

Smoking is Not a Good Prognostic Factor following First-Ever Acute Ischemic Stroke

Ju-Hun Lee, Ju Young Lee, So Hyun Ahn, Min Uk Jang, Mi Sun Oh, Chul-Ho Kim, Kyung-Ho Yu, Byung-Chul Lee

Department of Neurology, Hallym University Medical Center, Hallym Neurological Institute, Hallym University College of Medicine, Anyang, Korea

Background and Purpose There is evidence that smoking increases stroke risk; however, the effect of smoking on functional outcome after stroke is unclear. The aim of this study was to explore the effect of smoking status on outcome following acute ischemic stroke.

Methods We assessed 1,117 patients with first-ever acute cerebral infarction and no pre-stroke disability whose functional outcome was measured after three months. A poor outcome was defined as a modified Rankin Scale score of ≥ 2 . Smoking within one month prior to admission was defined as current smoking. Our analysis included demographics, vascular risk factors, initial National Institutes of Health Stroke Scale (NIHSS) score, stroke subtype, onset-to-admission time, thrombolytic therapy, initial blood pressure, and prognostic blood parameters as covariates.

Results At baseline, current smokers were predominantly male, approximately 10 years younger than non-smokers (mean age, 58.6 vs. 68.3 years), and less likely to have hypertension and atrial fibrillation (53.9% vs. 65.4% and 8.7% vs. 25.9%, respectively), with a lower mean NIHSS score (4.6 vs. 5.7). The univariate analyses revealed that current smokers had a better functional outcome and significantly fewer deaths at three months follow-up when compared with non-smokers (functional outcome: 64.0% vs. 58.4%, $P=0.082$; deaths: 3.0% vs. 8.4%, $P=0.001$); however, these effects disappeared after adjusting for covariates ($P=0.168$ and $P=0.627$, respectively).

Conclusions In this study, smoking was not associated with a good functional outcome, which does not support the paradoxical benefit of smoking on functional outcome following acute ischemic stroke.

Keywords Smoking; Acute ischemic stroke; Prognosis

Introduction

Smoking is a modifiable and established risk factor for stroke.^{1,2} The age-standardized prevalence of current smoking in Korean adults is substantially high when compared with the US population, in particular in men (48.1% of Korean men vs. 21.2% of US men).^{3,4} The population attributable risk of smoking for stroke is also high in Korean men (26.5%).⁵ Therefore, antismoking cam-

paigns are an important health-related intervention for stroke prevention in Korea.

Despite the increased risk of stroke from smoking, there is debate regarding its effect on functional outcome following acute ischemic stroke. Current smoking prior to stroke is a poor⁶⁻⁸ or neutral prognostic factor according to the results of some studies.⁹⁻¹³ Surprisingly, smoking has been reported as a beneficial prognostic factor in acute ischemic stroke.¹⁴⁻¹⁷ It is postulated that

Correspondence: Byung-Chul Lee
Department of Neurology, Hallym Neurological Institute, 22 Gwanpyeong-ro 170 beon-gil, Anyang 431-796, Korea
Tel: +82-31-380-3741
Fax: +82-31-381-4659
Email: ssbrain@hallym.ac.kr

Received: January 15, 2015
Revised: March 24, 2015
Accepted: March 25, 2015

This study was supported by a grant from the Korea Health 21 R&D Project, Ministry of Health, Welfare and Family Affairs, Republic of Korea (HI10C2020).

The authors have no financial conflicts of interest.

chronic exposure to smoking or nicotine may promote angiogenesis or ischemic preconditioning with enhanced collateral flows. In addition, there might be a greater susceptibility to spontaneous or therapeutic thrombolysis of cerebral thrombi in smokers.

Due to these conflicting results, we aimed to explore whether cigarette smoking was independently associated with the functional outcome of patients after acute ischemic stroke using our prospective registry database. In addition, we investigated whether any smoking effect differed across subgroups, including ischemic stroke subtypes.

Methods

Study design and subjects

Subjects were consecutive patients with first-ever ischemic stroke and without previous functional disability (modified Rankin Scale [mRS] score > 1) who were admitted to Hallym University Medical Center within 7 days of symptom onset between October 2007 and July 2012. The data were populated from the Hallym Stroke Registry, a prospective hospital-based stroke database. The Institutional Review Board of Hallym University Medical Center approved the stroke registry and waiver of informed consent from registered patients. Patient information was anonymized and de-identified prior to analysis. Of the 1,248 patients who met our inclusion criteria, we excluded 131 patients (10.5%) because they did not have 3-month functional outcome data. Therefore, 1,117 subjects were included in the outcome analysis.

Smoking status and covariate factors

We defined current smokers as those with any history of smoking within one month prior to index stroke. We subdivided non-smokers into former-smokers and never-smokers. Former-smokers did not smoke at least one month before the index stroke and never-smokers were those with no smoking history.

We included the following covariates in our analysis: demographics, body mass index (BMI), vascular risk factors, initial National Institutes of Health Stroke Scale (NIHSS) score, stroke subtype (according to Trial of ORG 10172 in Acute Stroke Treatment [TOAST] criteria), onset-to-admission time, tissue plasminogen activator (tPA) therapy, mean value of initial systolic blood pressure (systolic BP), and prognostic blood parameters including blood glucose, low density lipoprotein (LDL) cholesterol, white blood cell (WBC) count, and hemoglobin count. Blood glucose and LDL cholesterol were measured in a fasting state during the first morning after admission.

Hypertension was assigned based on the presence of one or more of the following: history of hypertension and antihyperten-

sive medication, repeated BP measurements > 140/90 mmHg at 1 week intervals, or evidence of hypertensive damage on echocardiogram. Diabetes was assigned if there was a history of diabetes mellitus while also receiving anti-hyperglycemic therapy, fasting blood glucose level > 126 mg/dL, or postprandial blood glucose level > 200 mg/dL. Hyperlipidemia was assigned if there was a history of hyperlipidemia with concurrent pharmacotherapy or fasting LDL cholesterol level > 160 mg/dL (or total cholesterol > 240 mg/dL if LDL was not available).

Outcome assessment

Functional outcome and death were assessed at three months after stroke through face-to-face or telephone interview with patients or caregivers. Functional outcome was measured by mRS. A poor functional outcome was defined as an mRS score \geq 2.

Statistical analysis

We compared the baseline characteristics of current smokers with non-smokers, former-smokers, and never-smokers (Table 1). We also compared the baseline characteristics of patients with a 3 month post-stroke mRS score available and those lost to follow-up (Supplementary Table 1). The χ^2 test and *t* test were used for categorical and continuous variables, respectively. NIHSS scores were split into quartiles. We divided BMI into high (\geq 25 kg/m²), normal (< 25 but > 20 kg/m²), and low BMI (\leq 20 kg/m²).

Univariate and binary logistic regression analyses were used to determine the association between smoking status and functional outcome at three months. All variables in the univariate analysis were included in the multivariate analysis because they were potential prognostic factors. Small vessel disease was regarded as the reference among stroke subtypes. Those with undetermined and other determined stroke subtypes were not included in the univariate and multivariate analyses.

We also evaluated the effect of smoking through subgroup analysis of sex, age, stroke subtype, risk factors (hypertension, diabetes mellitus, hyperlipidemia, and atrial fibrillation), BMI, and tPA therapy.

We excluded the cases with missing data from all analyses. The significance level was set at $P < 0.05$ for all statistical analyses.

Results

Baseline characteristics

The 1,117 patients included 639 men (57.2%) and 487 women with a mean age of 65.3 (\pm 13.5) years. Median NIHSS was 3 (interquartile range 1-7). Mean onset-to-admission time was 28.6 (\pm 37.1) hours. Data for atrial fibrillation were missing in 3

Table 1. Baseline characteristics according to smoking habit

Parameters	Current smokers n=336	Non-smokers n=777	Pvalue	Former smokers n=126	Pvalue*	Never-smokers n=651	Pvalue†
Onset-to-admission time (hour), (mean±SD)	28.6±37.2	28.6±37.2	0.974	23.9 (30.5)	0.167	29.5±38.3	0.749
Males, n (%)	308 (91.7)	328 (42.2)	<0.001	119 (94.4)	0.315	209 (32.1)	<0.001
Age (mean±SD)	58.6±12.8	68.3±12.7	<0.001	67.1 (11.4)	<0.001	68.5±12.9	<0.001
Body mass index (kg/m ²), (mean±SD)	23.7±3.0	23.7±3.3	0.821	24.2 (3.1)	0.098	23.6±3.3	0.833
High BMI (≥25), n (%)	108 (32.9)	246 (32.7)	0.988	45 (36.9)	0.670	201 (31.9)	0.913
Normal BMI, n (%)	187 (57.0)	428 (56.9)		67 (54.9)		361 (57.3)	
Low BMI (<20), n (%)	33 (10.1)	78 (10.4)		10 (8.2)		68 (10.8)	
Hypertension, n (%)	181 (53.9)	508 (65.4)	<0.001	85 (67.5)	0.008	423 (65.0)	<0.001
Diabetes Mellitus, n (%)	99 (29.5)	230 (29.6)	0.963	41 (32.5)	0.522	189 (29.0)	0.999
Hyperlipidemia, n (%)	107 (31.8)	225 (29.0)	0.334	42 (33.3)	0.761	183 (28.1)	0.427
Atrial fibrillation, n (%)	29 (8.7)	201 (25.9)	<0.001	27 (21.6)	<0.001	174 (26.8)	<0.001
Stroke subtype, n (%)							
Large artery disease	123 (36.6)	215 (27.7)	<0.001	42 (33.3)	0.034	173 (26.6)	<0.001
Small vessel disease	121 (36.0)	238 (30.6)		32 (25.4)		206 (31.6)	
Cardioembolism	46 (13.7)	196 (25.2)		23 (18.3)		173 (26.6)	
Undetermined	28 (8.4)	81 (10.4)		19 (15)		62 (9.5)	
Other determined	18 (5.4)	47 (6.0)		10 (7.9)		37 (5.7)	
Received tPA thrombolysis, n (%)	25 (7.4)	67 (8.6)	0.511	15 (11.9)	0.129	52 (8.0)	0.827
Initial NIHSS score (mean±SD)	4.6 (4.9)	5.7 (6.5)	0.001	6.2 (6.2)	0.010	5.7 (6.6)	0.005
Initial NIHSS ≤1	99 (29.5)	231 (29.7)	0.003	32 (25.4)	0.025	199 (30.6)	0.005
2-3	95 (28.3)	202 (26.0)		32 (25.4)		170 (26.1)	
4-8	88 (26.2)	150 (19.3)		26 (20.6)		124 (19.0)	
≥9	54 (16.1)	194 (25.0)		36 (28.6)		158 (24.3)	
Initial systolic BP (mean±SD)	144.5±24.9	142.0±23.6	0.103	145.1 (20.9)	0.828	141.4±24.0	0.054
Initial blood parameters (mean±SD)							
Fasting glucose (mg/dL)	121.5±52.3	117.3±46.0	0.222	119.4 (63.8)	0.728	116.9±41.7	0.149
LDL - cholesterol (mg/dL)	119.1±35.5	115.2±36.5	0.101	112.2 (37.6)	0.068	115.8±36.3	0.174
WBC (/mm ³)	8,675.7±2784.7	8,030.3±3052.8	0.001	8,480.8 (3094.9)	0.516	7,943.0±3029.3	<0.001
Hemoglobin (g/dL)	14.5 (1.8)	13.3 (1.8)	<0.001	14.0 (1.9)	0.004	13.2 (1.8)	<0.001

In these analysis, there were missing data for atrial fibrillation in 3 patients (0.3%), smoking status in 4 (0.36%), BMI in 33 (3.0%), WBC in 1 (0.1%), LDL-C in 22 (2.0%), and fasting glucose in 98 (8.8%) patients.

*current smokers vs. former smokers; †current smokers vs. never-smokers.

BMI, body mass index; BP, blood pressure; LDL, low density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator; WBC, white blood cell.

(0.3%), smoking status in 4 (0.36%), BMI in 33 (3.0%), WBC in 1 (0.1%), LDL-C in 22 (2.0%), and fasting glucose in 98 (8.8%) patients.

The study participants included 336 current smokers (30.2%), 126 former-smokers (11.3%), and 651 never-smokers (58.5%). Each group had significantly different baseline characteristics. Current smokers were mostly male and younger than former-smokers or never-smokers. Atrial fibrillation and cardioembolic stroke were significantly less frequent in current smokers than in former-smokers or never-smokers. Detailed comparisons of the baseline characteristics of the groups are presented in Table 1.

Smoking status was not significantly different between end-point patients and those lost to follow-up. However, lost to follow-up patients had more severe strokes (higher mean initial NIHSS score) and had longer onset-to-admission times (Supplementary Table 1).

Smoking status and initial stroke severity

Initial mean NIHSS score was lower in current smokers than in former-smokers or never-smokers (Table 1). Figure 1 shows the frequency distribution of the quartiles of NIHSS scores in current smokers and non-smokers. Interestingly, the multivariate analysis revealed that current smoking was an independent predictor of severe stroke (defined as an NIHSS score of ≥4, Table 2). When we defined severe stroke as an NIHSS score of ≥6, current smoking remained as a significant predictor of severe stroke (Supplementary Table 2).

Smoking status and functional outcomes

The univariate analysis showed that current smoking status was more frequent among patients with a good functional outcome than in those with a poor outcome (32.1% vs. 27.3%, $P=0.082$). A good functional outcome was more common in current smokers than non-smokers: 64.0% (215/336) of cur-

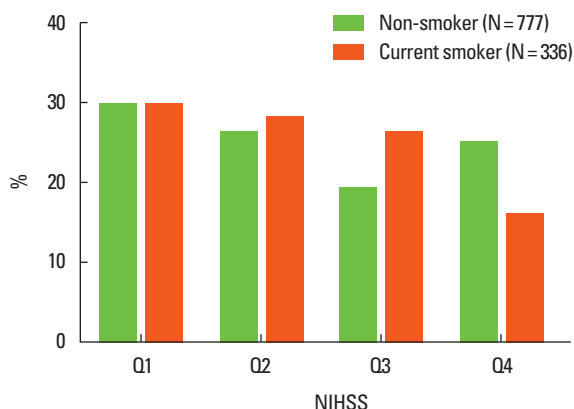


Figure 1. The frequency distribution of the quartiles of NIHSS scores in current smokers and in non-smokers.

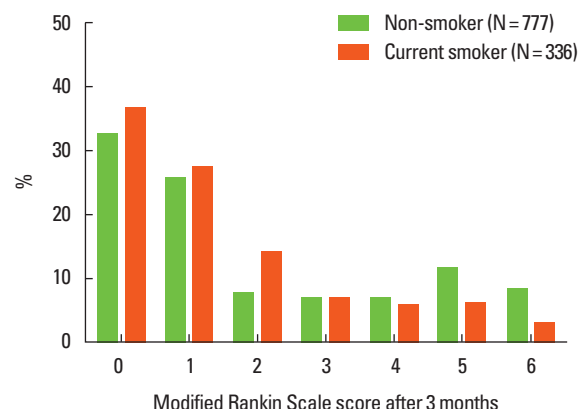


Figure 2. The frequency distribution of mRS scores in current smokers and in non-smokers.

Table 2. Factors associated with severe stroke (\geq NIHSS 4) in the multivariate analysis

Parameters	Model 1			Model 2		
	Adjusted OR	95% CI	Pvalue	Adjusted OR	95% CI	Pvalue
Onset-to-admission time, per 10 hours	0.91	0.87 0.95	<0.001	0.91	0.87 0.95	<0.001
Demographics						
Sex: males	0.59	0.43 0.83	0.002	0.51	0.35 0.74	<0.001
Age, per 10 years	1.18	1.04 1.35	0.009	1.18	1.04 1.34	0.011
Body mass index (kg/m²)						
High BMI (\geq 25)	0.63	0.45 0.86	0.004	0.62	0.45 0.86	0.004
Normal BMI				ref.		
Low BMI (<20)	1.11	0.69 1.78	0.680	1.09	0.68 1.76	0.725
Smoking status						
Current smoker	1.65	1.15 2.38	0.007			
Non-smoker	ref.					
Current smoker				1.65	0.97 2.82	0.001
Former smoker				1.92	1.28 2.87	0.065
Never-smoker				ref.		
Vascular risk factors						
Hypertension	1.12	0.82 1.52	0.487	1.10	0.81 1.50	0.532
Diabetes mellitus	1.54	1.12 2.11	0.007	1.56	1.13 2.13	0.006
Hyperlipidemia	0.97	0.71 1.33	0.852	0.96	0.70 1.32	0.802
Atrial fibrillation	1.90	1.00 3.63	0.051	1.93	1.01 3.70	0.046
Stroke subtype						
Small vessel disease				ref.		
Large artery disease	2.20	1.57 3.06	<0.001	2.18	1.56 3.05	<0.001
Cardioembolism	2.35	1.28 4.31	0.006	2.38	1.30 4.36	0.005

In Model 1, current smokers were compared with non-smokers. In Model 2, current smokers and former smokers were compared with never-smokers. NIHSS, National Institutes of Health Stroke Scale; BMI, body mass index.

rent smokers and 58.4% (454/777) of non-smokers (57.9% [73/126] of former-smokers and 58.5% [381/651] of never-smokers) had a good functional outcome. However, these differences were not statistically significant. Figure 2 shows the frequency distribution of the mRS scores in current smokers and non-smokers.

The percentage of smokers was lower among the patients who died within three months compared with that in the survivor group (13.3% vs. 31.4%, $P=0.001$). In particular, 3-month mor-

tality was higher in non-smokers than in current smokers: 8.4% (65/777) vs. 3.0% (10/336).

Other parameters, including age, sex, BMI, vascular risk factors, initial NIHSS score, stroke subtype, onset-to-admission time, tPA therapy, mean value of initial systolic BP, and blood parameters were primarily associated with patients' outcomes. The results of the univariate analysis are described in Supplementary Tables 3 and 4.

In the multivariate analysis, smoking status was not associat-

Table 3. Factors associated with poor functional outcome (MRS 2-6) in the multivariate analysis

Parameters	Model 1			Model 2		
	Adjusted OR	95% CI	Pvalue	Adjusted	95% CI	Pvalue
Onset-to-admission time, per 10 hours	0.98	0.93 1.03	0.390	0.98	0.93 1.03	0.409
Demographics						
Sex: males	0.66	0.43 1.00	0.052	0.58	0.37 0.93	0.024
Age, per 10 years	1.17	1.01 1.37	0.041	1.17	1.00 1.36	0.046
Body mass index (kg/m ²)						
High BMI (≥ 25)	0.66	0.45 0.97	0.036	0.66	0.45 0.97	0.033
Normal BMI	ref.			ref.		
Low BMI (< 20)	0.81	0.45 1.43	0.461	0.80	0.45 1.42	0.440
Smoking status						
Current smoker	1.36	0.88 2.11	0.168			
Non-smoker	ref.					
Current smoker				1.53	0.95 2.48	0.083
Former smoker				1.48	0.78 2.82	0.234
Never-smoker				ref.		
Vascular risk factors						
Hypertension	0.88	0.61 1.29	0.515	0.88	0.60 1.28	0.494
Diabetes mellitus	0.90	0.59 1.38	0.622	0.90	0.59 1.38	0.638
Hyperlipidemia	0.68	0.46 1.02	0.062	0.68	0.45 1.02	0.060
Atrial fibrillation	0.82	0.36 1.83	0.620	0.82	0.37 1.84	0.632
Initial NIHSS ≤ 1						
2-3	1.54	0.95 2.50	0.081	1.53	0.94 2.48	0.088
4-8	4.86	2.98 7.94	<0.001	4.80	2.93 7.84	<0.001
≥ 9	16.66	8.98 30.93	<0.001	16.46	8.86 30.57	<0.001
Stroke subtype						
Small vessel disease	ref.		ref.	ref.		
Large artery disease	1.79	1.19 2.69	0.005	1.78	1.18 2.68	0.006
Cardioembolism	1.85	0.86 3.98	0.113	1.88	0.87 4.03	0.106
Received tPA thrombolysis	0.39	0.20 0.76	0.006	0.39	0.20 0.76	0.006
Initial systolic BP, per 10 mmHg	1.04	0.97 1.12	0.284	1.04	0.96 1.12	0.303
Initial blood parameters						
Fasting glucose, per 10 mg/dL	1.05	1.00 1.09	0.034	1.05	1.00 1.09	0.032
LDL-cholesterol, per 10 mg/dL	1.02	0.97 1.07	0.476	1.02	0.97 1.07	0.490
WBC, per 1,000/mm ³	1.05	0.98 1.11	0.152	1.05	0.98 1.11	0.157
Hemoglobin, per 1 g/dL	0.98	0.88 1.09	0.667	0.98	0.88 1.09	0.688

In Model 1, current smokers were compared with non-smokers. In Model 2, current smokers and former smokers were compared with never-smokers. All variables in the univariate analysis were included in the multivariate analysis.

BMI, body mass index; BP, blood pressure; LDL, low density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator; WBC, white blood cell.

ed with functional outcome and death. Age, initial high stroke severity, large artery disease, high fasting blood glucose, and WBC count were independent prognostic factors for a poor outcome. Male gender, high BMI, and tPA therapy were good prognostic factors (Tables 3 and 4).

Effect of smoking status in the subgroups

In most subgroups, the functional outcome was not significantly different between current smokers and non-smokers (Figure 3 and Supplementary Table 5); however, current smoking was associated with a poor functional outcome in patients treated with tPA therapy and with a low BMI ($P=0.036$ and $P=0.031$, respectively; Supplemental Table 5).

Discussion

The baseline characteristics of patients experiencing acute ischemic stroke were significantly different according to smoking status. Current smokers were predominantly young and male with a relatively benign baseline. A history of hypertension and atrial fibrillation were less frequent when compared with non-smokers. In addition, initial stroke severity was milder in current smokers. However, after adjustment for confounding variables, current smoking was independently associated with severe stroke. In the univariate analyses revealed that smokers displayed a good functional outcome and significantly less mortality within three months when compared with non-smokers;

Table 4. Factors associated with 3-month death in the multivariate analysis

Parameters	Model 1				Model 2			
	Adjusted OR	95% CI		Pvalue	Adjusted OR	95% CI		Pvalue
Onset-to-admission time, per 10 hours	0.86	0.71	1.03	0.109	0.85	0.71	1.03	0.107
Demographics								
Sex: males	1.19	0.48	2.95	0.710	0.94	0.33	2.66	0.906
Age, per 10 years	2.72	1.71	4.33	0.000	2.74	1.71	4.38	0.000
Body mass index (kg/m ²)								
High BMI (≥ 25)	1.09	0.42	2.85	0.859	1.07	0.41	2.82	0.884
Normal BMI	ref.				ref.			
Low BMI (< 20)	0.50	0.15	1.66	0.256	0.46	0.14	1.56	0.213
Smoking status								
Current smoker	1.34	0.41	4.34	0.627				
Non-smoker	ref.							
Current smoker					1.73	0.47	6.34	0.411
Former smoker					1.88	0.53	6.75	0.330
Never-smoker					ref.			
Vascular risk factors								
Hypertension	0.80	0.32	1.99	0.628	0.77	0.31	1.93	0.575
Diabetes mellitus	0.46	0.17	1.24	0.124	0.50	0.18	1.36	0.175
Hyperlipidemia	0.54	0.17	1.64	0.273	0.51	0.16	1.59	0.247
Atrial fibrillation	0.47	0.08	2.79	0.405	0.46	0.07	2.77	0.393
Initial NIHSS ≤ 1								
2-3	3.58	0.33	38.80	0.294	3.60	0.33	39.33	0.293
4-8	4.86	0.49	48.08	0.176	4.87	0.49	48.49	0.177
≥ 9	17.87	2.07	154.18	0.009	17.87	2.05	155.64	0.009
Stroke subtype								
Small vessel disease	ref.				ref.			
Large artery disease	1.78	0.40	7.98	0.448	1.71	0.38	7.73	0.484
Cardioembolism	4.02	0.46	35.60	0.211	4.20	0.47	37.63	0.199
Received tPA thrombolysis	0.80	0.26	2.45	0.698	0.80	0.26	2.47	0.703
Initial systolic BP, per 10 mmHg	1.08	0.92	1.26	0.354	1.07	0.91	1.26	0.410
Initial blood parameters								
Fasting glucose, per 10 mg/dL	1.10	1.02	1.17	0.010	1.09	1.02	1.17	0.016
LDL-cholesterol, per 10 mg/dL	1.11	0.98	1.25	0.109	1.10	0.98	1.25	0.113
WBC, per 1,000/mm ³	1.16	1.03	1.30	0.014	1.15	1.02	1.30	0.018
Hemoglobin, per 1 g/dL	0.81	0.66	1.01	0.057	0.82	0.66	1.01	0.062

In Model 1, current smokers were compared with non-smokers. In Model 2, current smokers and former smokers were compared with never-smokers. All variables in the univariate analysis were included in the multivariate analysis.

BMI, body mass index; BP, blood pressure; LDL, low density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator; WBC, white blood cell.

however, smoking status was not independently related with functional outcome after adjustment for demographics and other prognostic indicators. These results were consistent in subgroups that were stratified by gender and stroke subtype.

The baseline profile of smokers in our study corresponded well to the results from previous studies.^{6,8-10,12-14,17} The younger mean age in smokers may be associated with smokers having strokes at an earlier age than non-smokers. Cigarette smoking is known to be an independent risk factor for atrial fibrillation and hypertension.^{18,19} However, as with previous studies,^{6,8-10,12,14,17} our research reported a lower prevalence of atrial fibrillation and hypertension in current smokers with acute ischemic stroke when compared with non-smokers. Our univariate analysis showed a milder

stroke severity in current smokers compared with non-smokers. This might be attributed to the lower frequency of atrial fibrillation (thereby low prevalence of cardioembolic stroke) in current smokers than that in non-smokers. These counterintuitive findings can be partially explained by a selective survival bias and demographic differences; atrial fibrillation and hypertension may be less frequent in current smokers because they are approximately 10 years younger than non-smokers in our study. In addition, patients with vascular risk factors may be less inclined to smoke as they have encountered non-smoking education or counseling more often. Other unmeasured confounding factors may be involved in different baseline characteristics that are related to smoking status. Other unidentified health problems may

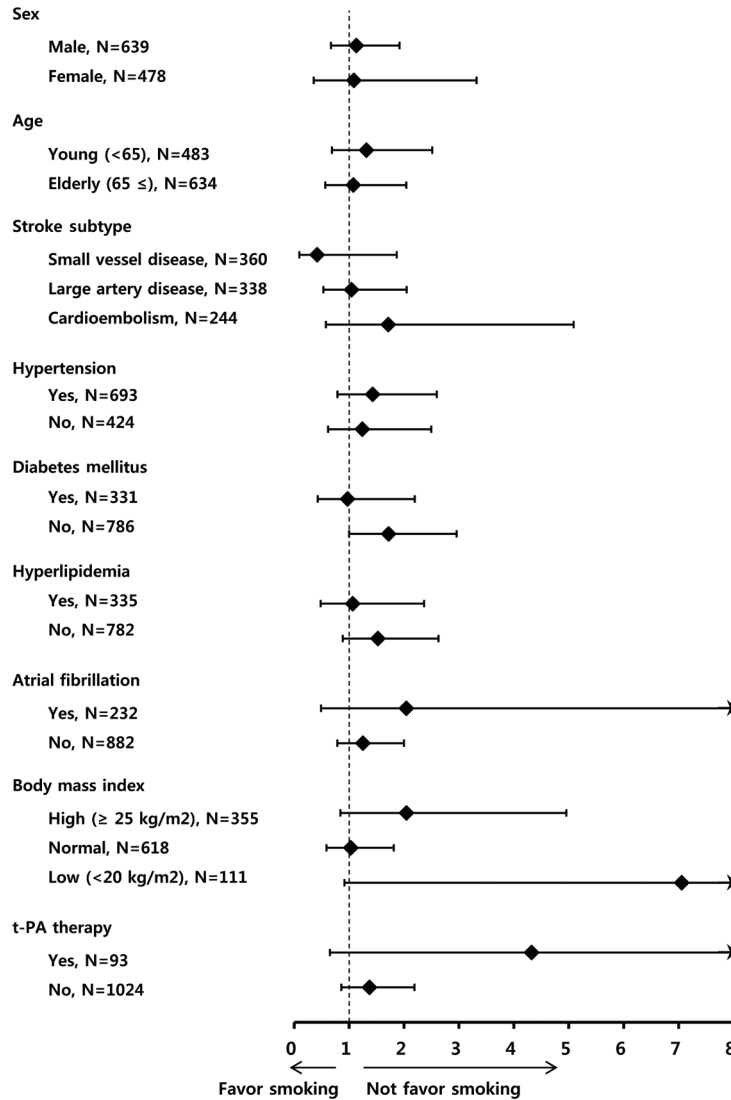


Figure 3. The effect of current smoking on functional outcome in different subgroups (current smoker versus non-smoker). The diamond represents the point estimate of the adjusted odds ratio and the horizontal line represents the 95 percent confidence intervals. Poor functional outcome was defined as modified Rankin Scale score of ≥ 2 , measured at three months after stroke. All variables in the main analysis were included as confounders in this subgroup analysis.

exist that are underlying drivers of non-smoking behavior. It is a more reasonable hypothesis that health-related behavior modification or health-seeking behavior is driving these findings rather than the presence of a protective effect of smoking.

The variables that are known to be potential prognostic factors required careful statistical analysis as there was a wide discrepancy between the baseline characteristics of the different groups. In both our study and the literature, there are some important limitations in performing this task; despite including a considerable number of well-known prognostic factors in the multivariable analysis, unmeasured confounding variables may contribute to erroneous conclusions. We believe that the utility of using smoking as a prognostic tool is controversial as it may be largely attributed to unaccounted confounding variables.

Socioeconomic status is likely to be an important confounder that has not been measured in this study. Low socioeconomic status may be a predictor of poor outcome after stroke.²⁰ Most previous studies have not included socioeconomic status in multivariable analyses.⁷⁻¹⁷ Kim et al.⁶ included socioeconomic status when analyzing the effect of baseline smoking status on the long-term risk of a poor outcome (first vascular event or death) in stroke patients. Although the univariate analysis showed that smokers have a better outcome than people who have never smoked ($P=0.03$), they had a greater risk of a poor outcome in the multivariate analysis ($P=0.003$). In addition, changes in smoking habits after the index stroke may affect stroke outcome. These were not evaluated in our research or previous studies.^{6-13,15-17} Although little is known about the effects of smoking cessation on short-term

stroke recovery, smoking cessation as a long-term protective measure with respect to mortality and cardiovascular events is well defined.^{21,22} Current smokers with mild or no disability may continue smoking compared with those who experienced severe stroke,²³ which may affect the functional outcome. Moreover, smoking habits can be affected by previous stroke or functional status, which may be an important confounding factor.^{15,23} In previous studies, smokers are less likely to report a history of prior strokes than non-smokers (20.6% vs. 33.8%);¹⁵ therefore, we only included patients with first-ever stroke and no functional disability to exclude their confounding effects. However, many previous studies did not exclude or adjust for these factors in the multivariate analysis.^{7,8,10,12,13,16,17}

Two previous studies have shown that patients with thrombolytic therapy experience a paradoxical short-term benefit of smoking.^{16,17} Smoking was associated with either improved recanalization¹⁶ or short-term improvement of stroke severity.¹⁷ The authors of these studies have hypothesized that smokers may have thrombi with more dissoluble characteristics. Nevertheless, smoking status was not associated with the functional outcome at three months. No association between baseline smoking status and functional outcome is reproduced in other studies.^{9,12} In these studies, despite an association with good outcomes in descriptive or univariate analyses, current smoking was not independently associated with the functional outcome after adjusting for confounding variables. In our subgroup analysis, smokers with thrombolytic therapy tended to have a poorer outcome than non-smokers; however, the false positive rates associated with the application of multiple statistical tests may be high; the probability of one or more false positive findings when 9 subgroup tests are performed is about 40 percent.²⁴ Despite this limitation, our finding suggested that smoking might not predict improved functional outcome after thrombolytic therapy, irrespective of a reported high recanalization rate.¹⁶

A previous study has discussed the differing prognostic effect of smoking in relation to stroke subtypes: smoking is found to be beneficial only in atherosclerotic stroke.¹⁵ In contrast, another study has shown that male smokers with acute atherosclerotic stroke have an increased risk of a poor 90-day functional outcome, independent of other variables.⁷ Smoking was not independently associated with the functional outcome in atherosclerotic stroke in our subgroup analysis. The effect of smoking on functional outcome according to stroke subtypes needs to be further studied.

Our study has limitations. First, there may be a selection bias as patients lost to follow-up were excluded. These patients may have a poor functional outcome; in our data, this group had greater initial stroke severity and higher glucose levels (Supplementary Ta-

ble 1), which are well known poor prognostic factors. Nevertheless, smoking status between the included and excluded (patients lost to follow-up) patients were not significantly different in our study (Supplementary Table 1); therefore, excluding these data would not significantly affect our study findings. Second, similar to many previous studies, it was not possible to analyze the dose effect of smoking because detailed information about quantity and potency was not available. Moreover, given that the risk of cardiovascular events increases with the number of cigarettes smoked, the impact of smoking on stroke outcome is likely to differ between light and heavy smokers.^{1,2,25} This effect needs to be explored in more detail. Third, there were some missing data in our study, in particular the fasting blood glucose levels and body mass index. These omissions were random because most baseline characteristics, such as smoking status and initial stroke severity were not different relative to the presence of blood parameters (Supplementary Table 6). Fourth, although we included only patients without prior stroke or functional disability, smokers are likely to have other medical problems, such as coronary artery and pulmonary disease. These medical problems may contribute to the functional outcome after stroke. Unfortunately, we were not able to adjust for these potential confounding factors.

Conclusions

In this study, smoking was not associated with a good functional outcome. This does not support the paradoxical benefit of smoking on functional outcome following acute ischemic stroke, which might be attributed to unmeasured confounding variables.

Acknowledgments

We thank Dr. Sean Hashemi (Department of Otolaryngology, Head and Neck Surgery, Boston University Medical Center, 820 Harrison Blvd, FGH 4th Floor, Boston, MA USA 02118, email: Sean.Hashemi@bu.edu) for helping us prepare this manuscript.

References

1. Kondo T, Osugi S, Shimokata K, Honjo H, Morita Y, Maeda K, et al. Smoking and smoking cessation in relation to all-cause mortality and cardiovascular events in 25,464 healthy male Japanese workers. *Circ J* 2011;75:2885-2892.
2. Wolf PA, D'Agostino RB, Kannel WB, Bonita R, Belanger AJ. Cigarette smoking as a risk factor for stroke. The Framingham Study. *JAMA* 1988;259:1025-1029.
3. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Bor-

- den WB, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation* 2013; 127:e6-e245.
4. Hong KS, Bang OY, Kang DW, Yu KH, Bae HJ, Lee JS, et al. Stroke statistics in Korea: part I. Epidemiology and risk factors: a report from the Korean stroke society and clinical research center for stroke. *J Stroke* 2013;15:2-20.
 5. Park TH, Kim MK, Lee KB, Park JM, Lee SJ, Jung KH, et al. Population Attributable Risk of Major Risk Factors for Ischemic Stroke in the Korean Population. *Korean J Stroke* 2008; 10:125-133.
 6. Kim J, Gall SL, Dewey HM, Macdonell RA, Sturm JW, Thrift AG. Baseline smoking status and the long-term risk of death or nonfatal vascular event in people with stroke: a 10-year survival analysis. *Stroke* 2012;43:3173-3178.
 7. Kumagai N, Okuhara Y, Iiyama T, Fujimoto Y, Takekawa H, Origasa H, et al. Effects of smoking on outcomes after acute atherothrombotic stroke in Japanese men. *J Neurol Sci* 2013; 335:164-168.
 8. Ovbiagele B, Weir CJ, Saver JL, Muir KW, Lees KR. Effect of smoking status on outcome after acute ischemic stroke. *Cerebrovasc Dis* 2006;21:260-265.
 9. Aries MJ, Uyttenboogaart M, Koch MW, Langedijk M, Vroomen PC, Luijckx GJ, et al. Does smoking influence outcome after intravenous thrombolysis for acute ischaemic stroke? *Eur J Neurol* 2009;16:819-822.
 10. Edjoc RK, Reid RD, Sharma M, Fang J, Registry of the Canadian Stroke N. The prognostic effect of cigarette smoking on stroke severity, disability, length of stay in hospital, and mortality in a cohort with cerebrovascular disease. *J Stroke Cerebrovasc Dis* 2013;22:e446-454.
 11. Fekete K, Szatmari S, Szocs I, Szekeres C, Szasz J, Mihalka L, et al. Prestroke alcohol consumption and smoking are not associated with stroke severity, disability at discharge, and case fatality. *J Stroke Cerebrovasc Dis* 2014;23:e31-37.
 12. Moulin S, Padjen-Bogosavljevic V, Marichal A, Cordonnier C, Jovanovic DR, Gautier S, et al. Influence of differences in case mix on the better outcome of smokers after intravenous thrombolysis for acute cerebral ischemia. *Eur Neurol* 2012;67:178-183.
 13. Weng WC, Huang WY, Chien YY, Wu CL, Su FC, Hsu HJ, et al. The impact of smoking on the severity of acute ischemic stroke. *J Neurol Sci* 2011;308:94-97.
 14. Ali SF, Smith EE, Bhatt DL, Fonarow GC, Schwamm LH. Paradoxical association of smoking with in-hospital mortality among patients admitted with acute ischemic stroke. *J Am Heart Assoc* 2013;2:e000171.
 15. Bang OY, Park HY, Lee PH, Kim GM, Chung CS, Lee KH. Improved outcome after atherosclerotic stroke in male smoker. *J Neurol Sci* 2007;260:43-48.
 16. Kufner A, Nolte CH, Galinovic I, Brunecker P, Kufner GM, Endres M, et al. Smoking-thrombolysis paradox: recanalization and reperfusion rates after intravenous tissue plasminogen activator in smokers with ischemic stroke. *Stroke* 2013;44:407-413.
 17. Ovbiagele B, Saver JL. The smoking-thrombolysis paradox and acute ischemic stroke. *Neurology* 2005;65:293-295.
 18. Bowman TS, Gaziano JM, Buring JE, Sesso HD. A prospective study of cigarette smoking and risk of incident hypertension in women. *J Am Coll Cardiol* 2007;50:2085-2092.
 19. Heeringa J, Kors JA, Hofman A, van Rooij FJ, Witteman JC. Cigarette smoking and risk of atrial fibrillation: the Rotterdam Study. *Am Heart J* 2008;156:1163-1169.
 20. Addo J, Ayerbe L, Mohan KM, Crichton S, Sheldenkar A, Chen R, et al. Socioeconomic status and stroke: an updated review. *Stroke* 2012;43:1186-1191.
 21. Gellert C, Schottker B, Muller H, Holleczer B, Brenner H. Impact of smoking and quitting on cardiovascular outcomes and risk advancement periods among older adults. *Eur J Epidemiol* 2013;28:649-658.
 22. Wannamethee SG, Shaper AG, Whincup PH, Walker M. Smoking cessation and the risk of stroke in middle-aged men. *JAMA* 1995;274:155-160.
 23. 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;33:2263-2269.
 24. Lagakos SW. The challenge of subgroup analyses--reporting without distorting. *N Engl J Med* 2006;354:1667-1669.
 25. Jacobs DR, Jr, Adachi H, Mulder I, Kromhout D, Menotti A, Nissinen A, et al. Cigarette smoking and mortality risk: twenty-five-year follow-up of the Seven Countries Study. *Arch Intern Med* 1999;159:733-740.

Supplementary Table 1. Baseline characteristics of patients lost to follow-up

Parameters	Included n=1,117	Follow-up loss n=131	Pvalue
Onset-to-admission time (hour), (mean ± SD)	28.6 (37.1)	38.2 (44.0)	0.017
Males, n (%)	639 (57.2)	82 (62.6)	0.237
Age (mean ± SD)	65.3 (13.5)	66.6 (15.0)	0.322
Body mass index (kg/m ²), (mean ± SD)	3.2 (0.1)	3.2 (0.3)	0.374
High BMI (≥25), n (%)	37 (29.8)	355 (32.7)	0.756
Normal BMI, n (%)	75 (60.5)	618 (57.0)	
Low BMI (<20), n (%)	111 (10.2)	12 (9.7)	
Smoking status, n (%)			
Current smoker	336 (30.2)	34 (26.4)	0.368
Non-smoker	777 (69.3)	95 (73.6)	
Former smoker	126 (11.3)	16 (12.4)	
Never-smoker	651 (58.5)	79 (61.2)	
Hypertension, n (%)	693 (62.0)	79 (60.3)	0.699
Diabetes Mellitus, n (%)	331 (29.6)	45 (34.4)	0.265
Hyperlipidemia, n (%)	335 (30.0)	38 (29.0)	0.816
Atrial fibrillation, n (%)	232 (20.8)	23 (17.7)	0.402
Stroke subtype, n (%)			
Large artery disease	338 (30.3)	49 (37.4)	0.061
Small vessel disease	360 (32.2)	32 (24.4)	
Cardioembolism	244 (21.8)	27 (20.6)	
Undetermined			
Incomplete	10 (0.9)	4 (3.1)	
2 or more	41 (3.7)	2 (1.5)	
Negative	58 (5.2)	10 (7.6)	
Other determined	66 (5.9)	7 (5.3)	
Received tPA thrombolysis, n (%)	93 (8.3)	15 (11.5)	0.229
Initial NIHSS score (mean ± SD)	5.4 (6.1)	6.9 (6.7)	0.015
Initial NIHSS ≤ 1	331 (29.6)	32 (24.4)	0.004
2-3	297 (26.6)	24 (18.3)	
4-8	239 (21.4)	28 (21.4)	
≥ 9	250 (22.4)	47 (35.9)	
Initial systolic BP (mean ± SD)	142.8 (24.0)	140.5 (27.0)	0.304
Initial blood parameters (mean ± SD)			
Fasting glucose (mg/dL)	118.6 (47.9)	128.9 (59.7)	0.071
LDL - cholesterol (mg/dL)	116.4 (36.3)	114.2 (35.2)	0.505
WBC (/mm ³)	8,231 (2987)	8,497 (2946)	0.335
Hemoglobin (g/dL)	13.7 (1.9)	13.5 (2.0)	0.271

In these analysis, there were missing data for atrial fibrillation in 4 (0.3%), smoking in 6 (0.5%), BMI in 40 (3.2%), WBC in one (0.1%), LDL-cholesterol in 26 (2.1%), and fasting blood glucose in 109 (8.7%) patients.

BMI, body mass index; BP, blood pressure; LDL, low density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator; WBC, white blood cell.

Supplementary Table 2. Factors associated with severe stroke (\geq NIHSS 6) in the multivariate analysis

Parameters	Model 1			Model 2				
	Adjusted OR	95% CI		Pvalue	Adjusted OR	95% CI		Pvalue
Onset-to-admission time, per 10 hours	0.84	0.79	0.89	<0.001	0.84	0.79	0.89	<0.001
Demographics								
Sex:males	0.68	0.47	1.00	0.050	0.60	0.39	0.92	0.019
Age, per 10 years	1.22	1.06	1.42	0.007	1.22	1.05	1.41	0.009
Body mass index (kg/m ²)								
High BMI (\geq 25)	0.44	0.29	0.64	<0.001	0.43	0.29	0.64	<0.001
Normal BMI	ref.				ref.			
Low BMI (<20)	0.85	0.51	1.42	0.525	0.83	0.50	1.39	0.483
Smoking status								
Current smoker	1.57	1.03	2.39	0.037				
Non-smoker	ref.							
Current smoker					1.78	1.12	2.83	0.014
Former smoker					1.53	0.84	2.80	0.167
Never-smoker					ref.			
Vascular risk factors								
Hypertension	0.97	0.68	1.38	0.863	0.95	0.67	1.37	0.800
Diabetes mellitus	1.13	0.79	1.63	0.497	1.15	0.80	1.65	0.457
Hyperlipidemia	1.23	0.85	1.78	0.270	1.22	0.84	1.77	0.289
Atrial fibrillation	2.16	1.08	4.32	0.029	2.19	1.09	4.38	0.027
Stroke subtype								
Small vessel disease	ref.				ref.			
Large artery disease	4.99	3.22	7.73	<0.001	4.98	3.22	7.72	<0.001
Cardioembolism	5.29	2.60	10.79	<0.001	5.36	2.63	10.93	<0.001

In Model 1, current smokers were compared with non-smokers. In Model 2, current smokers and former smokers were compared with never-smokers. NIHSS, National Institutes of Health Stroke Scale; BMI, body mass index.

Supplementary Table 3. Factors associated with functional outcomes in the univariate analysis

Parameters	mRS 0-1 n=670	mRS 2-6 n=447	OR	95% CI		Pvalue
Onset-to-admission time (hour), (mean ± SD)	30.1 ± 38.0	24.9 ± 35.6	0.96	0.92	1.00	0.007
Males, n (%)	227 (50.8)	220 (49.2)	0.58	0.46	0.74	<0.001
Age (mean ± SD)	63.1 ± 13.0	68.6 ± 13.5	1.38	1.25	1.52	<0.001
Body mass index (kg/m ²), (mean ± SD)	24.1 ± 3.2	23.1 ± 3.1	0.90	0.87	0.94	<0.001
High BMI (≥ 25), n (%)	248 (37.7)	107 (25.1)	0.58	0.44	0.77	<0.001
Normal BMI (ref.), n (%)	355 (54.0)	263 (61.7)	ref.	ref.	ref.	
Low BMI (< 20), n (%)	55 (8.4)	56 (13.1)	1.37	0.92	2.06	0.124
Current smokers, n (%)	215 (32.1)	121 (27.3)	0.79	0.61	1.03	0.082
Non-smokers, n (%)	454 (67.9)	323 (72.7)	ref.	ref.	ref.	
Current smokers, n (%)	215 (32.1)	121 (27.3)	0.79	0.61	1.04	0.097
Former smokers, n (%)	73 (10.9)	53 (11.9)	1.03	0.70	1.51	0.902
Never-smokers, n (%)	381 (57.0)	270 (60.8)	ref.	ref.	ref.	
Hypertension, n (%)	402 (60.0)	291 (65.1)	1.24	0.97	1.59	0.085
Diabetes mellitus, n (%)	183 (27.3)	148 (33.1)	1.32	1.02	1.71	0.038
Hyperlipidemia, n (%)	225 (33.6)	110 (24.6)	0.65	0.49	0.84	0.001
Atrial fibrillation, n (%)	100 (15.0)	132 (29.6)	2.39	1.78	3.20	<0.001
Stroke subtype, n (%)						
Small vessel disease	271 (47.8)	89 (23.7)	ref.	ref.	ref.	
Large artery disease	183 (32.3)	155 (41.3)	2.58	1.87	3.56	<0.001
Cardioembolism	113 (19.9)	131 (34.9)	3.53	2.49	5.00	<0.001
Received tPA thrombolysis, n (%)	39 (5.8)	54 (12.1)	2.22	1.45	3.42	<0.001
Initial NIHSS ≤ 1	279 (41.6)	52 (11.6)	ref.	ref.	ref.	
2-3	225 (33.6)	72 (16.1)	1.72	1.15	2.56	0.008
4-8	118 (17.6)	121 (27.1)	5.50	3.73	8.12	<0.001
≥ 9	48 (7.2)	202 (45.2)	22.58	14.66	34.78	<0.001
Initial systolic BP (mean ± SD)	141 ± 24	146 ± 24	1.09	1.04	1.15	0.001
Fasting glucose (mg/dL), (mean ± SD)	113 ± 42	127 ± 55	1.07	1.04	1.10	<0.001
LDL - cholesterol (mg/dL), (mean ± SD)	117 ± 36	115 ± 37	0.98	0.95	1.01	0.246
WBC (/mm ³), (mean ± SD)	7,802 ± 2,367	8,871 ± 3,348	1.13	1.08	1.17	<0.001
Hemoglobin (g/dL), (mean ± SD)	13.8 (1.8)	13.4 (2.1)	0.78	0.57	0.98	0.001

In these analysis, there were missing data for atrial fibrillation in 3 patients (0.3%), smoking status in 4 (0.36%), BMI in 33 (3.0%), WBC in one (0.1%), LDL-C in 22 (2.0%), and fasting glucose in 98 (8.8%) patients.

BMI, body mass index; BP, blood pressure; LDL, low density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator; WBC, white blood cell.

Supplementary Table 4. Factors associated with 3-month death in the univariate analysis

Parameters	No death n= 1,042	Death n=75	OR	95% CI		Pvalue
Onset-to-admission time (hour), (mean ± SD)	29.3 ± 37.4	18.0 ± 31.3	0.89	0.81	0.98	0.013
Males, n (%)	610 (58.5)	29 (38.7)	0.45	0.28	0.72	0.001
Age (mean ± SD)	64.5 ± 13.3	76.6 ± 10.9	2.47	1.92	3.17	<0.001
Body mass index (kg/m ²), (mean ± SD)	23.8 ± 3.2	23.1 ± 3.6	0.93	0.86	1.01	0.083
High BMI (≥ 25), n (%)	336 (33.1)	19 (27.9)	0.86	0.49	1.52	0.611
Normal BMI (ref.), n (%)	580 (57.1)	38 (55.9)	ref.	ref.	ref.	
Low BMI (< 20), n (%)	100 (9.8)	11 (16.2)	0.86	0.49	1.52	0.611
Current smokers, n (%)	326 (31.4)	10 (13.3)	0.34	0.17	0.66	0.001
Non-smokers, n (%)	712 (68.6)	65 (86.7)	ref.	ref.	ref.	
Current smokers, n (%)	326 (31.4)	10 (13.3)	0.36	0.18	0.72	0.004
Former smokers, n (%)	112 (10.8)	14 (18.7)	1.47	0.79	2.75	0.226
Never-smokers, n (%)	600 (57.8)	51 (68.0)	ref.	ref.	ref.	
Hypertension, n (%)	641 (61.5)	52 (69.3)	1.41	0.85	2.35	0.180
Diabetes mellitus, n (%)	308 (29.6)	23 (30.7)	1.05	0.63	1.75	0.839
Hyperlipidemia, n (%)	323 (31.0)	12 (16.0)	0.42	0.23	0.80	0.008
Atrial fibrillation, n (%)	193 (18.6)	39 (52.0)	4.75	2.94	7.67	<0.001
Stroke subtype, n (%)						
Small vessel disease	356 (40.1)	4 (7.3)	ref.	ref.	ref.	
Large artery disease	322 (36.3)	16 (29.1)	4.42	1.46	13.37	0.008
Cardioembolism	209 (23.6)	35 (63.6)	14.90	5.22	42.53	<0.001
Received tPA thrombolysis, n (%)	79 (7.6)	14 (18.7)	2.80	1.50	5.22	0.001
Initial NIHSS ≤ 1	329 (31.6)	2 (2.7)	ref.	ref.	ref.	
2-3	291 (27.9)	6 (8.0)	3.39	0.68	16.94	0.137
4-8	232 (22.3)	7 (9.3)	4.96	1.02	24.11	0.047
≥ 9	190 (18.2)	60 (80.0)	51.95	12.56	214.93	<0.001
Initial systolic BP (mean ± SD)	142 ± 24	147 ± 25	1.08	0.98	1.19	0.104
Fasting glucose (mg/dL), (mean ± SD)	117 ± 46	146 ± 60	1.08	1.04	1.13	<0.001
LDL - cholesterol (mg/dL), (mean ± SD)	117 ± 36	109 ± 36	0.94	0.97	1.01	0.072
WBC (/mm ³), (mean ± SD)	8,097 ± 2,853	10,089 ± 4,036	1.19	1.12	1.27	<0.001
Hemoglobin (g/dL), (mean ± SD)	13.7 (1.9)	12.8 (2.3)	0.29	0.18	0.39	<0.001

In these analysis, there were missing data for atrial fibrillation in 3 patients (0.3%), smoking status in 4 (0.36%), BMI in 33 (3.0%), WBC in one (0.1%), LDL-C in 22 (2.0%), and fasting glucose in 98 (8.8%) patients.

BMI, body mass index; BP, blood pressure; LDL, low density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator; WBC, white blood cell.

Supplementary Table 5. Adjusted odd ratio for poor functional outcome in different subgroups

Subgroups	Smoking status	Adjusted OR	95% CI	Pvalue	
Sex	Male, n=639	Current vs. non-smoker	1.13	0.67 1.92	0.643
		Current vs. never-smoker	1.34	0.75 2.40	0.328
	Female, n=478	Current vs. non-smoker	1.09	0.36 3.32	0.089
		Current vs. never-smoker	1.07	0.35 3.28	0.906
Age	Young (< 65), n=483	Current vs. non-smoker	1.31	0.69 2.51	0.408
		Current vs. never-smoker	1.52	0.73 3.14	0.262
	Elderly (65 ≤), n=634	Current vs. non-smoker	1.07	0.57 2.04	0.826
		Current vs. never-smoker	1.26	0.63 2.54	0.515
Stroke subtype	SVO, n=360	Current vs. non-smoker	0.42	0.09 1.87	0.253
		Current vs. never-smoker	2.41	0.94 6.15	0.066
	LVD, n=338	Current vs. non-smoker	1.04	0.53 2.05	0.903
		Current vs. never-smoker	1.01	0.47 2.17	0.975
	CE, n=244	Current vs. non-smoker	1.71	0.58 5.09	0.333
		Current vs. never-smoker	1.88	0.60 5.87	0.279
Hypertension	Yes, n=693	Current vs. non-smoker	1.43	0.79 2.60	0.242
		Current vs. never-smoker	1.61	0.83 3.11	0.156
	No, n=424	Current vs. non-smoker	1.24	0.62 2.50	0.546
		Current vs. never-smoker	1.43	0.67 3.08	0.359
Diabetes mellitus	Yes, n=331	Current vs. non-smoker	0.97	0.43 2.19	0.943
		Current vs. never-smoker	1.33	0.54 3.28	0.534
	No, n=786	Current vs. non-smoker	1.72	1.00 2.96	0.050
		Current vs. never-smoker	1.81	0.99 3.29	0.052
Hyperlipidemia	Yes, n=335	Current vs. non-smoker	1.07	0.48 2.37	0.875
		Current vs. never-smoker	1.38	0.57 3.35	0.472
	No, n=782	Current vs. non-smoker	1.53	0.89 2.63	0.128
		Current vs. never-smoker	1.62	0.89 2.94	0.116
Atrial fibrillation	Yes, n=232	Current vs. non-smoker	2.04	0.49 8.54	0.328
		Current vs. never-smoker	1.41	0.84 2.38	0.192
	No, n=882	Current vs. non-smoker	1.25	0.78 2.00	0.348
		Current vs. never-smoker	2.21	0.49 9.91	0.302
Body mass index	High (≥ 25 kg/m ²), n=355	Current vs. non-smoker	2.04	0.84 4.96	0.114
		Current vs. never-smoker	1.80	0.70 4.62	0.221
	Normal, n=618	Current vs. non-smoker	1.03	0.59 1.81	0.915
		Current vs. never-smoker	1.29	0.69 2.40	0.431
	Low (< 20 kg/m ²), n=111	Current vs. non-smoker	7.06	0.91 54.48	0.061
		Current vs. never-smoker	18.34	1.38 244.03	0.028
tPA therapy	Yes, n=93	Current vs. non-smoker	4.32	0.65 28.64	0.129
		Current vs. never-smoker	15.33	1.30 180.20	0.030
	No, n=1024	Current vs. non-smoker	1.37	0.86 2.19	0.186
		Current vs. never-smoker	1.51	0.90 2.52	0.116

SVO, small vessel disease; LVD, large artery disease; CE, cardioembolism; tPA, tissue plasminogen activator.

Supplementary Table 6. Baseline characteristics of patients with missing data

Parameters	Patients with FBS data n=1,019	Patients without FBS data n=98	Pvalue	Patients with BMI data n=1,084	Patients without BMI data n=33	Pvalue
Onset-to-admission time (hour), (mean ± SD)	28.2 (37.0)	32.0 (40.3)	0.331	28.1 (36.7)	43.4 (46.3)	0.020
Demographics						
Sex:males, n (%)	590 (57.9)	49 (50.0)	0.131	623 (57.5)	16 (48.5)	0.304
Age (mean ± SD)	65.3 (13.5)	65.4 (13.3)	0.952	65.2 (13.5)	70.3 (12.4)	0.030
Body mass index (kg/m ²), (mean ± SD)	23.8 (3.2)	23.4 (3.4)	0.327			
High BMI (≥ 25), n (%)	328 (33.1)	27 (28.7)	0.656			
Normal BMI, n (%)	562 (56.8)	56 (59.6)				
Low BMI (< 20), n (%)	100 (10.1)	11 (11.7)				
Smoking status, n (%)						
Current smoker	306 (30.1)	30 (30.6)	0.924	328 (30.4)	8 (24.2)	0.450
Non-smoker	709 (69.9)	68 (69.4)		752 (69.6)	25 (75.8)	
Former smoker	117 (11.5)	9 (9.2)		122 (11.3)	4 (12.1)	
Never-smoker	592 (58.3)	59 (60.2)		630 (58.3)	21 (63.6)	
Hypertension, n (%)	634 (62.2)	59 (60.2)	0.695	672 (62.0)	21 (63.6)	0.848
Diabetes mellitus, n (%)	301 (29.5)	30 (30.6)	0.824	320 (29.5)	11 (33.3)	0.637
Hyperlipidemia, n (%)	311 (30.5)	24 (24.5)	0.213	328 (30.3)	7 (21.2)	0.264
Atrial fibrillation, n (%)	210 (20.7)	22 (22.4)	0.679	226 (20.9)	6 (18.2)	0.704
Stroke subtype, n (%)						
Large artery disease	318 (36.9)	20 (24.7)	0.070	326 (35.7)	12 (40.0)	0.841
Small vessel disease	326 (37.9)	34 (42.0)		350 (38.4)	10 (33.3)	
Cardioembolism	217 (25.2)	27 (33.3)		236 (25.9)	8 (26.7)	
Received tPA thrombolysis, n (%)	85 (8.3)	8 (8.2)	0.951	91 (8.4)	2 (6.1)	0.633
Initial NIHSS score (mean ± SD)						
Initial NIHSS ≤ 1	303 (29.7)	28 (28.6)	0.630	323 (29.8)	8 (24.2)	0.427
2-3	273 (26.8)	24 (24.5)		288 (26.6)	9 (27.3)	
4-8	213 (20.9)	26 (26.5)		234 (21.6)	5 (15.2)	
≥ 9	230 (22.6)	20 (20.4)		239 (22.0)	11 (33.3)	

FBS, fasting blood sugar; BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator.