencing the occurrence and clinical outcomes of OHCA.[5-10]

Excessive alcohol consumption is known to be associated with a range of adverse health effects, such as atrial fibrillation, stroke, hypertension, heart failure, seizures, cirrhosis, and various types of cancers. Numerous studies have consistently established a clear correlation between excessive alcohol intake and increased risks of all-cause and cause-specific mortality.[11-13] However, some studies have suggested a potential inverse relationship between light-to-moderate alcohol consumption and the risk of cardiovascular disease, type 2 diabetes mellitus, and all-cause mortality.[14-17]

Previous studies suggest that alcohol may exert cardioprotective effects through mechanisms such as cardiac preconditioning, which helps protect tissues from ischemia-reperfusion injury.[18,19] Moderate alcohol consumption has been shown to mimic this preconditioning effect, thereby reducing neuronal damage and enhancing cellular survival during ischemic episodes; however, clinical evidence supporting these findings remains limited.[20]

Although the primary objective of resuscitation is the restoration of spontaneous circulation, it is crucial to identify and comprehend the predictors associated with survival and neurological outcomes in patients with OHCA. Such knowledge is essential for developing post-arrest care strategies aimed at improving clinical and neurological outcomes.[21,22] Despite existing research concerning the negative consequences of excessive alcohol consumption on mortality and critical illness, to the best of our knowledge, no research has been conducted on the association between alcohol intake and neurological prognosis, specifically in patients with OHCA.

Consequently, this study aimed to examine the potential association between the frequency of alcohol consumption and neurological outcomes in patients with OHCA through a retrospective analysis using a multicenter nationwide registry.

METHODS

Study design and setting

This retrospective observational study utilized prospectively collected data from the Korean Cardiac Arrest Research Consortium (KoCARC) registry between October 2015 and December 2021. The KoCARC registry represents a comprehensive nationwide database comprising 62 participating hospitals in Korea that focuses explicitly on OHCA cases transported by public emergency medical services (EMSs) and adheres to Utstein templates for standardized reporting.[23] In Korea, the National Fire Agency oversees the public EMS system comprising 18 provincial fire departments. Each provincial fire department operates its own EMS system, designed according to the structure of the fire department.

Upon assessment by the fire-department-based EMS, patients are transported to the most appropriate emergency department (ED) based on factors such as hospital resources and proximity to the incident location.[24]

Selection of participants

Patients aged > 18 years who were transported by public EMS to the ED after OHCA were included. Patients with incomplete alcohol consumption data were excluded from the analysis. Additional exclusion criteria from the time of registration to the KoCARC registry included patients who were pronounced dead upon arrival without the need for resuscitation, had documented terminal illnesses, were under hospice care, were pregnant, or had a previously documented "Do Not Resuscitate" order. Moreover, patients with OHCA resulting from a definitive nonmedical cause were excluded from the registry enrolment process. The eligible patients were categorized into four groups based on alcohol consumption frequency: lifetime abstainers, minimal drinkers, light to moderate drinkers, and heavy drinkers. This categorization was informed by the hypothesis that moderate alcohol consumption may confer protective effects through ischemic preconditioning, potentially leading to improved outcomes in patients. Lifetime abstainers were defined as individuals who had never consumed alcohol. Minimal drinkers included former drinkers who had not consumed alcohol in the past year and occasional drinkers who consumed alcohol less than once per month. Light to moderate drinkers were defined as those who consumed alcohol more than twice a month but less than three times per week. This threshold was based on national statistics indicating that 57.4% of the Korean population reported drinking alcohol at least once a month over a one-year period, with an average frequency of 2.25 times per week, thereby representing social drinking patterns.[25,26] Finally, heavy drinkers were defined as individuals who consumed alcohol more than four times per week. This conceptual framework was chosen over a purely quantitative classification, such as quartiles, to better reflect the potential impact of different drinking patterns on ischemic preconditioning and patient outcomes.

Data collection

We extracted the following variables from the KoCARC registry: age; sex; medical history data such as hypertension, diabetes mellitus, dyslipidemia, alcohol consumption information, information regarding prehospital resuscitation such as whether or not a cardiac arrest was witnessed, place of cardiac arrest, bystander cardiopulmonary resuscitation (CPR), bystander use of automated external defibrillation, cardiac arrest rhythm upon first medical contact, defibrillation by EMS providers, prehospital return of spontaneous circulation (ROSC), and prehospital epinephrine use; information from hospital stages such as extracorporeal cardiopulmonary resuscitation (E-CPR) and targeted temperature management (TTM); and time from cardiac arrest to discontinuation of CPR.

Outcomes measured

The primary outcome was a favorable neurological outcome, defined as a cerebral performance category (CPC) score of 1 or 2 at the time of hospital discharge. In contrast, CPC scores 3, 4, or 5 were considered poor neurological outcomes.[27]

Statistical analyses

Continuous variables are presented as means ± standard deviations or medians with interquartile ranges, and categorical variables are presented as frequencies (percentages). Independent two-sample *t*-tests or the Wilcoxon rank-sum test were used to compare

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continuous variables, and the χ^2 or Fisher's exact tests were used to compare categorical variables. Univariate logistic regression analysis was performed to evaluate the predictive ability of each variable for the primary outcome. This was followed by a multivariate logistic regression analysis with variables that had a *P* value < 0.1 and accounted for less than 20% of missing data in the univariate binary logistic regression. The statistical significance of the predictors on the dependent variable was determined using odds ratios (ORs) and 95% confidence intervals (CIs); *P* values < 0.05 were considered statistically significant. The significance of the regression model was assessed using the χ^2 value and the corresponding significance probability obtained from the Hosmer–Lemeshow test. All statistical analyses were performed using the R version 4.0.3 for Windows (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org).

Ethics statement

This study adhered to the ethical principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Yonsei University College of Medicine, Severance Hospital (No. 4-2015-1162) and the IRBs of each participating hospital. The Korean Cardiac Arrest Research Consortium (KoCARC) registry database is registered at clinicaltrials.gov (protocol number NCT03222999).

RESULTS

A total of 17,039 patients with OHCA were registered in the KoCARC registry during the study period. Of them, 376 patients aged < 17 years were excluded from the study. In addition, 9,992 patients with no information regarding alcohol consumption were excluded. Consequently, 6,671 patients were enrolled in this study (**Fig. 1**).

Among them, 982 patients (14.7%) had CPC scores of 1 or 2 at hospital discharge, while 5,689 patients (85.3%) were classified as having CPC scores of 3, 4, or 5. Significant differences were observed between the patient groups, with good and poor neurological outcomes for all variables except for E-CPR (**Table 1**).

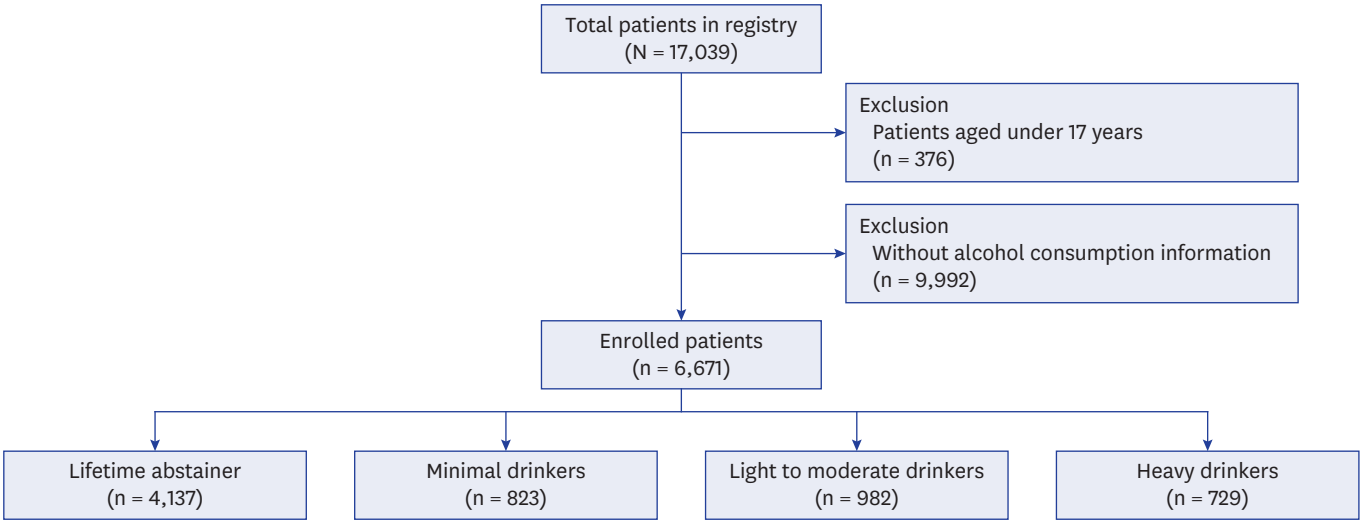

Fig. 1. Study flow chart.

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Table 1. Patient demographics and clinical characteristics

Variables	Overall (N = 6,671)	Neurologic outcomes		
		Poor (n = 5,689)	Good (n = 982)	*P* value
Age, yr	67.0 ± 15.9	68.8 ± 15.5	56.0 ± 13.7	< 0.001
Sex, male	4,333 (65.0)	3,541 (62.2)	792 (80.7)	< 0.001
Past medical history				
Hypertension, yes	3,097 (46.4)	2,704 (47.5)	393 (40.0)	< 0.001
Diabetes mellitus, yes	1,973 (29.6)	1,794 (31.5)	179 (18.2)	< 0.001
Dyslipidemia, yes	444 (6.7)	362 (6.4)	82 (8.4)	0.041
Alcohol consumption				< 0.001
Lifetime abstainer	4,137 (62.0)	3,683 (64.7)	454 (46.2)	
Minimal drinker	823 (12.3)	713 (12.5)	110 (11.2)	
Light to moderate drinker	982 (14.7)	681 (12.0)	301 (30.7)	
Heavy drinker	729 (10.9)	612 (10.8)	117 (11.9)	
Witnessed cardiac arrest, yes	4,293 (64.4)	3,463 (60.9)	830 (84.5)	< 0.001
Place of cardiac arrest, public	1,704 (25.5)	1,266 (22.3)	438 (44.6)	< 0.001
Bystander BLS				
Chest compression, yes	3,494 (52.4)	2,891 (50.8)	603 (61.4)	< 0.001
AED, yes	112 (1.7)	64 (1.1)	48 (4.9)	< 0.001
Prehospital phase information				
Prehospital shockable rhythm, yes	1,474 (22.1)	779 (13.7)	695 (70.8)	< 0.001
Prehospital defibrillation by EMS, yes	1,808 (27.1)	1,062 (18.7)	746 (76.0)	< 0.001
Prehospital epinephrine use, yes	1,015 (15.2)	949 (16.7)	66 (6.7)	< 0.001
Prehospital ROSC, yes	1,273 (19.1)	514 (9.0)	759 (77.3)	< 0.001
Hospital stage information				
E-CPR	264 (4.0)	215 (3.8)	49 (5.0)	0.095
TTM	1,032 (15.5)	696 (12.2)	336 (34.2)	< 0.001
Time from cardiac arrest to discontinuation of CPR	52.0 (41.0–64.0)	53.0 (42.0–65.0)	37.0 (30.0–52.5)	< 0.001

Variables are shown as mean ± standard deviation and median (Q1–Q3) or number (percentages). The variable "time from cardiac arrest to discontinuation of CPR" had missing data exceeding 20%.
BLS = basic life support, AED = automated external defibrillation, EMS = emergency medical service, ROSC = return of spontaneous circulation, E-CPR = extracorporeal cardiopulmonary resuscitation, TTM = targeted temperature management, CPR = cardiopulmonary resuscitation, Q = quartile.

Consequently, age (OR, 0.968; 95% CI, 0.960–0.977; $P < 0.001$); alcohol consumption frequency, never drinkers (OR, 0.597; 95% CI, 0.444–0.802; $P < 0.001$), light drinkers (OR, 0.650; 95% CI, 0.431–0.983; $P = 0.041$), or heavy drinkers (OR, 0.666; 95% CI, 0.448–0.989; $P = 0.044$); history of hypertension (OR, 1.283; 95% CI, 0.991–1.660; $P = 0.059$); history of diabetes mellitus (OR, 0.687; 95% CI, 0.511–0.923; $P = 0.013$); witnessed cardiac arrest (OR, 1.917; 95% CI, 1.435–2.560; $P < 0.001$); bystander CPR (OR, 0.768; 95% CI, 0.601–0.982; $P = 0.036$); prehospital shockable rhythm (OR, 3.755; 95% CI, 2.455–5.743; $P < 0.001$); prehospital defibrillation by EMS (OR, 2.012; 95% CI, 1.298–3.121; $P = 0.002$); prehospital ROSC (OR, 17.050; 95% CI, 13.393–21.706; $P < 0.001$); prehospital epinephrine use (OR, 0.231; 95% CI, 0.161–0.329; $P < 0.001$), E-CPR (OR, 0.471; 95% CI, 0.294–0.755; $P = 0.002$); and TTM (OR, 1.990; 95% CI, 1.544–2.564; $P < 0.001$) were identified as independent prognostic factors for favorable neurologic outcomes (**Table 2**). The clinical characteristics of patients within each drinking category are presented in **Table 3**.

DISCUSSION

By comprehensively analyzing the nationwide registry of patients with OHCA, this study revealed a nonlinear correlation between moderate alcohol consumption and an increased odd ratio of favorable neurological recovery.

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Table 2. Results of multivariate logistic regression analysis

Variables	OR (95% CI)	*P* value
Age, yr	0.968 (0.960–0.977)	< 0.001
Sex, male	1.114 (0.835–1.485)	0.463
Light to moderate drinker, reference		
Lifetime abstainer	0.597 (0.444–0.802)	< 0.001
Minimal drinker	0.650 (0.431–0.983)	0.041
Heavy drinker	0.666 (0.448–0.989)	0.044
Hypertension, yes	1.283 (0.991–1.660)	0.059
Diabetes mellitus, yes	0.687 (0.511–0.923)	0.013
Dyslipidemia, yes	1.060 (0.683–1.646)	0.794
Witnessed cardiac arrest, yes	1.917 (1.435–2.560)	< 0.001
Bystander CPR, yes	0.768 (0.601–0.982)	0.036
Bystander AED, yes	1.376 (0.595–3.180)	0.455
Prehospital shockable rhythm, yes	3.755 (2.455–5.743)	< 0.001
Prehospital defibrillation by EMS, yes	2.012 (1.298–3.121)	0.002
Prehospital epinephrine use, yes	0.231 (0.161–0.329)	< 0.001
Prehospital ROSC, yes	17.050 (13.393–21.706)	< 0.001
E-CPR	0.471 (0.294–0.755)	0.002
TTM	1.990 (1.544–2.564)	< 0.001

OR = odds ratio, CI = confidence interval, CPR = cardiopulmonary resuscitation, AED = automated external defibrillation, EMS = emergency medical service, ROSC = return of spontaneous circulation, E-CPR = extracorporeal cardiopulmonary resuscitation, TTM = targeted temperature management.

Table 3. Clinical characteristics of patients within each drinking category

Variables	Lifetime abstainer (n = 4,137)	Minimal drinker (n = 823)	Light to moderate drinker (n = 982)	Heavy drinker (n = 729)	*P* value
Age, yr	70.4 ± 15.5	68.8 ± 14.8	57.6 ± 14.5	57.8 ± 11.8	< 0.001
Sex, male	2,166 (52.4)	655 (79.6)	866 (88.2)	646 (88.6)	< 0.001
Past medical history					
Hypertension, yes	2,166 (52.4)	655 (79.6)	866 (88.2)	646 (88.6)	< 0.001
Diabetes mellitus, yes	1,310 (32.1)	300 (36.9)	197 (20.5)	166 (24.6)	< 0.001
Dyslipidemia, yes	265 (6.6)	74 (9.3)	62 (6.5)	43 (6.6)	0.050
Witnessed cardiac arrest, yes	2,647 (64.4)	522 (63.8)	673 (68.7)	451 (62.4)	0.028
Bystander BLS					
Chest compression, yes	2,134 (52.9)	447 (54.9)	556 (58.3)	357 (51.3)	0.010
AED, yes	66 (1.6)	13 (1.6)	23 (2.4)	10 (1.4)	0.353
Prehospital phase information					
Prehospital shockable rhythm, yes	732 (18.6)	154 (19.6)	397 (42.7)	191 (27.7)	< 0.001
Prehospital defibrillation by EMS, yes	649 (15.9)	144 (17.8)	316 (32.6)	164 (22.7)	< 0.001
Prehospital epinephrine use, yes	924 (22.7)	195 (24.2)	461 (47.9)	228 (31.7)	< 0.001
Prehospital ROSC, yes	588 (14.2)	128 (15.6)	151 (15.4)	148 (20.4)	< 0.001
Hospital stage information					
TTM, yes	579 (16.4)	109 (14.6)	229 (25.8)	115 (18.0)	< 0.001

Values are presented as number (%) or mean ± standard deviation.
BLS = basic life support, AED = automated external defibrillation, EMS = emergency medical service, ROSC = return of spontaneous circulation, TTM = targeted temperature management.

Contrary to the longstanding focus on the adverse effects of alcohol abuse, recent decades have witnessed the emergence of numerous peer-reviewed studies that have shed light on the favorable outcomes associated with moderate and controlled consumption of diverse alcoholic beverages. A previous meta-analysis that included 34 prospective studies indicated a nonlinear relationship between alcohol consumption and the risk of all-cause mortality characterized by a J-shaped pattern.[28] Moreover, several epidemiological studies have accumulated substantial evidence to establish a strong connection between moderate alcohol consumption and a significant reduction in the risk of developing coronary heart disease. A meta-analysis of 18 prospective studies revealed evidence suggesting that consuming light-to-moderate amounts of alcohol may confer a protective effect against mortality attributed explicitly to cardiovascular disease.[29] Although the relationship between moderate alcohol consumption and cerebral

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ischemia is currently supported by a relatively weak body of evidence, there are indications of a similar advantageous association, as observed in a previous study.[30]

Despite observing a J-shaped relationship between alcohol consumption and outcomes of various diseases, research on the association between alcohol consumption and neurological outcomes in patients with OHCA is lacking. Therefore, this study investigated the impact of alcohol consumption on the neurological outcomes of patients with OHCA. Specifically, we compared the neurological outcomes of moderate drinkers with those of never drinkers, light drinkers, and heavy drinkers. The odd ratio of a good neurological outcome was reduced by 0.597, 0.650, and 0.666 times for never-, light-, and heavy drinkers, respectively, compared to moderate drinkers. Moreover, when compared to individuals who never consumed alcohol, moderate drinkers exhibited a 1.676-fold higher odd ratio of achieving a favorable neurological outcome (OR, 1.676; 95% CI, 1.247–2.254; $P < 0.001$). Like the J-shaped pattern observed in the association between alcohol consumption and clinical outcomes in other diseases, this study demonstrated a J-shaped association between the frequency of alcohol consumption and neurological outcomes in patients with OHCA. This significant association highlights the potential positive impact of moderate alcohol consumption on neurological recovery in patients with OHCA.

The precise mechanisms underlying the J-shaped association between moderate alcohol consumption and favorable neurological outcomes in patients with OHCA are complex and not fully understood. Previous research has suggested several mechanisms that may explain the paradoxical effects of moderate alcohol intake, including ischemic preconditioning, where brief exposure to alcohol enhances the body's resistance to ischemic injury by triggering protective cellular pathways.[31] This process is well-documented in the cardiovascular system, with moderate alcohol consumption associated with improved cardiac outcomes and a reduced risk of ischemic heart disease. However, the neuroprotective effects of alcohol are less clearly established. Some studies indicate that moderate alcohol intake may modulate inflammatory responses or enhance the brain's resilience to ischemic damage by activating anti-inflammatory and cellular survival mechanisms.[18,32] It has been proposed that moderate alcohol consumption may induce mild stress responses that protect neurons from apoptosis or oxidative stress. Additionally, previous studies have reported neuroprotective effects in the brain through antecedent exposure, co-exposure, and preconditioning with moderate alcohol concentrations before experiencing ischemic insults.[20,33] The neuroprotective state associated with alcohol intake may involve the activation of signal transduction pathways, potentially involving reactive oxygen species, essential protein kinases, and increased expression of heat shock proteins.[34,35] While these mechanisms could potentially explain the observed association, our study did not directly assess neuroprotective pathways or specific drinking behaviors, such as binge drinking or chronic intake patterns, which may influence the outcomes. Given these limitations, our findings should be interpreted with caution. Although we observed a significant association between moderate alcohol consumption and better neurological outcomes, this does not establish causality.

Although this study specifically focused on the Korean population, it is important to note that Korea is not among the countries with the highest prevalence of alcohol consumption or alcohol intake compared to other nations.[36] Therefore, conducting similar research in such settings could potentially yield significant public health implications by providing insights into the characterization of patients with OHCA based on their alcohol consumption levels. Moreover, this information can potentially enhance our understanding of the clinical course of patients with OHCA undergoing post-cardiac arrest care.

Nonetheless, this study had some limitations that necessitate attention. First, as this was a retrospective observational study, there may have been undisclosed factors and biases arising from missing variables. Particularly, a large number of patients were excluded from the study due to unattainable information regarding their alcohol consumption. Second, we lacked data on the specific types and quantities of alcohol consumed as well as information about the patients' drinking habits. It is important to recognize that this study's retrospective design and the absence of direct data on the amount of alcohol consumed by patients limit the accuracy and reliability of the alcohol consumption categorization. Our estimation, based on the frequency of alcohol consumption reported by primary caregivers, may not accurately reflect the true amount of alcohol intake. This approach may have captured lifestyle characteristics or general health status prior to cardiac arrest rather than actual alcohol consumption. Future studies should aim to collect more detailed, objective data on alcohol intake to better evaluate its association with neurological outcomes. Third, there was a potential for bias because information on alcohol consumption could only be obtained from primary contacts, such as family members, which may be less reliable. Fourth, the low rate of TTM utilization in our cohort may have introduced selection bias. This underutilization, despite TTM being a routine practice for improving neurological outcomes, potentially confounds our analysis of alcohol consumption's impact on neurological recovery. While we adjusted for TTM status in our regression models, residual confounding could still exist. Future studies with more uniform TTM application are needed to better assess this relationship. Moreover, the clinical characteristics observed in light to moderate drinkers indicate a higher prevalence of factors commonly associated with favorable outcomes in cardiac arrest patients, such as baseline characteristics linked to improved recovery, alongside a higher rate of TTM implementation. Although logistic regression was utilized to adjust for confounding factors, the relatively limited range of variables included in the model raises the possibility of residual confounding. Finally, it is essential to conduct additional evaluations to determine the generalizability of the findings, as alcohol consumption patterns and tolerance levels vary among different nationalities and ethnic groups.

In conclusion, this study revealed a nonlinear association between alcohol consumption frequency and neurological prognoses in patients with OHCA. However, to gain a deeper understanding of the impact of alcohol on neurological recovery following OHCA, future research should focus on uncovering the mechanism underlying the potential brain-protective effects of alcohol.

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SUPPLEMENTARY MATERIAL

Supplementary Data 1

Data sharing statement

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