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In acute ischemic stroke patients with smoking incidence, are more women than men more likely to be included or excluded from thrombolysis therapy?

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Abstract

Background: Clinical factors associated with exclusion from recombinant tissue plasminogen activator in both men and women are not completely understood. The aim of this study is to determine whether there is a gender difference in clinical risk factors that excluded ischemic stroke patients with a history of smoking from recombinant tissue plasminogen activator.

Methods: Retrospective data from a stroke registry were analyzed, and multivariable linear regression models were used to determine gender differences. Logistic regression models determined exclusion clinical risk factors for thrombolysis in male and female acute ischemic stroke patients with a history of smoking, while sequentially adjusting for sociodemographic, clinical, and stroke-related variables. The Kaplan–Meier survival analysis was used to determine the exclusion probabilities of men and women with a history of smoking within the stroke population.

Results: Of the 1,446 acute ischemic stroke patients eligible for recombinant tissue plasminogen activator, 379 patients with a history of smoking were examined, of which 181 received recombinant tissue plasminogen activator while 198 were excluded from receiving recombinant tissue plasminogen activator. Of the 198 patients, 75 females and 123 males were excluded from receiving recombinant tissue plasminogen activator. After multivariable adjustment for age, National Institutes of Health scores, and stroke-related factors, females who present with weakness/paresis on initial examination (OR = 0.117, 95% CI, 0.025–0.548) and men who present with a history of previous transient ischemic attack (OR = 0.169, 95% CI, 0.044–0.655), antiplatelet medication use (OR = 0.456, 95% CI, 0.230–0.906), and weakness/paresis on initial examination (OR = 0.171, 95% CI, 0.056–0.521) were less likely to be excluded from recombinant tissue plasminogen activator (thrombolysis therapy).

Conclusions: In an ischemic stroke population with a history of smoking, female smokers are more likely to be excluded from thrombolysis therapy in comparison to men, even after adjustment for confounding variables.

Keywords

gender, ischemic stroke, recombinant tissue-type plasminogen activator (rtPA), smoking

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Introduction

The 'smoker's paradox' is an observational phenomenon of an unexpected favorable outcome after thrombolysis.[1,2] Several mechanisms have been proposed to support the phenomenon, including greater thrombotic component in the plaque with comparatively less atherosclerotic plaque

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burden,[3] which is more susceptible to complete reperfusion.[4] The existence of the smoker's paradox phenomenon is controversial. Given the inconsistent evidence, the current study investigates possible facilitators of this relationship and whether it can be explained by the difference in demographic and clinical characteristics. Although cigarette smoking is known to be directly linked with the recanalization and reperfusion in tobacco smokers treated with recombinant tissue plasminogen activator (rtPA) for ischemic stroke,[5] the danger of smoking is shown in the observed incidence of stroke many years earlier in smokers compared to nonsmokers.[6] The favorable response to thrombolytic therapy in smokers with higher rates of recanalization was attributed to the hypercoagulable state of arterial occlusions in smokers.[7,8] Therefore, smoking induced hypercoagulation,[9] which regulates hematocrit and fibrin-rich clots, enhances fibrinogen levels, and inhibits endogenous fibrinolytic capability.[10] Moreover, smoking is associated with an increased plasma level modulated by carbon monoxide.[11,12] In turn, carbon monoxide, which is a gasotransmitter, triggers ischemic preconditioning and reinforces endogenous cellular cytoprotective responses to ischemic tissue damage.[13] Among nonsmokers, classified as "not ever smokers," "infrequent smokers," and "passive smokers,"[14] cardio-embolism occurred more often compared to smokers.[6] Cardioembolic strokes are characterized by large territorial infarcts with an extended time in the formation of a tough thrombus, which is a hard clot made of fibrin and platelets found inside the blood vessel that obstructs the flow of blood, which causes a risk of hemorrhage resulting in negative clinical outcomes.[15] Therefore, noncardioembolic strokes may be independently associated with positive outcomes in smokers treated with thrombolysis therapy.[6,14] This implies that if there are few cardio-embolism patients treated with thrombolytic therapy, the benefit of smoking will be higher in the stroke population. This explains the idea of favorable outcomes in smokers (smoking paradox), an indication of a link between smoking and an improved clinical outcome in stroke patients treated with thrombolytic therapy.

Furthermore, National Institutes of Health Stroke Scale (NIHSS) on admission is known as an independent predictor of functional recovery, whereas such a link between smoking status and outcome has yet to be established. Therefore, it is not clear whether the observed differences in clinical outcome, the inclusion or exclusion for thrombolysis therapy in smokers and nonsmokers with acute ischemic stroke, are attributed to clinical risk factors at pretreatment or the differential effects of smoking. In general, cigarette smoking and its major subtypes in all individuals are a major independent risk factor for stroke in both men and women.[16] The risk of stroke is known to be greater among female smokers compared to males who smoke,[14] indicating that the proportion of male and female smokers in acute ischemic stroke may not be the same. The first objective is to determine differences between the respective male and female populations of stroke patients with a history of smoking. In the general population, male and female stroke patients do not present with the same exclusion criteria for thrombolysis therapy.[17–19] For instance, since the risk of stroke is greater in women with a history of smoking, a higher proportion of female stroke patients with a history of smoking can therefore be excluded from intravenous thrombolytic therapy. Therefore, the second objective is to determine whether more pretreatment clinical risk factors will contribute to the exclusion of more female compared to male stroke patients with a history of smoking. Understanding the exclusion clinical risk factors of rtPA for both men and women with stroke and a history of smoking could help identify the association between smoking and stroke outcome. In addition, it could help identify future research target to improve thrombolysis in stroke patients with a history of smoking.

Methods

Data collection

This study used data from acute ischemic stroke patients between January 1, 2010, and June 30, 2016, from the Greenville Health System (GHS). A total of 4665 ischemic stroke patients were identified. Of this population, 1446 patients were eligible for rtPA and 3219 were not. Of the 1,446 acute ischemic stroke patients eligible for rtPA, 379 present with a history of smoking. The GHS stroke registry is well standardized in accordance with the Get With The Guidelines (GWTG)-Stroke registry designed by the American Heart Association (AHA) and the American Stroke Association (ASA) in a combined effort to increase the quality of care for stroke patients.[20] Previous studies[21,22] reported the full description of this registry, and approval for this study was obtained from the Institutional Review Board (IRB) ethical committee. Briefly, a standardized data collection method was developed to collect data on pretreatment factors such as stroke evaluation that considered NIH scores, and ambulatory status including the ability to walk on admission, during admission, and after discharge. Other variables include language/aphasia, arm deficit on admission, care indicators to measure compliance (such as stroke unit care and evaluations by allied health), and health results (including discharge destination and dependence at discharge). Clinical risk factors were retrospectively abstracted from patients' medical records: coronary artery disease (CAD), carotid stenosis, diabetes, dyslipidemia, atrial fibrillation/flutter, congestive heart failure (CHF), hypertension, transient ischemic attack (TIA) or previous stroke, smoking history, peripheral vascular disease (PVD), and neurological status at the time of presentation. Additional data such as in-hospital procedures, treatments,

evidence of antithrombotic treatment, contraindications to anticoagulant, and discharge guidelines were collected retrospectively. All data submitted to GHS stroke registry went through an extensive quality and detailed evaluations. This involves using established protocol to ascertain the quality of the data and to avoid several types of errors including the interpretation or coding of data.

Statistical analysis

Our sample consisted of 379 acute ischemic stroke patients with a history of smoking. Patients' data were deidentified and divided into two groups based on receipt of rtPA—rtPA group (included for treatment) and no rtPA group (excluded from treatment).

Following the analysis of gender differences between the rtPA exclusion and the inclusion rtPA group, further analysis was determined using a multivariate analysis. Variables associated in the univariate analysis with $P < 0.05$ representing statistical significance were incorporated into a stepwise logistic regression model to determine variables independently associated with exclusion or inclusion (adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were considered) in the total study population as well as in the male and female subgroups. We added other variables including NIHSS score and age as continuous variables in the model. The goal is to identify demographic and clinical characteristics associated with exclusion from rtPA administration in the total study population as well as in the male and female subgroups. In the regression model, rtPA treatment was used as the dependent variable. In addition, gender was included as the primary independent variable in the regression model for the whole ischemic stroke population with a history of smoking, while the male and female subcohorts were analyzed separately. Although smoking was an inclusion criterion in the model, it may not appear in the final stepwise regression model if it was not significantly associated with the dependent variable in order to meet the criteria for stepwise consideration. In our analysis, the predictor variables for each logistic regression model were selected by stepwise regression and variables with $P < 0.05$ remained in the model. All statistical analyses were performed utilizing SAS version 9.4, and statistical significance was established at $P < 0.05$ for all group comparisons.

Results

A total of 379 stroke patients with a history of smoking were examined, of which 181 received rtPA while 198 were excluded from rtPA. Baseline demographic and clinical characteristics of rtPA and non-rtPA groups are presented in Table 1. Patients excluded from rtPA tended to be older (59.52 ± 11.48 vs 56.69 ± 12.25, $P = 0.02$) with a lower NIHSS (7.23 ± 6.34 vs 9.41 ± 6.36, $P < 0.01$). Patients with a history of dyslipidemia, atrial fibrillation, previous TIA, carotid artery stenosis, antiplatelet medication, and weakness/paresis on initial examination were associated with exclusion from rtPA in stroke patients with a history of smoking.

Table 2 presents acute ischemic stroke patients with a history of smoking characterized by rtPA status and by gender. A total of 75 female and 123 male stroke patients with a history of smoking were excluded from rtPA. In the no rtPA group (versus the rtPA group), females had higher rates of previous stroke (65.12% vs 34.9%), carotid artery stenosis (100% vs 0%), and usage of a cholesterol reduction medication (61.8% vs 38.2 %). At the time of presentation, they had a lower calculated NIHSS score (6.95 ± 6.05 vs 8.99 ± 6.35) and lower rates of weakness/paresis (46.9 % vs 53.1%). In male stroke patient smokers, excluded patients presented with lower rates of CAD (41.8% vs 58.2%), dyslipidemia (42.9% vs 57.1%), previous TIA (14.3% vs 85.7%), antiplatelet medication use (38.7% vs 61.3%), and use of a cholesterol reducer (40.9% vs 59.1%). At the time of presentation, they also had a lower calculated NIHSS score (7.41 ± 6.53 vs 9.69 ± 6.39) and lower rates of weakness/paresis (48% vs 52%).

Table 3 presents factors associated with rtPA exclusion in an acute ischemic stroke population with a history of smoking. As shown in the table, seven demographic and clinical characteristics are significantly associated with rtPA exclusion: increasing age (OR = 1.020 95% CI, 1.003–1.037, $P < 0.05$), increased rates of atrial fibrillation/flutter (OR = 2.388 95% CI, 1.069–5.332, $P < 0.05$), increased rates of carotid artery stenosis (OR = 5.571 95% CI, 1.605–19.338, $P < 0.01$), reduced rates of previous TIA (OR = 0.384 95% CI, 0.192–0.767, $P < 0.01$), lower NIHSS scores (OR = 0.948, 95% CI, 0.917–0.979, $P < 0.01$), and reduced rates of weakness/paresis at the time of presentation (OR = 0.159 95% CI, 0.069–0.365, $P < 0.01$).

Table 4 presents factors associated with rtPA exclusion or inclusion in male and female acute ischemic stroke patients with a history of smoking. Table 4 indicates that only four factors were significantly associated with rtPA exclusion or inclusion in female stroke smokers: increasing rates of previous stroke (OR = 2.224 95% CI, 1.064–4.649, $P < 0.05$), use of a cholesterol reducer (OR = 1.947 95% CI, 0.997–3.909, $P = 0.05$), lower NIHSS scores (OR = 0.948 95% CI, 0.898–1.000, $P = 0.05$), and reduced rates of weakness/paresis at the time of presentation (OR = 0.126, 95% CI, 0.028–0.578, $P < 0.01$). Six factors were significantly associated with rtPA exclusion or inclusion in males: reduced dyslipidemia (OR = 0.481 95% CI, 0.284–0.813, $P < 0.01$), reduced rates of previous TIA (OR = 0.128 95% CI, 0.037–0.447, $P < 0.01$), reduced rates of antiplatelet use (OR = 0.385 95% CI, 0.224–0.660, $P < 0.01$), antihypertensive use (OR = 0.535, 95% CI, 0.313–0.917, $P < 0.05$), use of a cholesterol reducer (OR = 0.462, 95% CI, 0.269–0.792, $P < 0.01$), lower

Table 1. Characteristics of acute ischemic stroke patients with a history of smoking stratified by rtPA. Continuous variables are represented as mean ± S.D. and comparisons between groups are made with a Student's *t* test. Discrete variables are represented as count (percent frequency), and comparisons between groups were made using Pearson's chi-square test.

N = 379	rtPA (181; control group)	No rtPA (198; experimental group)	P value
Age group: (%)			
< 50	45 (55.56)	36 (44.44)	0.4733
50–59	61 (48.03)	66 (51.97)	
60–69	50 (45.87)	59 (54.13)	
70–79	20 (40.82)	29 (59.18)	
⩾ 80	5 (38.46)	8 (61.54)	
Mean ± SD	56.69 ± 12.25	59.52 ± 11.84	0.0239*
Race: (%)			
Caucasian	136 (48.06)	147 (51.94)	0.5534
African-American	44 (46.32)	51 (53.68)	
Gender: (%)			
Male	110 (47.21)	123 (52.79)	0.7877
Female	71 (48.63)	75 (51.37)	
Body mass index (%)			
< 18.5	10 (50.00)	10 (50.00)	0.9397
18.5–24.9	55 (45.83)	65 (54.17)	
25–29.9	62 (50.82)	60 (49.18)	
30–34.9	25 (43.10)	33 (56.90)	
35–39.9	18 (50.00)	18 (50.00)	
⩾ 40	11 (47.83)	12 (52.17)	
Mean ± SD			
Medical history: (%)			
Hypertension			
Yes	137 (48.93)	143 (51.07)	0.4426
No	44 (44.44)	55 (55.56)	
Coronary artery disease			
Yes	51 (52.58)	46 (47.42)	0.2706
No	130 (46.10)	152 (53.90)	
Dyslipidemia			
Yes	93 (52.84)	83 (47.160	0.0651*
No	88 (43.35)	115 (56.65)	
Atrial fibrillation/flutter			
Yes	9 (29.03)	22 (70.97)	0.0294*
No	172 (49.43)	176 (50.57)	
Previous stroke			
Yes	48 (41.74	67 (58.26)	0.1216
No	133 (50.38)	131 (49.62)	
Previous TIA			
Yes	28 (68.29)	13 (31.71)	0.0053*
No	153 (45.27)	185 (54.73)	
Congestive heart failure			
Yes	12 (37.50)	20 (62.50)	0.2247
No	169 (48.70)	178 (51.30)	
Carotid artery stenosis			
Yes	3 (15.00)	17 (85.00)	0.0026*
No	178 (49.58)	181 (50.42)	
Peripheral vascular disease			
Yes	9 (39.13)	14 (60.87)	0.3928
No	172 (48.31)	184 (51.69)	
Diabetes			
Yes	43 (45.26)	52 (54.74)	0.574
No	138 (48.590	146 (51.41)	

(Continued)

Table 1. (Continued)

N = 379	rtPA (181; control group)	No rtPA (198; experimental group)	P value
Medication history: (%)			
Antiplatelet			
Yes	84 (54.90)	69 (45.10)	0.0220*
No	97 (42.92)	129 (57.08)	
Antihypertensive			
Yes	119 (50.85)	115 (49.15)	0.1251
No	62 (42.76)	83 (57.24)	
Cholesterol reducer medications			
Yes	73 (51.05)	70 (48.95)	0.318
No	108 (45.76)	128 (54.24)	
Diabetes medication			
Yes	33 (47.83)	36 (52.17)	0.9899
No			
Initial NIH stroke scale	148 (47.74)	162 (52.26)	
Group: (%)			
0–9	109 (43.60)	141 (56.40)	
10–14	30 (55.56)	24 (44.44)	
15–20	24 (52.17)	22 (47.83)	
21–25	18 (62.07)	11 (37.93)	
Mean ± SD	9.41 ± 6.36	7.23 ± 6.34	0.0009*
Risk of mortality GWTG			
Mean ± SD	4.46 ± 4.41	3.66 ± 3.92	0.0776
Initial exam findings: (%)			
Weakness/paresis			
Yes	174 (52.41)	158 (47.59)	< 0.0001*
Not Improved	7 (14.89)	40 (85.11)	
Altered level of consciousness			
Yes	44 (41.12)	63 (58.88)	0.1048
Not improved	137 (50.37)	135 (49.63)	
Aphasia/language disturbance			
Yes	117 (48.55)	124 (51.45)	0.6839
No	64 (46.38)	74 (53.62)	
Ambulation improvement			
Improved	124 (53.68)	107 (46.32)	0.0039*
Not improved	57 (38.51)	91 (61.49)	
Location of treatment: (%)			
Specialized stroke unit	105 (46.05)	123 (53.95)	0.4225
Non-specialized stroke unit	75 (51.02)	72 (48.98)	
Missing	1 (25.00)	3 (75.00)	

SD: standard deviation; TIA: transient ischemic attack; NIH: National Institutes of Health; GWTG: Get With The Guidelines.

NIHSS scores (OR = 0.947 95% CI, 0.909–0.986, P < 0.01), and reduced rates of weakness/paresis at the time of presentation (OR = 0.178 95% CI, 0.066–0.481, P < 0.01).

Demographic and clinical factors associated with exclusion or inclusion in acute ischemic stroke patients with a history of smoking are presented in Table 5. Following an adjusted analysis for confounding variables, Table 5 reveals seven variables that are independently associated with rtPA in acute ischemic stroke patients with a history of smoking. Three variables were more associated with rtPA exclusion: increasing age (OR = 1.024 95% CI, 1.004–1.044, P < 0.05), atrial fibrillation/flutter (OR = 3.208 95% CI, 1.308–7.868 P < 0.05), and carotid artery stenosis (OR = 11.419 95% CI 2.904–44.899, P < 0.01). Four other variables were more associated with rtPA inclusion: higher calculated NIHSS score (OR = 0.960 95% CI, 0.926–0.996, P < 0.05), history of previous TIA (OR = 0.369 95% CI 0.161–0.844 P < 0.05), weakness/paresis on initial examination (OR = 0.184 95% CI 0.075–0.450 P < 0.01), and antiplatelet medication use (OR = 0.406 95% CI 0.246–0.672, P < 0.01). A similar

Table 2. Demographic and clinical characteristics of acute ischemic stroke patients with a history of smoking stratified by rtPA and gender. Continuous variables are represented as mean ± S.D. and comparisons between groups are made with a Student's *t* test. Discrete variables are represented as count (percent frequency) and comparisons between groups were made using Pearson's chi-square test.

	Female smokers (146)		P value	Male smokers (233)		P value
	rtPA (71; control)	No rtPA (75)		rtPA (110; control)	No rtPA (123)	
Age group: (%)						
< 50	24 (58.54)	17 (41.46)	0.2293	47 (52.22)	19 (47.50)	0.5422
50–59	14 (37.84)	23 (62.16)		29 (40.28)	43 (47.78)	
60–69	21 (56.76)	16 (43.24)		10 (41.67)	43 (59.72)	
70–79	10 (40.00)	15 (60.00)		21 (52.50)	14 (58.33)	
⩾ 80	2 (33.33)	4 (66.67)		3 (42.86)	4 (57.14)	
Mean ± SD	56.01 ± 14.92	59.55 ± 12.91	0.1277	57.13 ± 10.21	59.5 ± 11.19	0.0931
Race: (%)						
Caucasian	54 (48.65)	57 (51.35)	0.5799	82 (47.67)	33 (54.10)	Nil
African-American	16 (47.06)	18 (52.94)		28 (45.90)	0	
Body mass index (%)						
< 18.5	4 (33.33)	8 (66.67)	0.5186	6 (75.00)	2 (25.00)	0.2488
18.5–24.9	20 (51.28)	19 (48.72)		35 (43.21)	46 (56.79)	
25–29.9	20 (43.48)	26 (56.52)		42 (55.26)	34 (44.74)	
30–34.9	10 (45.45)	12 (54.55)		15 (41.67)	21 (58.33)	
35–39.9	10 (66.67)	5 (33.33)		8 (38.10)	13 (61.90)	
⩾ 40	7 (58.33)	5 (41.67)		4 (36.36)	7 (63.64)	
Mean ± SD	29.28 ± 7.5	28.1 ± 11.04	0.4518	27.35 ± 5.87	27.9 ± 6.54	0.5031
Medical history: (%)						
Hypertension						
Yes	50 (46.73)	57 (53.27)	0.4465	87 (50.29)	86 (49.71)	0.1099
No	21 (53.85)	18 (46.15)		23 (38.33)	37 (61.67)	
Coronary artery disease						
Yes	12 (40.00)	18 (60.00)	0.2887	39 (58.21)	28 (41.79)	0.0326*
No	59 (50.86)	57 (49.14)		71 (42.77)	95 (57.23)	
Dyslipidemia						
Yes	33 (46.48)	38 (53.52)	0.6128	60 (57.14)	45 (42.86)	0.0059*
No	38 (50.670	37 (49.33)		50 (39.06)	78 (60.94)	
Atrial fibrillation/flutter						
Yes	4 (28.57)	10 (71.43)	0.1143	5 (29.41)	12 (70.59)	0.1268
No	67 (50.76)	65 (49.24)		105 (48.61)	111 (51.39)	
Previous stroke						
Yes	15 (34.88)	28 (65.12)	0.0318*	33 (45.83)	39 (54.17)	0.7783
No	56 (54.37)	47 (45.63)		77 (47.83)	84 (52.17)	
Previous TIA						
Yes	10 (50.00)	10 (51.590	0.895	18 (85.71)	3 (14.29)	0.0002*
No	61 (48.410	65 (51.59)		92 (43.40)	120 (56.60)	
Congestive heart failure						
Yes	4 (33.33)	8 (66.67)	0.2684	8 (40.00)	12 (60.00)	0.4993
No	67 (50.00)	67 (50.00)		102 (47.89)	111 (52.11)	
Carotid artery stenosis						
Yes	0 (0.00)	10 (100.00)	0.0014*	3 (30.00)	7 (70.00)	0.2651
No	71 (52.21)	65 (47.79)		107 (47.98)	116 (47.98)	
Peripheral vascular disease						
Yes	4 (33.33)	8 (66.67)	0.2684	5 (45.45)	6 (54.55)	0.9049
No	67 (50.00)	67 (50.00)		105 (47.30)	117 (52.70)	
Diabetes						
Yes	15 (38.46)	24 (61.54)	0.1378	28 (50.00)	28 (50.00)	0.6314
No	56 (52.34)	51 (47.66)		82 (46.33)	95 (53.67)	

(Continued)

Table 2. (Continued)

	Female smokers (146)		P value	Male smokers (233)		P value
	rtPA (71; control)	No rtPA (75)		rtPA (110; control)	No rtPA (123)	
Medication history: (%)						
Antiplatelet						
Yes	27 (45.00)	33 (55.00)	0.4635	57 (61.29)	36 (38.71)	0.0005*
No	44 (51.16)	42 (48.84)		53 (37.86)	87 (62.14)	
Antihypertensive						
Yes	43 (47.25)	48 (52.75)	0.6684	76 (53.15)	67 (46.85)	0.0221*
No	28 (50.91)	27 (49.09)		34 (37.78)	56 (62.22)	
Cholesterol reducer medication						
Yes	21 (38.18)	34 (61.82)	0.0496*	52 (59.09)	36 (40.91)	0.0047*
No	50 (54.95)	41 (45.05)		58 (40.00)	87 (60.00)	
Diabetes medication						
Yes	15 (46.88)	17 (53.13)	0.8221	18 (48.65)	19 (51.35)	0.8485
No	56 (49.12)	58 (50.88)		92 (46.94)	104 (53.06)	
Initial NIH Stroke Scale						
Group: (%)						
0–9	45 (45.00)	55 (55.00)	0.3637	17 (51.52)	86 (57.33)	0.2688
10–14	13 (61.90)	8 (38.10)		18 (56.25)	16 (48.48)	
15–20	6 (42.86)	8 (57.14)		64 (42.67)	14 (43.75)	
21–25	7 (63.64)	4 (36.36)		11 (61.11)	7 (38.89)	
Mean ± SD	8.99 ± 6.35	6.95 ± 6.05	0.0488*	9.69 ± 6.39	7.41 ± 6.53	0.0076*
Risk of mortality GWTG						
Mean ± SD	4.18 ± 4.4	3.36 ± 3.81	0.2512	4.65 ± 4.43	3.84 ± 3.99	0.1769
Initial exam findings: (%)						
Weakness/paresis						
Yes	69 (53.08)	61 (46.92)	0.0022*	105 (51.98)	97 (48.02)	0.0002*
No	2 (12.50)	14 (87.50)		5 (16.13)	26 (83.87)	
Altered level of consciousness						
Yes	14 (38.89)	22 (61.11)	0.1779	30 (42.25)	41 (57.75)	0.3157
No	57 (51.82	53 (48.18)		80 (49.38)	82 (50.62)	
Aphasia/language disturbance						
Yes	43 (51.19)	41 (48.81)	0.4712	74 (47.13)	83 (52.87)	0.9732
No	28 (45.16)	34 (54.84)		36 (47.37)	40 (52.63)	
Location of treatment: (%)						
Specialized stroke unit	0	1 (100.00)	0.4823	1 (33.33)	2 (66.67)	0.7267
Nonspecialized stroke unit	30 (52.63)	27 (47.37)		45 (50.00)	45 (50.00)	
Missing	41 (46.59)	47 (53.41)		64 (45.71)	76 (54.29)	

SD: standard deviation; TIA: transient ischemic attack; NIH: National Institutes of Health; GWTG: Get With The Guidelines.

stepwise conditional logistic regression was performed for the male and female stroke patients with a history of smoking subgroups separately to identify variables that were associated with rtPA exclusion. In the female subgroup (Table 6), only one factor, weakness/paresis on initial examination (OR = 0.117 95% CI 0.025–0.548, $P < 0.01$), was associated with rtPA exclusion. In male subgroup patients (Table 7), three factors were independently associated with rtPA exclusion: history of previous TIA (OR = 0.169 95% CI 0.044–0.655, $P < 0.05$), antiplatelet medication use (OR = 0.456 95% CI 0.230–0.906, $P < 0.05$), and weakness/paresis on initial examination (OR = 0.171 95% CI 0.056–0.521 $P < 0.01$).

Discussion

Three major findings arise from this study. First, we found that more ischemic stroke patients with a history of smoking were excluded from rtPA compared to stroke patients with a history of smoking that received thrombolysis therapy. Second, although the number of male smokers was higher than female smokers in the stroke population, there was no significant difference in male and female patients excluded from thrombolysis therapy in the univariate analysis. Third, following adjustment, more clinical risk factor variables were significantly associated with reduced exclusion of male compared to female stroke patients with a history of

Table 3. Factors associated with rtPA exclusion in acute ischemic stroke patients with a history of smoking. Positive B values (OR > 1) denote variables more associated with rtPA exclusion, while negative B values (OR < 1) denote variables more associated with rtPA inclusion.

	Odds ratio	P value
Age group	1.020 (1.003–1.037)	0.0239*
Race W vs. B	0.933 (0.585–1.486)	0.7688
Gender F vs. M	0.945 (0.624–1.429)	0.7877
Body mass index	0.998 (0.972–1.025)	0.8730
Hypertension Y vs. N	0.835 (0.527–1.32)	0.4429
Coronary artery disease Y vs. N	0.771 (0.486–1.225)	0.2709
Dyslipidemia Y vs. N	0.683 (0.455–1.025)	0.0655
Atrial fibrillation/flutter Y vs. N	2.388 (1.069–5.332)	0.0337*
Previous stroke	1.417 (0.911–2.205)	0.1223
Previous TIA	0.384 (0.192–0.767)	0.0067*
Congestive heart failure	1.582 (0.750–3.336)	0.2279
Carotid artery stenosis	5.571 (1.605–19.338)	0.0068*
Peripheral vascular disease	1.454 (0.614–3.446)	0.3951
Diabetes	1.143 (0.717–1.821)	0.5749
Antiplatelet	0.618 (0.409–0.934)	0.0223
Antihypertensive	0.722 (0.476–1.095)	0.1256
Cholesterol reducer medication	0.809 (0.534–1.227)	0.3182
Diabetes medication	0.997 (0.591–1.680)	0.9899
Initial NIH Stroke Scale	0.948 (0.917–0.979)	0.0011*
Risk of mortality GWTG	0.954 (0.905–1.006)	0.0802
Weakness/paresis Y vs. N	0.159 (0.069–0.365)	< 0.0001*
Altered level of consciousness Y vs. N	1.453 (0.924–2.285)	0.1056
Aphasia/language disturbance Y vs. N	0.917 (0.603–1.394)	0.6842
Risk of mortality GWTG	0.954 (0.905–1.006)	0.0802
Ischemic stroke		
Stroke unit Y vs. N	1.220 (0.806–1.848)	0.3474

TIA: transient ischemic attack; NIH: National Institutes of Health; GWTG: Get With The Guidelines.
Y vs N: Yes vs No.

smoking. This finding suggests that females are more likely to be excluded than males from thrombolysis therapy. Moreover, the effect of the only common factor in males and females (weakness) is stronger in males (17.1 % vs 11.7% less likelihood for rtPA exclusion). The primary outcome of this analysis was clinical risk factors associated with exclusion from rtPA in females and males with acute ischemic stroke and a history of smoking. Other outcomes included individual components of the ischemic stroke and comorbidities associated with stroke or smoking.

In the univariate analysis, female patients with a history of previous stroke, carotid artery stenosis, and use of cholesterol reduction medication were excluded from rtPA. This effect was attenuated in the adjusted analysis in the female patients, indicating that the proportion of exclusion does not depend on the female gender but rather on clinical risk factors within the stroke population. Following adjustment with regression analysis, we found that male patients are less likely to have CAD, dyslipidemia, a previous trans ischemic attack (TIA), weakness, are less likely to take antiplatelet medication or cholesterol reduction medication and have a lower calculated NIHSS score. Several clinical characteristics identified in male stroke patients with a history of smoking are similar to those found in other studies in male stroke patients.[23–28] For example, we found that after adjusting for age and comorbidities, male stroke patients with a history of smoking with a previous TIA and weakness are more likely to receive rtPA. This is supported by other studies where a previous TIA[29] and weakness[30] did not affect the favorable outcome following thrombolysis therapy in male stroke patients. In our study, male stroke patients with a history of smoking that take antiplatelet medication had lower odds of receiving thrombolysis therapy. This finding is supported by other studies[31–35] that found the use of antiplatelet medication to be associated with an increased risk of bleeding among female in comparison to male stroke patients. This finding, together with our current result, indicates that the benefits of antiplatelet therapy may be different among male and female stroke patients with a history of smoking.

In the univariate analysis, age was not significant in the female or male patients who did not receive or received thrombolysis. However, the effect of age was significantly associated with exclusion in the whole stroke population

Table 4. Factors associated with rtPA exclusion in male and female acute ischemic stroke patients with a history of smoking. Positive B values (OR > 1) denote variables more associated with rtPA exclusion while negative B values (OR < 1) denote variables more associated with rtPA inclusion.

	Female smokers	P value	Male smokers	P value
	Odds ratio		Odds ratio	
Age group	1.019 (0.995–1.043)	0.1286	1.021 (0.996–1.046)	0.0949
Race W vs. B	0.938 (0.435–2.025)	0.8711	0.931 (0.518–1.673)	0.8119
Gender F vs. M				
Body mass index	0.987 (0.952–1.023)	0.4604	1.014 (0.973–1.058)	0.5015
Hypertension Y vs. N	1.330 (0.637–2.774)	0.4476	0.614 (0.337–1.119)	0.1115
Coronary artery Disease Y vs. N	1.553 (0.686–3.512)	0.2907	0.537 (0.302–0.953)	0.0337
Dyslipidemia Y vs. N	1.183 (0.617–2.265)	0.6132	0.481 (0.284–0.813)	0.0062*
Atrial Fibrillation/flutter Y vs. N	2.577 (0.769–8.630)	0.1248	2.269 (0.773–6.660)	0.1358
Previous stroke	2.224 (1.064–4.649)	0.0336*	1.083 (0.620–1.891)	0.7785
Previous TIA	0.938 (0.365–2.411)	0.8950	0.128 (0.037–0.447)	0.0013*
Congestive heart failure	2.000 (0.575–6.959)	0.2761	1.378 (0.542–3.508)	0.5007
Carotid artery stenosis	> 999.999 (< 0.001–> 999.999)	0.9703	2.151 (0.543–8.532)	0.2757
Peripheral vascular disease	2.000 (0.575–6.959)	0.2761	1.077 (0.319–3.631)	0.9051
Diabetes	1.757 (0.831–3.713)	0.1400	0.863 (0.473–1.575)	0.6311
Antiplatelet	1.280 (0.661–2.481)	0.4639	0.385 (0.224–0.660)	0.0005*
Antihypertensive	1.158 (0.592–2.262)	0.6685	0.535 (0.313–0.917)	0.0228*
Cholesterol reducer medication	1.974 (0.997–3.909)	0.0509*	0.462 (0.269–0.792)	0.0050*
Diabetes medication	1.094 (0.499–2.400)	0.8223	0.934 (0.462–1.886)	0.8483
Initial NIH Stroke Scale	0.948 (0.898–1.000)	0.0514*	0.947 (0.909–0.986)	0.0086*
Risk category	0.951 (0.873–1.037)	0.2540	0.955 (0.894–1.021)	0.1791
Weakness/paresis Y vs. N	0.126 (0.028–0.578)	0.0077*	0.178 (0.066–0.481)	0.0007*
Altered level of consciousness Y vs. N	1.690 (0.785–3.640)	0.1802	1.333 (0.760–2.340)	0.3163
Aphasia/language disturbance Y vs. N	0.785 (0.407–1.516)	0.4715	1.009 (0.583–1.747)	0.9732
Risk of mortality GWTG	0.951 (0.873–1.037)	0.2540	0.955 (0.894–1.021)	0.1791
Stroke unit Y vs. N	1.274 (0.653–2.483)	0.4776	1.187 (0.699–2.018)	0.5254

TIA: transient ischemic attack; NIH: National Institutes of Health; GWTG: Get With The Guideline.
Y vs N: Yes vs No.

Table 5. Factors associated with acute ischemic stroke patients with a history of smoking. Positive B values (adjusted OR > 1) denote variables more associated with rtPA exclusion, while negative B values (adjusted OR < 1) denote variables more associated with rtPA inclusion. Multicollinearity and interactions among independent variables were checked. Hosmer–Lemeshow test (P = 0.9095), Cox & Snell (R^2 = 0.1702), Max-rescaled R-square (R^2 = 0.2270), and classification table (overall correctly classified percentage = 67%) were applied to check the model fitness.

	B-value	Adjusted odds ratio	Wald	P value
Age	0.0234	1.024 (1.004–1.044)	1.4886	0.0184*
Initial NIH Stroke Scale	−0.0404	0.960 (0.926–0.996)	4.7512	0.0293*
Atrial fibrillation/flutter Y vs. N	1.1655	3.208 (1.308–7.868)	6.4825	0.0109*
Previous TIA Y vs. N	−0.9981	0.369 (0.161–0.844)	5.5766	0.0182*
Carotid artery stenosis Y vs. N	2.4353	11.419 (2.904–44.899)	12.1534	0.0005*
Weakness/paresis Y vs. N	−1.6952	0.184 (0.075–0.450)	13.7595	0.0002*
Antiplatelet Y vs. N	−0.9007	0.406 (0.246–0.672)	12.2832	0.0005*

NIH: National Institutes of Health; TIA: transient ischemic attack.
Y vs N: Yes vs No.

following the adjusted analysis and was eliminated in the male or female stroke patients. Therefore, it seems that the unadjusted variables in the acute ischemic stroke smokers' population could have been strongly confounded by several factors including age and related comorbidities. In a stroke population, the mean age of women is higher than that of men,[36] but in our study, the mean age of men and women who did not receive rtPA (59.3 vs 59.5) was

Table 6. Factors more associated with female acute ischemic stroke patients with a history of smoking. Positive B values (adjusted OR > 1) denote variables more associated with rtPA exclusion, while negative B values (adjusted OR < 1) denote variables more associated with rtPA inclusion. Multicollinearity and interactions among independent variables were checked. Hosmer–Lemeshow test (P = 0.9790), Cox & Snell ($R^2 = 0.1147$), Max-rescaled R-square ($R^2 = 0.1529$), and classification table (overall correctly classified percentage = 58.2%) were applied to check the model fitness.

	Adjusted odds ratio	P value
Previous stroke Y vs. N	1.877 (0.858–4.108)	0.1150
Cholesterol reducer medication	1.918 (0.926–3.971)	0.0796
Weakness/paresis Y vs. N	0.117 (0.025–0.548)	0.0065*

Y vs N: Yes vs No.

Table 7. Factors more associated with male acute ischemic stroke patients with a history of smoking. Positive B values (adjusted OR > 1) denote variables more associated with rtPA exclusion, while negative B values (adjusted OR < 1) denote variables more associated with rtPA inclusion. Multicollinearity and interactions among independent variables were checked. Hosmer–Lemeshow test (P = 0.6565), Cox & Snell ($R^2 = 0.1725$), Max-rescaled R-square ($R^2 = 0.2303$), and classification table (overall correctly classified percentage = 63.5%) were applied to check the model fitness.

	Adjusted odds ratio	P value
Initial NIH Stroke Scale	0.958 (0.916–1.003)	0.0646
Previous TIA Y vs. N	0.169 (0.044–0.655)	0.0101*
Weakness/paresis Y vs. N	0.171 (0.056–0.521)	0.0019*
Antiplatelet Y vs. N	0.456 (0.230–0.906)	0.0249*
Cholesterol reducer medication	0.687 (0.353–1.338)	0.2699

NIH: National Institutes of Health; TIA: transient ischemic attack.
Y vs N: Yes vs No.

younger and not significantly different. Therefore, it is possible that our young male and female stroke smoker patients probably combine many comorbid conditions to exclude patients from thrombolysis. Although our patient population also contains elderly men and women (> 70 years old), the adjusted analysis generally abolished any effect of old age on the male and female population. In general, the risk of stroke is known to be greater among female smokers compared to male smokers,[14] lower in women than in men under the age of 75, but similar when comparing women and men above age 75.[37] In our study, more clinical risk factors were associated with a less likelihood of excluding more male than female stroke patients with a history of smoking. This finding suggests that the age structure (< 75) in our stroke population with a history of smoking probably translates into more clinical risk factors, rather than age, to exclude more women than men from thrombolysis therapy. Therefore, gender difference in stroke with a history of smoking related to exclusion risk factors is unlikely to be mediated by differences in smoking-related behavior (such as greater degree of smoking by men or women), because such a gender effect is associated with clinical risk factors of stroke. For example, many stroke-related studies reported that women who survive stroke have less favorable clinical outcomes than men,[38] have a worse clinical prognosis than men,[39] are more likely to have comorbidities and activity limitations on follow-up,[40] and have a lower overall quality of life than men after stroke.[16,41] These findings support our current result that the observed differences in exclusion from thrombolysis between women and men stroke patients with a history of smoking may be attributed to pretreatment clinical risk factors that excluded more women than men instead of the differential effects of smoking on men and women. There is no doubt that smoking is a major risk factor for acute ischemic stroke patients and causes damage to both men and women. In addition, the risk of stroke is greater among women smokers compared to men who smoke.[16] This finding is supported by our study that in a stroke population with a history of smoking, women are more likely to be excluded from thrombolysis therapy compared to men, even after adjustment.

Several limitations may hamper the interpretation of the results of this study. There is potential under-reporting of smoking status, which could have resulted in misclassification of some current smokers as nonsmokers, resulting in an inaccurately reduced relationship between smoking and stroke risk. Furthermore, lack of information on the duration of smoking did not allow for in-depth analysis for gender differential effects and duration of smoking on stroke. The single-center approach and the retrospective data could introduce a selection bias in the dataset. There was also a lack of data on some clinical risk factors that have a role in stroke onset, including metabolic syndrome, and sex-hormone-related factors. Finally, because information on menopausal status and use of hormone replacement therapies were not available, we were unable to evaluate whether they had any modifying effect on the relationship between smoking and risk of stroke in women. A major strength of this study is the use of data from a large stroke center that provides quality dataset of acute ischemic stroke population with a history of smoking. These data provide the opportunity to develop predictive models to identify clinical risk factors that excluded men and women stroke patients with a history of smoking from thrombolysis therapy. An important contribution of this study to stroke neurology is 1) the investigation of exclusion criteria for rtPA in stroke among women and men with a history of smoking and 2) our finding that observed gender difference in stroke population with a history of smoking is attributed to the pretreatment risk factors that excluded more women than men.

Conclusion

Smokers, irrespective of gender, have an increased risk of incurring a stroke during their lifetime compared to non-smokers. Our findings suggest that women are more likely to be excluded from thrombolysis therapy compared to men stroke patients with a history of smoking. The exclusion appears to be associated with pretreatment clinical risk factors that excluded more women than men, rather than the effects of smoking on women than men. The observed gender difference suggests that more studies are needed to improve the use of thrombolysis therapy in stroke patients with a history of smoking irrespective of gender.

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Author contributions

ORR, IFA, and TIN designed the concept, experimental, and data analysis. AP, SL, BW, and BB critically revised the drafts read and approved the last version of this article.

Availability of data and materials

All materials are available for use from the corresponding author.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval and consent to participate

This study was performed with the approval of the Institutional Review Board of Greenville Health System and the institutional Committee for Ethics (ID no: Pro00046787). Consent was waived because this is a retrospective chart review for data analysis with blinded data, and qualifies for exempt in line with Health Insurance Policy and Accountability Act (HIPAA) privacy regulations.

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