Effect of Cigarette Smoking on Functional Outcomes in Patients with Spontaneous Intracerebral Hemorrhage

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Background: Nicotine may have neuroprotective effects on the injured brain through modulation of the cholinergic anti-inflammatory pathway. *Aims:* This study aimed to evaluate the relationship between cigarette smoking and outcomes in patients with spontaneous intracerebral hemorrhage (ICH). *Methods:* This was a retrospective review of consecutive ICH patients enrolled in the ICH Outcomes Project from 2009 to 2017. Patients with age ≥18 years and baseline modified Rankin Scale (mRS) score 0-2 were included. Smoking patterns were categorized as recent smoker (≤30 days prior to ICH) and not recent smoker (>30 days prior to ICH). Not recent smokers were further categorized into former smokers and nonsmokers. The primary outcome was good outcome (90-day mRS ≤ 2). Secondary outcomes were excellent outcome (90-day mRS 0-1), 90-day Barthel Index, and in-hospital and 90-day mortality. *Results:* The study cohort comprised 545 patients, including 60 recent smokers and 485 not recent smokers. Recent smokers had higher rates of good (35% versus 23%; odds ratio [OR] = 1.787, $P = .047$) and excellent (25% versus 13%; OR = 2.220, $P = .015$) outcomes compared to not recent smokers. These differences were not significant after baseline adjustments. Recent smokers had higher rates of good (36% versus 24%; OR = 1.732, $P = .063$) and excellent (25% versus 13%; OR = 2.203, $P = .018$) outcomes compared to nonsmokers. These differences were not significant after baseline adjustments. A 90-day Barthel Index, in-hospital, and 90-day mortality were comparable between recent and not recent smokers, recent and nonsmokers, and former and nonsmokers. *Conclusions:* Despite potential neuroprotective effects of nicotine found in cigarettes, these may be outweighed by the detrimental effects of cigarette smoking on health outcomes.

Key Words: Intracerebral hemorrhage—stroke—smoking—outcomes—survival—functional independence—morbidity

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Introduction

Spontaneous intracerebral hemorrhage (ICH), which has an approximate annual incidence ranging from 15 to 25 per 100,000 persons, carries the highest rate of stroke-related death and long-term disability.[1-4] After the initial ictus, secondary injury cascades, including inflammation and degradation of heme products, are important contributors to patient morbidity and mortality.[5] Inflammatory processes, which can be observed within hours after ICH onset and can persist for days and weeks, are potential therapeutic targets in ICH patients.[5-7]

The negative effects of smoking on cardiovascular health have been well established, and there is a potential association between cigarette smoking and risk of ICH.[8-17] Despite this, the effects of nicotine, found within cigarettes, on ICH recovery are not well understood. Stimulation of the α7-nicotinic acetylcholine receptor (α7-nAChR), a principal mediator of the cholinergic anti-inflammatory pathway, has been associated with improved neurological outcomes in preclinical ICH models.[18-20] Therefore, we hypothesized that a translational neuroprotective effect of nicotine might

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be observed among ICH patients who were smokers prior to admission. The goal of this study was to investigate the effects of recent cigarette smoking on functional outcomes in patients presenting with ICH using a large single-center, prospective database.

Methods

Study Design

Between February 2009 and November 2017, consecutive patients presenting with spontaneous ICH at our institution were prospectively enrolled in the Intracerebral Hemorrhage Outcomes Project (ICHOP). The ICHOP study methods have been previously described in detail.[21,22] This study was approved by the institutional review board committee at our institution, and written informed consent was obtained from all patients (or respective legal guardians) participating in the study. All participants or designated proxies underwent a standardized data collection protocol, which included a personal interview and medical chart abstraction. This study follows the guidelines set forth by the Strength of Observational Studies in Epidemiology statement.[23]

Patient Identification and Selection

ICH was defined as an acute (<24 hours) spontaneous, nontraumatic, abrupt onset of severe headache, altered level of consciousness, or focal neurological deficit that was associated with a focal collection of blood within the brain parenchyma seen on neuroimaging or at autopsy. Patient care was in accordance with the American Heart Association/American Stroke Association guidelines.[24] The inclusion criteria for this study were: (1) age ≥18 years; (2) smoking status recorded on admission; and (3) baseline modified Rankin Scale (mRS) score of 0-2 prior to ICH. Primary intraventricular hemorrhage and ICH related to trauma, brain tumor, hemorrhagic transformation of cerebral infarction, vascular malformation, or any other suspected secondary causes were excluded from the study.

Data Collection

Baseline demographic and medical history data included age, sex, ethnicity, alcohol consumption and/or cocaine use ≤6 months prior to admission, history of atrial fibrillation, congestive heart failure, coronary artery disease (CAD), hyperlipidemia, hypertension, and diabetes mellitus. Clinical and laboratory data included admission systolic blood pressure, blood glucose, international normalized ratio, prothrombin time, partial thromboplastin time, National Institute of Health Stroke Scale score, and Glasgow coma scale (GCS) score.[25] Radiographic characteristics included ICH volume, ICH location, and presence of intraventricular hemorrhage. The ICH score for each patient was calculated.[24] Interventions during hospitalization included craniotomy/craniectomy for ICH and external ventricular drain placement.

Patients were categorized based on smoking status at the time of presentation. Patients with first-hand cigarette smoke exposure within 30 days of presentation were defined as recent smokers. Patients without first-hand cigarette smoke exposure within 30 days of presentation were defined as not recent smokers. Subsequently, not recent smokers were further categorized into former smokers and nonsmokers based on prior first-hand cigarette smoke exposure or lack thereof, respectively. Cumulative cigarette use, defined as the number of pack-years prior to admission, was also collected for all smokers.

Outcomes

The primary outcome was defined as good functional outcome (mRS score of 0-2) at 90 days.[26] The secondary outcomes were excellent functional outcome (mRS score of 0-1) at 90 days, Barthel Index (measured on a scale ranging from 0 to 100, with 100 indicating complete functional independence) at 90 days, and in-hospital and 90-day mortality.[27,28] Functional outcome assessments utilized standardized questionnaires that were administered by trained study staff to participants or their legal representatives via in-person or telephone-based interviews at the time of hospital discharge and at 90 days.

Statistical Analysis

All statistical analyses were performed using SPSS Statistics (version 25.0; IBM Corp, Armonk, NY). Comparisons between recent and not recent smokers, and subsequently between nonsmokers, former smokers, and recent smokers, were performed. Baseline patient demographics, laboratory, clinical, radiographic, and intervention data were compared between cohorts using Pearson's χ^2 or Fisher's exact test for categorical data, and Student's t test, one-way analysis of variance, Mann-Whitney U, or Kruskal-Wallis H tests for continuous data, as appropriate. Univariable logistic and linear regression analyses were performed to assess the relationships between smoking status and the primary and secondary outcomes. The findings from the univariable analyses were adjusted for covariates with $P < .05$ in multivariable models. Missing data were not imputed. Statistical significance was defined as $P < .05$, and all tests were 2 tailed.

Results

Patient Cohort

Of the 719 enrolled patients, 174 were excluded from the present study (65 patients due to lack of smoking status data and 109 patients for baseline mRS score > 2; Fig 1). The remaining patients comprised 60 recent smokers and 485 not recent smokers. The not recent

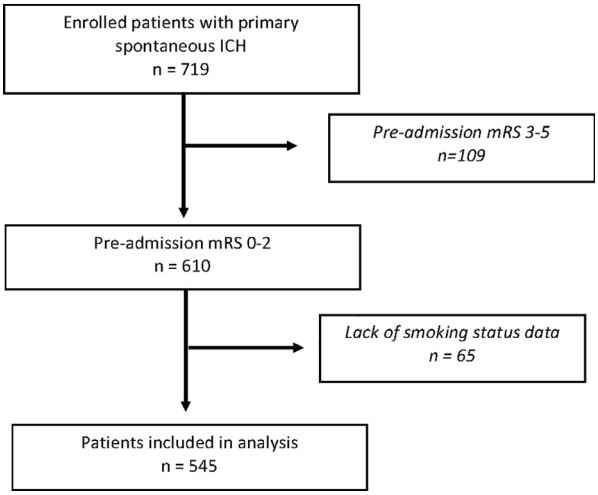

Figure 1. *Outline of the patient selection process.*

smokers comprised 398 nonsmokers and 87 former smokers.

Recent Smokers Versus Not Recent Smokers

Table 1 compares the baseline demographic, clinical, and radiological variables between patients who were recent smokers and those who were not recent smokers at the time of presentation. Recent smokers were more likely to be younger (mean 59 versus 62 years old, $P < .0001$) and have a history of alcohol consumption (73% versus 27%, $P < .0001$) or cocaine use (32% versus 3%, $P < .0001$). Patients who were not recent smokers were more likely to have CAD (12% versus 3%, $P = .048$) and hyperlipidemia (27% versus 13%, $P = .024$). There were significant differences ($P < .0001$) in the ethnicity distribution between recent and not recent smokers.

Table 2 compares the primary and secondary outcomes between patients who were recent smokers and those who were not recent smokers at the time of presentation. Recent smokers had higher rates of 90-day good functional outcome (35% versus 23%; odds ratio [OR] = 1.787 [1.009, 3.165]; $P = .047$). However, this was no longer significant after adjustment for baseline differences (aOR = 1.019 [.517, 2.008]; $P = .956$). Recent smokers had higher rates of 90-day excellent functional outcome (25% versus 13%; OR = 2.220 [1.168, 4.221]; $P = .015$). However, this was no longer significant after adjustment for baseline differences (aOR = 1.131 [.526, 2.431]; $P = .752$). Rates of 90-day Barthel Index, in-hospital mortality, and 90-day mortality were comparable between the 2 cohorts in both unadjusted and adjusted models.

Nonsmokers Versus Former Smokers and Nonsmokers versus Recent Smokers

Table 3 compares the baseline demographic, clinical, and radiological variables among nonsmokers, former smokers, and recent smokers. The cumulative cigarette use between former and recent smokers was similar (22 versus 17 pack-years, $P = .390$). Differences in age ($P < .001$), ethnicity distribution ($P < .001$), history of congestive heart failure ($P = .021$), atrial fibrillation ($P = .011$), CAD ($P < .001$), diabetes mellitus ($P = .002$), hyperlipidemia ($P = .034$), alcohol consumption ($P < .0001$), and cocaine use ($P < .0001$) were observed among nonsmokers, former smokers, and recent smokers.

Table 4 compares the primary and secondary outcomes between nonsmokers versus former smokers, and nonsmokers versus recent smokers. Comparable 90-day good functional outcome rates were observed between nonsmokers and recent smokers (24% versus 35%; OR = 1.732 [.970, 3.094]; $P = .063$). This difference remained nonsignificant after adjustment for baseline differences (aOR = 1.014 [.510, 2.015]; $P = .968$). Comparable 90-day good functional outcome rates were also observed between nonsmokers and former smokers (24% versus 21%; OR = .839 [.475, 1.483]; $P = .546$). This difference remained nonsignificant after adjustment for baseline differences (aOR = 1.117 [.587, 2.126]; $P = .735$). Recent smokers had higher rates of 90-day excellent functional outcome compared to nonsmokers (25% versus 13%; OR = 2.203 [1.145, 4.238]; $P = .018$). However, this was no longer significant after adjustment for baseline differences (aOR = 1.138 [.514, 2.521]; $P = .750$). Rates of 90-day excellent functional outcome were comparable between nonsmokers and former smokers (13% versus 13%; OR = .956 [.476, 1.921]; $P = .900$). This difference remained nonsignificant after adjustment for baseline differences (aOR = 1.581 [.713, 3.509]; $P = .260$). Rates of 90-day Barthel Index, in-hospital mortality, or 90-day mortality were comparable between nonsmokers and former smokers, and nonsmokers and recent smokers in both unadjusted and adjusted models.

Discussion

Spontaneous ICH is an important public health problem that is associated with high rates of death and functional disability in adults.[1,2,13,29] While the incidence of ICH has increased worldwide, rates of 30-day mortality and functional independence have remained unchanged at 40%-50% and 12%-36%, respectively.[2,13] Currently, no effective medical or surgical treatment has been established for ICH patients.[24] Therefore, efforts have been directed toward identifying novel therapies that target the second phase of cerebral injury after ICH.[24,30-35] In recent years, the proposed inflammatory mechanism of cerebral injury has garnered attention for its role as a potential therapeutic target.[5] The cholinergic anti-inflammatory pathway, principally mediated by the α7-subunit of the nAChR, is an endogenous mechanism for regulating the inflammatory response in tissues.[36,37] In preclinical models, nicotine and synthetic nicotine receptor agonists have been investigated as potential therapies that may

Table 1. *Comparison of baseline demographic, clinical, and radiologic characteristics between patients who were recent smokers and those who were not recent smokers at the time of presentation*

	Not recent smokers (n = 485)	Recent smokers (n = 60)	*P* value
Demographics			
Age, years (mean ± S.D)	62.0 ± 17.2; 476	52.8 ± 14.4; 60	**<.0001**
Female, n (%)	215/476 (45.2)	30/60 (50.0)	.440
Ethnicity, n (%)			**<.0001**
White	147/485 (30.3)	13/60 (21.7)	
Black	106/485 (21.9)	33/60 (55.0)	
Asian	27/485 (5.6)	3/60 (5.0)	
Hispanic	175/485 (36.1)	9/60 (15.0)	
Other,	30/485 (6.2)	2/60 (3.3)	
Co-morbidities, n (%)			
CHF	25/485 (5.2)	1/60 (1.7)	.232
AF	41/485 (8.5)	1/60 (1.7)	.063
CAD	57/485 (11.8)	2/60 (3.3)	**.048**
Hyperlipidemia	130/485 (26.9)	8/60 (13.3)	**.024**
Hypertension	324/485 (66.8)	43/60 (71.7)	.449
Diabetes	147/485 (22.0)	8/60 (13.3)	.118
Substance use, n (%)			
Alcohol	133/485 (27.4)	44/60 (73.3)	**<.0001**
Cocaine	13/485 (2.7)	19/60 (31.7)	**<.0001**
Biochemistry			
Glucose*, mean mmol/L ± S.D.	152.1 ± 67.3; 451	150.0 ± 54.5; 57	.273
INR*, mean ± S.D.	1.58 ± 3.13; 447	1.21 ± .60; 59	.371
PT*, mean sec ± S.D.	14.7 ± 5.6; 425	14.7 ± 5.4; 58	.977
PTT*, mean sec ± S.D.	30.6 ± 15.1; 416	30.2 ± 5.6; 55	.843
Clinical parameters			
SBP*, mean mmHg ± S.D.	176 ± 43; 444	173 ± 40; 54	.689
DBP*, mean mmHg ± S.D.	95 ± 27; 443	100 ± 24; 54	.181
GCS*, median [IQR]	11 [7-15]; 467	12 [6-15]; 59	.856
NIHSS*, median [IQR]	14 [3-24]; 426	12 [3-24]; 52	.599
ICH volume, median mL [IQR]			.107
	14.0 [4.3-36.0]; 433	10.0 [2.2-35.0]; 59	
Location, n (%)			
Lobar	115/384 (29.9)	13/54 (24.1)	.374
Deep	202/384 (52.6)	31/54 (57.4)	.508
Infratentorial	67/384 (17.4)	10/54 (18.5)	.847
IVH present, n (%)	240/485 (49.5)	35/60 (58.3)	.196
ICH score, n (%)			.906
0	68/423 (16.1)	8/54 (14.8)	
1	132/423 (31.2)	19/54 (35.2)	
2	88/423 (20.8)	11/54 (20.4)	
3	79/423 (18.7)	12/54 (22.2)	
4	47/423 (11.1)	3/54 (5.6)	
5	8/423 (1.9)	1/54 (1.9)	
6	1/423 (.2)	0/54 (0)	
Interventions, n (%)			
Craniectomy/craniotomy	40/485 (8.2)	4/60 (6.7)	.672
EVD	123/485 (25.4)	21/60 (35.0)	.110

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure; DBP, diastolic blood pressure; EVD, external ventricular drain; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; INR, international normalized ratio; IQR, interquartile rangemRS, Modified Rankin Scale; n, number; PT, prothrombin time; PTT, partial thromboplastin time; SBP, systolic blood pressure; S.D., standard deviation.

Bold indicates statistical significance, defined as $p < 0.05$.

*On admission.

Table 2. *Comparison of outcomes between patients who were recent smokers and those who were not recent smokers at the time of presentation*

Outcome	Not recent smokers (n = 485)	Recent smokers (n = 60)	Effect variable	Unadjusted value [95% C.I.]	*P* value	Adjusted value* [95% C.I.]	*P* value
Primary outcome							
mRS 0-2 at 90 days, n (%)	110/475 (23.2)	21/60 (35.0)	Odds ratio	1.787 [1.009, 3.165]	**.047**	1.019 [.517, 2.008]	.956
Secondary outcomes							
mRS 0-1 at 90 days, n (%)	62/475 (13.1)	15/60 (25.0)	Odds ratio	2.220 [1.168, 4.221]	**.015**	1.131 [.526, 2.431]	.752
Barthel index at 90 days, median [IQR]	95 [55-100]	100 [70-100]	Beta	.052 [−7.228, 16.392]	.445	−.020 [−14.481, 10.958]	.785
In-hospital mortality	110/464 (23.7)	9/59 (15.2)	Odds ratio	.579 [.276, 1.216]	.149	.628 [.262, 1.505]	.297
90-day mortality	148/360 (40.8)	15/48 (31.3)	Odds ratio	.660 [.346, 1.259]	.207	.923 [.431, 1.977]	.836

Abbreviations: IQR, interquartile range; mRS, modified Rankin Scale score; *P* value, probability value.
Bold indicates statistical significance, defined as $p < 0.05$.
*Values were adjusted for age, ethnicity, history of coronary artery disease, history of hyperlipidemia, history of alcohol use, and history of cocaine use.

attenuate the chain of events that arise during the second phase of cerebral injury after ICH.[5,7,36,38,39]

In a murine collagenase-induced ICH model comparing administration of an intraperitoneal injection of nicotine tartrate dihydrate versus saline, Hijioka et al found a dose-dependent reduction in neuron loss with increased neuronal Bcl-2 and reduced Bax expression within the hematoma, as well as decreased levels of activated microglia/macrophages, infiltrating neutrophils, and oxidative stress 3 days after ICH induction.[18] In the same study, blinded evaluators observed improvements in post-ICH sensorimotor performance and survival rate in nicotine-treated subjects. In a follow-up study that compared nAChR subtype-specific agonists PNU-282987 (specific to α7-nAChR) and RJR-2403 (specific to α4β2-nAChR) to nicotine and saline controls using the same murine ICH model, Hijioka et al showed that α7-nAChR agonism with PNU-282987 abrogated neuron loss in both the central and peripheral regions of the hematoma, whereas α4β2-nAChR activation by RJR-2403 had no effect on neuron survival.[19] The authors also observed a dose-dependent reduction of activated microglia/macrophages in the perihematomal region with PNU-282987 treatment. In a subsequent study by Krafft et al that utilized an autologous whole blood murine ICH model, subjects were randomized to intraperitoneal administration of PNU-282987 and PHA-543613, another α7-nAChR-specific agonist or saline at 1 hour after ICH induction.[40] Blinded evaluations at 24 hours and 72 hours after ICH induction found α7-nAChR activation to improve neurological outcome and attenuate brain edema. In light of the promising results demonstrated by the aforementioned studies, it may be postulated that smokers may paradoxically have better outcomes after ICH compared to nonsmokers (smoker's paradox). However, the therapeutic effects of α7-nAChR agonists (eg, nicotine) in ICH patients have not been rigorously investigated beyond animal models.

While the plasma half-life of nicotine after intravenous infusion or cigarette smoking is 2 hours, the terminal half-life, which accounts for the slow release of nicotine from tissues, ranges between 11 and 17 hours.[41,42] Based on the terminal half-life of nicotine, significant levels of nicotine have been estimated to persist in circulation at approximately 48 hours (3-4 half-lives) after a single exposure to a nicotine containing product.[41] However, blood nicotine levels have been shown to vary widely between individuals and smoking represents a multiple dosing situation with considerable accumulation over time.[42,43] Therefore, the pharmacokinetics of nicotine clearance among regular smokers may differ from the estimates of controlled single exposure studies. Furthermore, cotinine, the main metabolite of nicotine, is present in higher plasma concentrations than nicotine and has a half-life that ranges between 19 and 24 hours.[44] Cotinine has been found to cross the blood-brain barrier to modulate the sensitivity of α7-nAChR to respective agonists.[42,44-46] The pharmacodynamic effects of

Table 3. *Comparison of baseline demographic, clinical, and radiologic characteristics between nonsmokers, former smokers, and recent smokers*

	Nonsmokers (n = 398)	Former smokers (n = 87)	Recent smokers (n = 60)	*P* value
Demographics				
Age, mean years ± S.D.	60.4 ± 17.5	68.8 ± 13.6	52.8 ± 14.4	**<.0001**
Female, n (%)	191/389 (49.1)	24/87 (27.6)	30/60 (50.0)	**.002**
Ethnicity, n (%)				**<.0001**
White	110/398 (27.6)	37/87 (42.5)	13/60 (20.3)	
Black	86/398 (21.6)	20/87 (23.0)	33/60 (53.1)	
Asian	24/398 (6.0)	3/87 (3.4)	3/60 (7.8)	
Hispanic	150/398 (37.7)	25/87 (28.7)	9/60 (15.6)	
Other	28/398 (7.0)	2/87 (2.3)	2/60 (3.1)	
Pack-years, median (IQR)		21.5 (10.0-41.5)	17.0 (7.0-36.5)	.390
Comorbidities, n (%)				
CHF	16/398 (4.0)	9/87 (10.3)	1/60 (1.7)	**.021**
AF	39/398 (9.8)	2/87 (2.3)	1/60 (1.7)	**.011**
CAD	34/398 (8.5)	23/87 (26.4)	2/60 (3.3)	**<.0001**
Diabetes	77/398 (19.3)	30/87 (32.2)	8/60 (13.3)	**.002**
Hyperlipidemia	102/398 (25.6)	28/87 (32.5); 83	8/60 (13.3)	**.034**
Hypertension	259/398 (65.0)	65/87 (74.7)	43/60 (71.7)	.166
Substance use, n (%)				
Alcohol	104/398 (26.1)	29/87 (33.3)	44/60 (73.3)	**<.0001**
Cocaine	11/398 (2.8)	2/87 (2.3)	19/60 (31.7)	**<.0001**
Laboratory values				
Glucose*, mean mmol/L ± S.D.	151.7 ± 68.6; 370	154.0 ± 61.2; 81	142.0 ± 54.5; 57	.528
INR*, mean sec ± S.D.	1.56 ± 3.24; 366	1.66 ± 2.54; 81	1.21 ± .60 ± 59	.648
PT*, mean sec ± S.D.	14.4 ± 5.5; 351	16.0 ± 6.0; 74	14.7 ± 5.4; 58	.088
PTT*, mean sec ± S.D.	30.1 ± 14.8; 340	33.1 ± 16.7; 76	30.2 ± 5.6; 55	.246
Clinical parameters				
SBP*, mean mmHg (IQR)	177 ± 44; 365	170 ± 38; 79	173 ± 40; 54	.354
DBP*, mean mmHg (IQR)	96 ± 28; 364	91 ± 22; 79	100 ± 24; 54	.118
NIHSS*, median (IQR)	14 (4-24); 348	12 (3-19); 78	12 (3-24); 52	.318
GCS*, median (IQR)	11 (6-15); 380	14 (8-15); 87	12 (6-15); 59	.216
ICH volume, median mL (IQR)				.866
	15.0 (4.4-37.0); 349	11.5 (3.4-34.0); 84	10.0 (2.2-35.0); 59	
Location, n (%)				.730
Lobar	90/315 (28.6)	25/69 (36.2)	13/54 (24.0)	.302
Deep	172/315 (54.6)	30/69 (43.5)	31/54 (57.4)	.197
Infratentorial	53/315 (16.8)	14/69 (20.3)	10/54 (18.5)	.776
IVH, n (%)	192/398 (48.2)	48/87 (55.2)	35/60 (58.3)	.218
ICH score, n (%)				.315
0	59/344 (17.2)	9/79 (11.4)	8/54 (14.8)	
1	102/344 (29.7)	30/79 (38.0)	19/54 (35.2)	
2	73/344 (21.2)	15/79 (19.0)	11/54 (20.4)	
3	62/344 (18.0)	17/79 (21.5)	12/54 (22.2)	
4	39/344 (11.3)	8/79 (10.1)	3/54 (5.6)	
5	8/344 (2.3)	0/79 (.0)	1/54 (1.9)	
6	1/344 (.3)	0/79 (.0)	0/54 (.0)	
Interventions, n (%)				
Craniectomy/Craniotomy	35/398 (8.8)	5/87 (5.7)	4/60 (6.7)	.585
EVD	103/398 (25.9)	20/87 (23.0)	21/60 (35.0)	.239

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure; DBP, diastolic blood pressure; EVD, external ventricular drain; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; INR, international normalized ratio; IQR, interquartile range; IVH, intraventricular hemorrhage; mRS, Modified Rankin Scale; n, number; NIHSS, National Institutes of Health Stroke Severity score; PT, prothrombin time; PTT, partial thromboplastin time; SBP, systolic blood pressure; S.D., standard deviation.

Bold indicates statistical significance, defined as $p < 0.05$.

*On admission.

Table 4. *Comparison of outcomes between non-smokers and former smokers, and non-smokers and recent smokers*

Outcome		Effect variable	Unadjusted value (95% C.I.)	*P* value	Adjusted value* (95% C.I.)	*P* value
Primary outcome						
mRS 0-2 at 90 days, n (%)		Odds ratio				
Nonsmokers	84/398 (23.7)		Ref.		Ref.	
Former smokers	20/87 (19.3)		.839 [.475, 1.483]	.546	1.117 [.587, 2.126]	.735
Recent smokers	14/60 (35.9)		1.732 [.970, 3.094]	.063	1.014 [.510, 2.015]	.968
Secondary outcomes						
mRS 0-1 at 90 days, n (%)		Odds ratio				
Nonsmokers	51/388 (13.1)		Ref.		Ref.	
Former smokers	11/87 (12.6)		.956 [.476, 1.921]	.900	1.581 [.713, 3.509]	.260
Recent smokers	15/60 (25.0)		2.203 [1.145, 4.238]	**.018**	1.138 [.514, 2.521]	.750
Barthel Index at 90 days, median (IQR)		Beta				
Nonsmokers	95 (55-100)		Ref.		Ref.	
Former smokers	90 (68-100)		.012 [−10.383, 12.419]	.860	.048 [−7.853, 15.854]	.507
Recent smokers	100 (70-100)		.054 [−7.246, 16.773]	.435	−.017 [−14.611, 11.591]	.820
In-hospital mortality		Odds ratio				
Nonsmokers	94/378 (24.9)		Ref.		Ref.	
Former smokers	16/86 (18.6)		.544 [.258, 1.148]	.110	1.063 [.580, 1.947]	.844
Recent smokers	9/59 (15.3)		.691 [.382, 1.247]	.220	.912 [.411, 2.022]	.820
90-day mortality		Odds ratio				
Nonsmokers	119/296 (40.2)		Ref.		Ref.	
Former smokers	29/67 (43.3)		1.135 [.664, 1.941]	.643	.582 [.302, 1.121]	.105
Recent smokers	15/48 (31.3)		.676 [.352, 1.299]	.240	.609 [.252, 1.470]	.270

Abbreviations: C.I., confidence interval; mRS, modified Rankin Scale score; p-value, probability value; Ref., reference category.

Bold indicates statistical significance, defined as $p < 0.05$.

*Values were adjusted for age, ethnicity, gender, history of atrial fibrillation, history of coronary artery disease, history of diabetes, history of hyperlipidemia, history of alcohol use, history of cocaine use, and diastolic blood pressure on admission.

chronic versus acute nicotine exposure on the cholinergic anti-inflammatory pathway remain poorly studied in humans. Therefore, in selecting a reasonable time window for nicotine or nicotine metabolites to be present in tissues while accounting for potential chronic effects of nicotine exposure, we hypothesized that any translational effect of nicotine may require first-hand cigarette smoke exposure within 30 days prior to ICH onset.

In the current study, recent smokers had higher rates of excellent and good functional outcomes at 90 days compared to not recent smokers. However, these differences did not remain significant after adjustments for baseline differences. In subsequent analyses, recent smokers had higher rates of excellent and good functional outcomes at 90 days compared to nonsmokers. However, these differences also did not remain significant after adjustments for baseline differences. In contrast, functional outcomes were comparable between nonsmokers and former smokers. Interestingly, cumulative pack-years were similar between recent and former smokers, which suggested that any potential protective effect of cigarette smoking on ICH outcomes was likely to be temporal rather than dose dependent in nature. It must, however, be acknowledged that the negative effects of smoking on cerebrovascular health are well established.[9,12,47-50] Furthermore the contribution of cigarette smoking to hypertension and to destruction of the arterial wall, which may precipitate the rupture of small intraparenchymal vessels, has been suggested by potential associations between cigarette smoking and ICH risk.[51-54]

The published literature reporting functional outcomes associated with smoking in patients with spontaneous ICH is conflicting. A recent retrospective study of 554 European patients investigating the relationship between prior substance use and outcomes in patients with spontaneous ICH did not find an association between cigarette use and risk of dependent functional status (35.3% versus 35.6%; $P = 1.00$ for nonsmokers versus smokers, respectively).[55] Chen et al, in a large multiethnic, multicenter study comprising 2932 ICH patients, found no difference in 90-day mRS scores between ever-smokers versus never-smokers (median: 3 [2-5] versus 3 [2-5]; aOR = 1.041; $P = .577$).[56] In the same study, 90-day mRS scores were also comparable between current (≤30 days prior to ICH) and never-smokers (median: 3 [2-5] versus 3 [2-5]; aOR = 1.178; $P = .098$), and between former (>30 days prior to ICH) and never-smokers (median: 3 [2-5] versus 3 [2-5]; aOR = .932; $P = .399$). However, the aforementioned studies did not distinguish recent smoking from not recent smoking status in their primary analyses. Therefore, combining former smokers and recent smokers into a single group may have missed any potential temporal effects of recent nicotine exposure. Go et al, in a review of 39 young adult ICH patients of mean age 33.2 ± 6.4 years, found current smoking status (defined as the consumption of ≥5 cigarettes per week over a period of 12 months) to be independently associated with increased odds of GCS ≥4 at discharge ($P = .008$) and at 6 months ($P = .019$).[57] However, the study authors did not adjust for admission GCS in their analyses, which may be a confounder in their pooled results.

Few studies have investigated the association between smoking and risk of mortality following spontaneous ICH. A prospective cohort study comprising 66,820 Chinese patients of age >65 years found higher ICH mortality risks for both current and former smokers (adjusted hazard ratio = 1.80, $P < .001$ and adjusted hazard ratio = 1.25, $P < .001$ for current and past smokers, respectively) compared to nonsmokers after a mean follow-up of 11 years.[58] These findings are consistent with several early prospective studies in American patients that found an increased risk of ICH-related mortality associated with smoking.[10,11,59,60] Although Chen et al, found a lower in-hospital mortality among former compared to never-smokers (9.3% versus 12.7%; aOR = .695; $P = .031$), no difference in 90-day mortality rates was found between the 2 groups (21.1% versus 22.8%; aOR = .978; $P = .472$).[56] Similarly, in the current study, there was no observed difference in 90-day mortality between recent smokers and not recent smokers, recent smokers and nonsmokers, and former smokers and nonsmokers. Clinical trials that investigate the safety and therapeutic potential of nicotinic receptor agonists and/or nicotine replacement therapy may be warranted in the setting of ICH. However, the findings from our study suggest that the potential neuroprotective effects of nicotine, if any, are likely to be outweighed by the overall detrimental effects of smoking on health outcomes.[50] In our cohort, smoking was associated with a younger age of ICH presentation, potentially highlighting the negative impacts of smoking on cerebrovascular health.

We acknowledge the limitations of our study, which include its design, wherein the study protocol was not specifically constructed to investigate the effects of cigarette smoking on ICH outcomes. Therefore, our retrospective analysis is subject to confirmation bias in that variables were chosen based upon data availability and hypothesis generation. Specifically, our data were not sufficiently detailed to isolate the precise method for nicotine ingestion (ie, pipe, cigar, cigarette, etc), nor were we able to quantify the nicotine dose consumed among individual patients. Further potential limitations include reporting, recall and missing data biases due to the conditional nature of our results on the accuracy of recorded data. Furthermore, the sourcing of this study data from a single center is subject to concomitant selection bias. Our association results should be interpreted with caution, given the multitude of modifiable and non-modifiable risk factors for ICH, each of which may exert an independent effect on patient outcomes. All patients enrolled in the ICHOP study were admitted to the neurological intensive care unit, which suggests that our results may be representative of a moderate-high baseline ICH severity, thus

limiting their generalizability. We were unable to account for potential differences in the do not resuscitate status and likelihood of care limitations between patient groups. Finally, over 7000 chemicals can be isolated from cigarette smoke[61] and one should exert caution in attributing observational findings to the effects of nicotine, in the absence of biological evidence from human studies. Despite these limitations, this study has benefited from the prospective enrolment of a large number of participants and the categorization of patients into recent, former and non-smokers.

Conclusions

Recent cigarette smoking was not associated with improved functional outcomes in spontaneous ICH patients. Differences in clinical risk profiles existed among patients with various smoking status who presented with ICH. The potential neuroprotective effects of nicotine are likely to be outweighed by the overall detrimental effects of smoking on health outcomes.

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Conflict of Interest

None.

Supplementary materials

Supplementary data to this article can be found online at doi:10.1016/j.jstrokecerebrovasdis.2019.06.013.

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