The Misleading "Smoker's Paradox" in Young Stroke

Cheng-Loong Liang
Eda Hospital: E-Da Hospital
Han-Jung Chen
I-Shou University
Yi-Che Lee
I-Shou University
Cheng-Chun Wu
I-Shou University
Chon-Haw Tsai
China Medical University
Po-Lin Chen
Taichung veterans general hospital
Wei-Lun Chang
Show Chwan Memorial Hospital
Po-Yen Yeh
St Martin De Porres Hospital
Cheng-Yu Wei
Chang bing show chwan hospital
Ming-Jun Tsai
annan Hospital
Yu Sun
En Chou hospital
Chih-Hao Lin
Lin shin hospital
Jiunn-Tay lee
Tri-Service General Hospital
Ta-Chang Lai
Cheng Hsin general hospital
Li-Ming lien
Shin kong Ho su hospital
Mei-Chen Lin
china medical university
Cheng-Li Lin
china medical university
hao kuang Wang (ed101393@gmail.com)
E-Da Hospital https://orcid.org/0000-0002-1928-7502

Chung Y. Hsu
China medical university

Research article

Keywords: stroke, smoking, Taiwan Stroke Registry, smoking cessation, proportional hazards regression analysis

Posted Date: May 26th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-558246/v1

Abstract

Objective: Stroke in young adults is uncommon, and the etiologies and risk factors of stroke in young adults differ from those in the older populations. Smoker's paradox is an unexpected favorable outcome, and age difference was used to explain the association between smoking and the favorable functional outcome. This study aimed to investigate the existence of this phenomenon in young stroke patients.

Methods: We analyzed a total of 9,460 young stroke cases registered in the nationwide stroke registry system of Taiwan between 2006 and 2016. Smoking criteria included having a past or current history of smoking more than 1 cigarette per day for more than 6 months. After matching for sex and age, a Cox model was used to compare complications, mortality and outcomes between smokers and non-smokers.

Results: Smoking was associated with older age, higher comorbidities, and higher alcohol consumption. Smoking patients with NIHSS scores of 11–15 had a worse functional outcome (adjusted OR, 0.81; 95% CI, 0.76–0.87), and smoking cessation would substantially reverse those effects.

Conclusion: The smoker's paradox definitely does not exist, and therefore we continue to strongly advocate the importance of smoking cessation.

Introduction

Stroke in young adults is relatively uncommon. The Follow-Up of Transient Ischemic Attack and Stroke Patients and Unelucidated Risk Factor Evaluation (FUTURE) study revealed that only 10% of all strokes occurred in patients aged 18–50 years [1, 2]. Most strokes can be explained by hypertension, diabetes, hyperlipidemia, obesity, atrial fibrillation, and smoking. However, stroke is far more common in the geriatric population, whereas in the young it is generally assumed to differ in risk factors and pathogenesis [3, 4]. Worldwide, more than two million young adults suffer from stroke yearly. Although the prognosis of young stroke is generally considered benign, young adults with stroke are at a higher risk of recurrent stroke and mortality than their healthy peers. Most survivors between 20 and 50 years may have emotional, social, or physical sequelae that impair their quality of life [4, 5]. In addition, young stroke victims are often responsible for providing child care or generating income for their families. Therefore, young stroke is a major health and socioeconomic problem.

Smoking is one of the biggest public health threats associated with many chronic diseases such as cardiovascular disease, and cancer [6–8]. More importantly, smoking is also aggregated with other adverse behaviors such as bet-but chewing and alcohol drinking. However, several recent studies observed an improved outcome in smokers with antithrombotic therapy after an index cardiovascular event, a phenomenon called "smoker's paradox" [9–13]. These studies are limited by short observation periods and small sample sizes [10, 11]. Moreover, no study has examined the effects of pre-stroke smoking on post-stroke complications that can prolong the patients' recovery and reduce their quality of life.

The purpose of this study was to evaluate whether smoking status was an independent prognostic factor in young stroke patients. In addition, we compared the influence of smoking on the stroke outcome in different clinical settings, in terms of gender and stroke subtypes.

Methods

Standard protocol approvals, registrations, and patient consents

The Taiwan Stroke Registry (TSR) is the first large nationwide stroke registry in Taiwan and is sponsored by the Taiwan Department of Health [14]. Details on the database's generation, monitoring, and maintenance are published by the Taiwan Stroke Society. [9–11] The data that support the findings of this study are available from Taiwan Stroke Registry but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. All researchers can submit their proposals to the research committee of the TSR (taiwanstrokeregistry@gmail.com). After study proposals are accepted, the results will be sent back to investigators. In this study, ethical approval was granted from China Medical University and the Institutional Review Boards (IRB) of the collaborating hospitals (CMUH104-REC2-115).

The TSR enrolls patients who are presented within 10 days of symptom onset to a TSR hospital because of 1 of the 4 major stroke types (i.e., ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, and transient ischemic attack). The TSR program was launched in 2006, and more than 100,000 stroke events had been recorded in the TSR up to 2018 [15–17]. Initially, 39 hospitals across the country participated in the registration project, and study protocols were approved by the Institutional Review Board of each participating hospital. Each stroke patient who signed the informed consent was followed up by the case managers of each hospital through their medical records and/or telephone visits every 3 months for at least 12 months after discharge. The severity of stroke was assessed using the National Institutes of Health Stroke Scale (NIHSS), and the outcome was determined using the modified Rankin Scale (mRS) by trained neurologists. The data entry was performed by study nurses (http://stroke.cmuh.org.tw/). The Taiwan Stroke Registry Investigators are listed in Appendix S1.

Study design and eligibility criteria

The study comprised all consecutive patients aged between 20 and 50 years who were diagnosed with any type of stroke from August 1, 2006 to May 20, 2016. Patient characteristics relevant to acute stroke, including stroke type, neurological deficit severity defined by the National Institute of Health Stroke Scale (NIHSS), medical history, pre-existing comorbidities, imaging, in-hospital management and complications, and functional outcomes, were collected according to a predefined system. Smokers were defined as those with a past or current history of smoking more than one cigarette per day for more than six months. Meanwhile, former smokers were those who stopped smoking over six months before stroke. In total, 9,460 young stroke patients were included in this cohort study.

Main outcome measures and statistical analysis

The primary outcomes included in-hospital mortality and the functional outcome measured by the modified Rankin Scale (mRS). Follow-up evaluations were conducted at 3 months, and outcome events were classified by using information from interviews (directly during follow-up visits or via telephone) with patients, or from hospital records. All descriptive data are expressed as numbers (N) and percentages (%) of patients. Hazard ratios (HRs) and 95% confidence intervals (CIs) were assessed by Cox proportional hazards models in

univariate analyses to compare demographic variables and risk factor prevalence at baseline, and in stratified multivariable analyses to detect the independent predictors of mortality. Then, we used logistic regression analysis to calculate the odds ratios (ORs) for the evaluation of potential factors associated with discharging stroke patients for the poor functional outcome (mRS score of 3–5) in the derivation group. Statistical significance was considered at a p value of < 0.05.

Results

Baseline characteristics of young stroke patients

In the TSR, 9,460 young stroke patients were identified, including 4,784 smokers and 4,676 non-smokers. Detailed demographic and clinical characteristics for this cohort are presented in Table 1. The smoker group had an older age and a higher stroke severity (NIHSS on admission) than the non-smoker group (Table 1). Compared with the non-smoker group, the smoker group had higher proportions of certain stroke risk factors, like hypertension, diabetes, total cholesterol, previous stroke, and alcohol consumption.

Table 1
Baseline characteristics of smokers/non-smokers and stroke risk factors, n (%)

	Non-Smokers	Smokers	p	Former	Current	p
	(n = 4784)	(n = 4676)	(Smokers vs. non-smokers)	(n = 373)	(n = 4303)	(Current vs. former)
Gender			< 0.0001			0.1243
Women	2551(53.32)	429(9.17)		26(6.97)	403(9.37)	
Men	2233(46.68)	4247(90.83)		347(93.03)	3900(90.63)	
Age (years)			< 0.0001			< 0.0001
20–29	389(8.13)	189(4.04)		6(1.61)	183(4.25)	
30–39	1132(23.66)	976(20.87)		50(13.40)	926(21.52)	
40–49	3263(68.21)	3511(75.09)		317(84.99)	3194(74.23)	
Median (Q1, Q3)	43.82(38.05, 47.53)	44.79(40.02, 47.73)	< 0.0001	46.08(42.48, 48.19)	44.67(39.84, 47.69)	0.6154
NIHSS score upon admission			< 0.0001			0.3651
0	908(18.99)	707(15.13)		61(16.35)	646(15.02)	
1–5	1811(39.96)	1994(42.67)		170(45.58)	1824(42.42)	
6–10	717(14.99)	736(15.75)		59(15.82)	677(15.74)	
11–15	370(7.74)	395(8.45)		32(8.58)	363(8.44)	
16–20	252(5.27)	237(5.07)		14(3.75)	223(5.19)	
> 20	624(13.05)	604(12.93)		37(9.92)	567(13.19)	
Median (Q1, Q3)	4(1, 11)	4(2, 11)	0.0041	4(1, 10)	4(2, 11)	0.0113
Stroke type			< 0.0001			0.0067
Infarct	2548(54.64)	2732(59.35)		229(62.40)	2503(59.09)	
TIA	330(7.08)	296(6.43)		32(8.72)	264(6.23)	
ICH	1354(29.04)	1245(27.05)		92(25.07)	1153(27.22)	
SAH	410(8.79)	320(6.95)		12(3.27)	308(7.27)	
Other	21(0.45)	10(0.22)		2(0.54)	8(0.19)	

Table 1
Continue, n (%)

	Non-Smokers	Smokers	p	Former	Current	p
	(n = 4784)	(n = 4676)	(Smokers vs. non-smokers)	(n = 373)	(n = 4303)	(Current vs. former)
History of hypertension			< 0.0001			0.0209
No	1921(40.42)	1544(33.59)		102(28.10)	1442(34.07)	
Yes	2831(59.56)	3052(66.41)		261(71.90)	2791(65.93)	
< 120	617(12.98)	464(9.97)		37(9.95)	427(9.97)	
120–139	890(18.72)	901(19.36)		72(19.35)	829(19.36)	
140–159	1021(21.47)	1085(23.31)		73(19.62)	1012(23.63)	
≧ 160	2227(46.83)	2205(47.37)		190(51.08)	2015(47.05)	
History of diabetes			0.0472			0.0678
No	3673(78.15)	3431(76.41)		258(72.47)	3173(76.75)	
Yes	1027(21.85)	1059(23.59)		98(27.53)	961(23.25)	
HbA1c < 7%	1147(66.57)	1165(65.52)		109(72.19)	1056(64.90)	
7 ≦ HbA1c < 8	105(6.09)	136(7.65)		11(7.28)	125(7.68)	
HbA1c ≧ 8	471(27.34)	477(26.83)		31(20.53)	446(27.41)	
Total cholesterol			< 0.0001			0.119
< 200	2428(73.91)	2353(68.48)		191(64.97)	2162(68.81)	
200–239	466(14.19)	537(15.63)		59(20.07)	478(15.21)	
240–299	248(7.55)	319(9.28)		29(9.86)	290(9.23)	
≧ 300	143(4.35)	227(6.61)		15(5.10)	212(6.75)	
Heart disease	694(14.91)	607(13.74)	0.1102	65(19.01)	542(13.29)	0.0032
Previous stroke	472(10.09)	513(11.50)	0.0296	73(20.74)	440(10.71)	< 0.0001
Uremia	124(2.70)	78(1.80)	0.004	10(3.00)	68(1.70)	0.0845
Alcohol	322(6.74)	1951(42.35)	< 0.0001	95(26.03)	1856(43.75)	< 0.0001

Smoking and mortality in young stroke patients

Table 2, 3, and 4 summarizes the risk of mortality in the Cox regression model, stratified by age, gender, the NIHSS score upon admission, stroke type, and stroke risk factor. The risk of mortality seemed to be lower among patients with infarct hazard ratio (HR), 0.65; 95% confidence interval (CI), 0.49–0.87] while higher in those with intracerebral hemorrhage (ICH) [HR, 1.25; 95%CI, 1.03–1.51] (Table 3). We further analyzed the HR values stratified by gender. The HRs for ICH in the male group were 1.31 (95%CI 1.04–1.64, $p < 0.05$), respectively (Table 4). However, no significant association was observed between smoking categories and mortality due to stroke in the multivariate Cox regression model.

Table 2
Mortality and hazard ratio (HR) for stroke events in smokers compared to non-smokers in all stroke patients

	Non-smoker			Smoker			HR (95% CI)	
	Deaths	py	Mortality	Deaths	py	Mortality	Crude	Adjusted
Overall	405	759088	0.53	372	741848.00	0.50	0.94(0.82–1.09)	0.89(0.72–1.10)
Age (years)								
20–29	34	62022	0.55	8	28497.00	0.28	0.51(0.23–1.10)	0.57(0.18–1.75)
30–39	78	182424	0.43	87	141386.00	0.62	1.33(0.98–1.81)	1.20(0.74–1.93)
40–49	293	514642	0.57	277	571965	0.48	0.87(0.74–1.03)	0.84(0.66–1.08)
Stroke type								
Infarct	109	437604	0.25	77	482344	0.16	0.65(0.49–0.87)**	0.79(0.54–1.16)
TIA	4	48378	0.08	1	42078	0.02	-	-
ICH	204	196205	1.04	226	165326	1.37	1.25(1.03–1.51)*	1.08(0.81–1.44)
SAH	79	58229	1.36	64	42753	1.50	1.06(0.76–1.47)	0.72(0.39–1.33)
Other	2	4065	0.49	0	2026	0.00	-	-

Table 3
Mortality and hazard ratio (HR) for stroke events in male smokers compared to male non-smokers

Male	Non-smoker			Smoker			HR (95% CI)	
	Deaths	py	Mortality	Deaths	py	Mortality	Crude	Adjusted
Overall	182	344592	0.53	331	675034	0.49	0.95(0.79–1.14)	0.91(0.71–1.15)
Age (years)								
20–29	13	27593	0.47	6	23365	0.26	0.52(0.20–1.39)	0.20(0.03–1.24)
30–39	43	91378	0.47	76	123947	0.61	1.22(0.84–1.77)	1.25(0.72–2.15)
40–49	126	225621	0.56	249	527722	0.47	0.90(0.72–1.11)	0.87(0.66–1.15)
Stroke type								
Infarct	35	185511	0.19	65	437994	0.15	0.83(0.55–1.25)	0.93(0.58–1.49)
TIA	2	24133	0.08	1	39477	0.03	0.30(0.03–3.33)	0.17(0.01–3.02)
ICH	114	114046	1.00	215	156749	1.37	1.31(1.04–1.64) *	1.05(0.77–1.43)
SAH	27	13003	2.08	46	32619	1.41	0.73(0.45–1.17)	0.54(0.26–1.12)
Other	1	1843	0.54	0	2026	0.00	-	-

Table 4
Mortality and hazard ratio (HR) for stroke events in female smokers compared to female non-smokers

Female	Non-smoker			Smoker			HR (95% CI)	
	Deaths	py	Mortality	Deaths	py	Mortality	Crude	Adjusted
Overall	223	414496	0.54	41	66814	0.61	1.10(0.79–1.54)	0.78(0.47–1.28)
Age (years)								
20–29	21	34429	0.61	2	5132	0.39	0.71(0.17–3.02)	1.99(0.41–9.57)
30–39	35	91046	0.38	11	17439	0.63	1.64(0.83–3.23)	0.75(0.21–2.66)
40–49	167	289021	0.58	28	44243	0.63	1.03(0.69–1.53)	0.72(0.40–1.28)
Stroke type								
Infarct	74	252093	0.29	12	44350	0.27	0.87(0.47–1.60)	0.58(0.26–1.26)
TIA	2	24245	0.08	0	2601	0.00	-	-
ICH	90	82159	1.10	11	8577	1.28	1.01(0.54–1.90)	1.17(0.49–2.79)
SAH	52	45226	1.15	18	10134	1.78	1.50(0.88–2.57)	1.25(0.47–3.34)
Other	1	2222	0.45	0	0	0.00	-	-

Smoking and the functional outcome in young stroke patients

Table 5 shows the crude and adjusted odds ratios (ORs) for the poor functional outcome (with the modified Rankin Scale score of 3–5) and the NIHSS score between the two cohorts. For NIHSS scores ranging between 16 and 20, adjusted ORs were only significant in current smokers (OR, 2.75, 95% CI, 1.12– 6.77, respectively).

Table 5
Crude and adjusted ORs with 95% CI for the long-term outcome (mRS 3–5 vs. 0–2) in current smokers compared with non-smokers stratified by the NIHSS score.

	Current		Former	
	Crude	Adjusted	Crude	Adjusted
Overall				
NIHSS score: 1–5	1.00(0.71–1.41)	0.97(0.62–1.51)	0.71(0.25-2.00)	0.53(0.15–1.84)
NIHSS score: 6–10	0.79(0.57–1.12)	0.95(0.60–1.52)	1.52(0.69–3.32)	1.30(0.47–3.61)
NIHSS score: 11–15	1.02(0.66–1.58)	1.57(0.83–2.96)	1.07(0.33–3.51)	1.05(0.23–4.90)
NIHSS score: 16–20	1.82(1.02–3.28)*	2.75(1.12–6.77)*	1.58(0.37–6.66)	1.09(0.15–7.86)
NIHSS score: > 20	1.60(0.93–2.75)	1.73(0.78–3.83)	4.30(0.55–33.81)	-

Discussion

In our community-based longitudinal study in young stroke, a total of 9,460 (10.63%) strokes were identified among patients aged ≤ 50 years. We observed a gender difference between smokers and nonsmokers. Smokers were associated with the higher severity of the initial stroke (NIHSS score upon admission) and more ischemic stroke. In addition, modifiable risk factors are prevalent in smokers, including hypertension (66.41%), diabetes (23.59%), hypercholesterolemia (31.52%), previous stroke (11.50%), and alcohol consumption (42.35%). According to the stratified analysis, smoking was an independent predictor of the functional outcome recorded at 3 months after stroke. However, only lower crude ratios for mortality, not adjusted hazard ratios, were observed in the smoker group. Due to the poorer outcome in the smoker group, the smoking paradox does not exist.

Approximately 10% of strokes occur at ages ≤ 50 years, and the proportion of strokes in young adults has increased over time [3, 4]. Despite their more favorable stroke outcome, younger adult patients still have an obvious socioeconomic consequence because a large proportion of them are at a higher risk of future cardiovascular events and labor productivity loss. Besides, the burden of disease is heavier in the case of recurrent events. Stroke is far more common in the geriatric population, and associations between risk factors for acute stroke and the clinical outcomes are stronger among older adults [1–4]. However, the knowledge gleaned from research on older adults cannot always be applied to younger adults. Lutski et al. showed that young adults have a high prevalence of modifiable vascular risk factors and especially a high rate of smoking [18]. In our study, we found that most strokes in young smokers were related to the existence of traditional stroke risk factors. There are several reasons why smokers may have a higher risk of developing stroke. Smoking increases the risk of complex atherosclerotic cardiovascular events, including deleterious effects on the endothelial function, inflammation, lipids, and thrombosis [9, 10]. Nicotine exposure could also induce a reduction in insulin release, and negatively affect insulin action, suggesting that nicotine could be a cause for the development of insulin resistance. Therefore, young stroke patients who smoked were more likely to have those comorbidities.

Initially, the term “smoker’s paradox” was an observational phenomenon of an unexpected favorable outcome in smokers who experienced acute myocardial infarction and had a smoking duration of over 25 years [9]. Recent studies in stroke have indicated a strong positive correlation between recanalization and smokers, indicating that thrombolytic therapy acts more effectively in smokers [11, 12]. Then smokers who experienced subarachnoid hemorrhage (SAH) were also reported with many paradoxically superior outcome measures, including reduced odds of a poor outcome in poor-grade patients [11, 12]. In other words, these studies stated that smoking predicted a better outcome following various reperfusion strategies. However, they had some shortcomings, including short observation durations, or their patients’ low clinical risk profiles and low NIHSS scores on admission. In addition, those studies showed that ignore smoking was associated with a younger age of stroke. The risk of recurrent stroke after the first stroke is about 10% at 1 year, 25% at 5 years, and 40% at 10 years, and about 40% of stroke survivors become disabled after stroke. Recurrent strokes often have a higher rate of death and disability. In our present study, we only investigated young stroke patients, and the data suggested that smoking was associated with the higher severity of the initial stroke, more modifiable risk factors and the poor functional outcome recorded at 3 months after stroke. Therefore, smoker’s paradox is misleading.

The difference in the incidence of stroke between two sexes have been well established. Several epidemiological studies reported higher age-specific stroke rates in men [19–21]. However, women still experience more frequent stroke events because of their increased longevity and high stroke incidence at older ages. The higher prevalence of traditional vascular risk factors, including hypertension, diabetes mellitus, and hyperlipidemia in middle-aged men may contribute to this result [22, 23]. Our findings are consistent with those of a meta-analysis and certain community-based reports on the relationship between stroke and sex. More interestingly, age-specific stroke rates are higher in men, and the higher prevalence of traditional vascular risk factors is associated with smoking.

Patients who cease smoking are expected to live longer and less likely to develop tobacco-related diseases, including coronary heart disease, stroke, cancer, and pulmonary disease [24–27]. In the present study, smoking cessation is particularly beneficial as it was shown to reverse the post stroke function outcome of young stroke patients. In 1997, Taiwan established its first comprehensive policy package for tobacco control, the Tobacco Hazards Prevention Act (THPA), to include pictorial health warnings, smoke-free worksites and restaurants, and a ban on most tobacco advertising [24, 25]. In 2018, Taiwan recorded an adult smoking rate of 13%, its lowest rate since 1990. This resulted from the efforts of the government to discourage smoking since the enactment of the Tobacco Hazards Prevention Act in 1997. Taiwan was the second Asian country after Bhutan to institute an indoor smoking ban. However, Taiwan's tobacco price still remains too low, and now, Taiwan government only levies one package of 20 cigarettes at NT$ 10 (US$ 0.3). According to a World Bank study, a 10-percent rise in the cigarette price leads to a 4-to 8-percent reduction in cigarette consumption. Therefore, it is imperative to raise the price of tobacco.

The TSR provides the opportunity to investigate these issues owing to its large sample size, the homogeneous demographic characteristics and clinical phenotypes of the study subjects, and the standard diagnostic workup [17, 28].

However, the present study has a number of limitations that need to be addressed. First, the baseline characteristics of the study groups were only obtained in the hospitals; hence, certain unadjusted potential confounders may still exist. Second, the sample sizes was sufficiently large, representing 3% of the total adult population in Taiwan. However, our cohort consisted of participants with an above-average socioeconomic status engaging in a medical screening program. This may affect the generalizability of our findings. Third, our data included only stroke survivors as the TSR does not include data on patients who died before reaching the hospital, leading to the possible underestimation of the mortality rate.

Conclusion

In conclusion, this study uncovers an intriguing relation between smoking and young stroke. High smoking rates are found among male young stroke patients, compared to much lower rates among females. Smoking is associated with higher comorbidities and poor long-term function outcomes. Smoking cessation would substantially reduce those effects. This implies that physicians should put more efforts into reducing cigarette smoking serves in Taiwan.

Declarations

Ethics approval and consent to participate

Ethics approval of this study was obtained from China Medical University and the Institutional Review Boards (IRB) of the collaborating hospitals (CMUH104-REC2-115). The written informed consent was obtained from all individual participants included in the study.

Consent to publish

Not applicable

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to the restrictions of the local ethics committee and institutional data security and privacy policies. The data access request needs institutional and ethics committee's approval.

Competing interests

The author(s) confirm that this article content has no conflicts of interest.

Funding

CYH is supported in part by Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW109-TDU-B-212-114004), MOST Clinical Trial Consortium for Stroke (MOST 108-2321-B-039-003-), Tseng-Lien Lin Foundation, Taichung, Taiwan. The funders had no role in the study design, data collection, analysis, or interpretation.

Authors' Contributions

PLC, WLC, PYY, CYW, MJT, YS, CHL, JTL, TCL, LML, MCL, CLL, and HKW designed research; CLL, HJC, YCL, CCW, CHT, and HKW analyzed data; HKW, and CYH wrote the paper.

Acknowledgements

Not Applicable

Authors' Information

Affiliations

School of Medicine, I-Shou University, Kaohsiung, Taiwan

Cheng-Loong Liang, Han-Jung Chen, Yi-Che Lee, Cheng-Chun Wu,

Hao-Kuang Wang

Division of Neurology, China Medical University Hospital, Taichung, Taiwan

Chon-Haw Tsai

Neurological Institute, Taichung Veterans General Hospital, Taichung, Taiwan

Po-Lin Chen

Department of Neurology, Show Chwan Memorial Hospital, Changhua County, Taiwan

Wei-Lun Chang

Department of Neurology, St. Martin De Porres Hospital, Chiayi, Taiwan

Po-Yen Yeh

Department of Neurology, Chang Bing Show Chwan Memorial Hospital, Changhua County, Taiwan

Cheng-Yu Wei

Department of Neurology, Tainan Municipal An-Nan Hospital-China Medical University, Tainan, Taiwan

Ming-Jun Tsai

Department of Neurology, En Chu Kong Hospital, Xinbei City, Taiwan

Yu Sun

Department of Neurology, Lin Shin Hospital, Taichung, Taiwan

Chih-Hao Lin

Department of Neurology, Tri-Service General Hospital, Taipei, Taiwan

Jiunn-Tay Lee

Department of Neurology, Cheng Hsin General Hospital, Taipei, Taiwan

Ta-Chang Lai

Department of Neurology, Shin Kong Wu Ho Su Memorial Hospital, Taipei, Taiwan

Li-Ming Lien

Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan

Mei-Chen Lin, Cheng-Li Lin

Graduate Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan

Chung Y. Hsu

References

1. Synhaeve NE, Arntz RM, Maaijwee NA, Rutten-Jacobs LC, Schoonderwaldt HC, Dorresteijn LD, de Kort PL, van Dijk EJ, de Leeuw FE. Poor long-term functional outcome after stroke among adults aged 18 to 50 years: Follow-Up of Transient Ischemic Attack and Stroke Patients and Unelucidated Risk Factor Evaluation (FUTURE) study. Stroke. 2014 Apr;45(4):1157–60.
2. Ekker MS, Verhoeven JI, Vaartjes I, Jolink WMT, Klijn CJM, de Leeuw FE. Association of Stroke Among Adults Aged 18 to 49 Years With Long-term Mortality. JAMA. 2019 Jun;4(21):2113–23. 321(.
3. Crespo Pimentel B, Willeit J, Töll T, Kiechl S, Pinho E, Melo T, Canhão P, Fonseca C, Ferro J. Etiologic Evaluation of Ischemic Stroke in Young Adults: A Comparative Study between Two European Centers. J Stroke Cerebrovasc Dis. 2019 May;28(5):1261–6.
4. Ekker MS, Boot EM, Singhal AB, Tan KS, Debette S, Tuladhar AM, de Leeuw FE. Epidemiology, aetiology, and management of ischaemic stroke in young adults. Lancet Neurol. 2018 Sep;17(9):790–801.
5. Putaala J, Haapaniemi E, Metso AJ, Metso TM, Artto V, Kaste M, Tatlisumak T. Recurrent ischemic events in young adults after first-ever ischemic stroke. Ann Neurol. 2010 Nov;68(5):661–71.
6. Shah RS, Cole JW. Smoking and stroke: the more you smoke the more you stroke. Expert Rev Cardiovasc Ther. 2010 Jul;8(7):917–32.
7. Chu NF, Lin FH, Wu YC. Prevalence and Trends of Cigarette Smoking Among.
8. Military Personnel. in Taiwan: Results of 10-Year Anti-Smoking Health.
9. Promotion Programs in Military. Mil Med. 2017 Jul;182(7):e1933-e1937. doi: 10.7205/MILMED-D-16-00361.
10. Kivioja R, Pietilä A, Martinez-Majander N, Gordin D, Havulinna AS, Salomaa V, Aarnio K, Curtze S, Leiviskä J, Rodríguez-Pardo J, Surakka I, Kaste M, Tatlisumak T, Putaala J. Risk Factors for Early-Onset Ischemic Stroke: A Case-Control Study. J Am Heart Assoc. 2018 Nov;6(21):e009774. 7(.

11. Venkatason P, Salleh NM, Zubairi Y, Hafidz I, Ahmad WA, Han SK, Zuhdi AS. The bizzare phenomenon of smokers' paradox in the immediate outcome post acute myocardial infarction: an insight into the Malaysian National Cardiovascular Database-Acute Coronary Syndrome (NCVD-ACS) registry year 2006–2013. Springerplus. 2016 Apr 26;5:534.
12. Aune E, Røislien J, Mathisen M, Thelle DS, Otterstad JE. The "smoker's paradox" in patients with acute coronary syndrome: a systematic review. BMC Med. 2011 Aug 23;9:97. doi: 10.1186/1741-7015-9-97.
13. Dasenbrock HH, Rudy RF, Rosalind Lai PM, Smith TR, Frerichs KU, Gormley WB, Aziz-Sultan MA, Du R. Cigarette smoking and outcomes after aneurysmal subarachnoid hemorrhage: a nationwide analysis. J Neurosurg. 2018 Aug;129(2):446–57. doi:10.3171/2016.10.JNS16748. Epub 2017 Oct 27.
14. Kufner A, Nolte CH, Galinovic I, Brunecker P, Kufner GM, Endres M, Fiebach JB, Ebinger M. Smoking-thrombolysis paradox: recanalization and reperfusion rates after intravenous tissue plasminogen activator in smokers with ischemic stroke. Stroke. 2013 Feb;44(2):407–13.
15. Hankey GJ. Stroke. Lancet. 2017 Feb;11(10069):641–54. 389(.
16. Hsieh FI, Lien LM, Chen ST, Bai CH, Sun MC, Tseng HP, Chen YW, Chen CH, Jeng JS, Tsai SY, Lin HJ, Liu CH, Lo YK, Chen HJ, Chiu HC, Lai ML, Lin RT, Sun MH, Yip BS, Chiou HY, Hsu CY. Taiwan Stroke Registry Investigators. Get With the Guidelines-Stroke performance indicators: surveillance of stroke care in the Taiwan Stroke Registry: Get With the Guidelines-Stroke in Taiwan. Circulation. 2010 Sep;14(11):1116–23. 122(.
17. Wang IK, Liu CH, Yen TH, Jeng JS, Hsu SP, Chen CH, Lien LM, Lin RT, Chen AC, Lin HJ, Chi HY, Lai TC, Sun Y, Lee SP, Sung SF, Chen PL, Lee JT, Chiang TR, Lin SK, Muo CH, Ma H, Wen CP, Sung FC, Hsu CY. Taiwan Stroke Registry Investigators. Cholesterol Levels Are Associated with 30-day Mortality from Ischemic Stroke in Dialysis Patients. J Stroke Cerebrovasc Dis. 2017 Jun;26(6):1349–56.
18. Wang IK, Liu CH, Yen TH, Jeng JS, Sung SF, Huang PH, Li JY, Sun Y, Wei CY, Lien LM, Tsai IJ, Sung FC, Hsu CY. Taiwan Stroke Registry Investigators. Renal function is associated with 1-month and 1-year mortality in patients with ischemic stroke. Atherosclerosis. 2018 Feb;269:288–93.
19. Wen CP, Liu CH, Jeng JS, Hsu SP, Chen CH, Lien LM, Chen AC, Lee JT, Chen PK, Hsu CS, Chern CM, Chen CC, Hsu MC, Lu K, Chen HJ, Wang HK, Muo CH, Hsu CY. Pre-stroke physical activity is associated with fewer post-stroke complications, lower mortality and a better long-term outcome. Eur J Neurol. 2017 Dec;24(12):1525–31. doi:10.1111/ene.13463. Epub 2017 Oct 16.
20. Lutski M, Zucker I, Shohat T, Tanne D. Characteristics and Outcomes of Young Patients with First-Ever Ischemic Stroke Compared to Older Patients: The National Acute Stroke ISraeli Registry. Front Neurol. 2017 Aug;21:8:421.
21. Hiraga A. Gender Differences and Stroke Outcomes. Neuroepidemiology. 2017;48(1–2):61–2.
22. Fraticelli L, Freyssenge J, Claustre C, Buisson M, Bischoff M, Nighoghossian N, Derex L, El Khoury C, on behalf of the RESUVal Group. Sex-Related Differences in Management and Outcome of Acute Ischemic Stroke in Eligible Patients to Thrombolysis. Cerebrovasc Dis. 2019;47(3–4):196–204.
23. Giroud M, Delpont B, Daubail B, Blanc C, Durier J, Giroud M, Béjot Y. Temporal Trends in Sex Differences With Regard to Stroke Incidence: The Dijon Stroke Registry (1987–2012). Stroke. 2017 Apr;48(4):846–9.
24. Förster A, Gass A, Kern R, Wolf ME, Ottomeyer C, Zohsel K, Hennerici M, Szabo K. Gender differences in acute ischemic stroke: etiology, stroke patterns and response to thrombolysis. Stroke. 2009

Jul;40(7):2428–32.
25. Appelros P, Stegmayr B, Terént A. Sex differences in stroke epidemiology: a systematic review. Stroke. 2009 Apr;40(4):1082–90.
26. Sanna M, Gao W, Chiu YW, Chiou HY, Chen YH, Wen CP, Levy DT. Tobacco control within and beyond WHO MPOWER: outcomes from Taiwan SimSmoke. Tob Control. 2018 Nov 5.
27. Huang WH, Hsu HY, Chang BC, Chang FC. Factors Correlated with Success Rate of Outpatient Smoking Cessation Services in Taiwan. Int J Environ Res Public Health. 2018 Jun 10;15(6).
28. Wen CP, Cheng TY, Lin CL, Wu HN, Levy DT, Chen LK, Hsu CC, Eriksen MP, Yang HJ, Tsai SP. The health benefits of smoking cessation for adult smokers and for pregnant women in Taiwan. Tob Control. 2005 Jun;14(Suppl 1):i56–61.
29. Bak S, Sindrup SH, Alslev T, Kristensen O, Christensen K, Gaist D. Cessation of smoking after first-ever stroke: a follow-up study. Stroke. 2002 Sep;33(9):2263–9.
30. Tang SC, Yin JH, Liu CH, Sun MH, Lee JT, Sun Y, Hsu CS, Sun MC, Lin CH, Chen CH, Lien LM, Muo CH, Jeng JS, Hsu CY. Taiwan Stroke Registry Investigators. Low Pulse Pressure After Acute Ischemic Stroke is Associated With Unfavorable Outcomes: The Taiwan Stroke Registry. J Am Heart Assoc. 2017 Jun 22;6(6).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SUPPLEMENTALMATERIAL.docx