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Smoking-Induced Sex Differences in Clinical Outcomes in Patients Undergoing Mechanical Thrombectomy for Stroke

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■ OBJECTIVE: Ischemic stroke is the fifth leading cause of death in the United States. Smoking accelerates the onset of stroke by 10 years. The effects of smoking status on percent change in National Institutes of Health Stroke Scale (NIHSS) score, infarct volume, and edema volume were examined following mechanical thrombectomy for large vessel occlusion in patients with acute ischemic stroke.

■ METHODS: Subjects ($N = 90$; >18 years old) were divided into 3 groups based on smoking status: current smokers, previous smokers (defined as having quit >6 months before the ischemic event), and nonsmokers. Percent change in NIHSS score was defined as score at admission minus score at discharge divided by score at admission and was used as a predictor of functional outcome. Linear regression analysis was performed based on infarct or edema volume versus percent change in NIHSS score and separated by sex.

■ RESULTS: Consistent with previous findings, smokers experienced a stroke 10 years earlier than nonsmokers ($P = 0.004$). Statistically significant linear regressions existed between infarct volume or edema volume in relation to worsening change in NIHSS score with female smokers only. Stroke-induced tissue damage, as measured by magnetic resonance imaging or computed tomography, was predictive of functional recovery only in female smokers.

■ CONCLUSIONS: These findings are valuable for patient counseling, particularly for women, for smoking cessation.

INTRODUCTION

Stroke is the second leading cause of death and third most common cause of disability worldwide.[1] Cigarette smoking is a modifiable risk factor for stroke, contributing to approximately 20% of stroke occurrences.[2] Interestingly, studies have suggested a link between smoking and favorable clinical outcomes following stroke, termed the smoking paradox. This was first described in patients with myocardial infarction.[3] Kurmann et al.[2] evaluated how smoking affects prognosis following intravenous thrombolysis treatment and found a favorable outcome for smokers attributed to higher recanalization rates in smokers than in nonsmokers. However, a recent meta-analysis including 21 different studies by Li et al.[4] found no difference in prognostic outcome of smokers with ischemic stroke. Further studies are necessary to determine the relationship between smoking and stroke outcome following mechanical thrombectomy (MT), which is becoming an increasingly more common method of stroke treatment. In the only study of its kind, von Martial et al.[5] found higher recanalization and lower mortality of smokers following endovascular treatment for large vessel occlusions. However, they noted the well-established 10-year age gap between smokers and nonsmokers experiencing stroke. Few studies incorporated sex-based differences in the context of smoking and

Key words
- Sex differences
- Smoking
- Stroke
- Thrombectomy

Abbreviations and Acronyms
BACTRAC: Blood And Clot Thrombectomy Registry And Collaboration
MT: Mechanical thrombectomy
NIHSS: National Institutes of Health Stroke Scale

Table 1. Demographics

	1. Nonsmoker	2. Previous Smoker	3. Current Smoker	*P* Value
Sex, male	24 (45%)	6 (43%)	11 (48%)	>0.999
Age, years				1 versus 3: 0.004*
	72.9 ± 15.7	65.7 ± 12.9	61.9 ± 12.9	1 versus 2: 0.118
				2 versus 3: 0.391
BMI				1 versus 3: 0.941
	28.2 ± 6.3	28.4 ± 7.2	28.2 ± 7.3	1 versus 2: 0.916
				2 versus 3: 0.895
Comorbidities				
Hypertension	35 (66%)	10 (71%)	15 (65%)	0.917
Diabetes mellitus type 2	17 (32%)	3 (21%)	7 (30%)	0.891
Hyperlipidemia	9 (17%)	6 (43%)	9 (39%)	0.014*
Previous stroke	8 (15%)	4 (29%)	3 (13%)	0.419
Myocardial infarction	1 (2%)	3 (21%)	4 (17%)	0.019*
NIHSS score on admission				
Minor (1—4)	3 (6%)	0 (0%)	0 (0%)	
Moderate (5—15)	21 (40%)	6 (43%)	9 (39%)	0.075
Moderate/severe (16—20)	9 (17%)	3 (21%)	11 (48%)	
Severe (≥21)	20 (37%)	5 (36%)	3 (13%)	
NIHSS score at discharge†				
Minor (1—4)	16 (41%)	2 (25%)	8 (47%)	
Moderate (5—15)	12 (31%)	5 (62%)	7 (41%)	0.496
Moderate/severe (16—20)	4 (10%)	1 (13%)	1 (6%)	
Severe stroke (≥21)	7 (18%)	0 (0%)	1 (6%)	
TICI score				
1/2A: <50% perfusion	2 (4%)	2 (14%)	2 (9%)	
2B: >50% perfusion	19 (36%)	6 (43%)	6 (26%)	0.463
3: full perfusion	32 (60%)	6 (43%)	15 (65%)	
LKN to thrombectomy completion time, minutes†	491 ± 299	550 ± 492	492 ± 347	1 versus 3: 0.983
				1 versus 2: 0.583
				2 versus 3: 0.687
Infarct volume, mm³‡	65,992 ± 84,544	42,967 ± 39,764	76,383 ± 115,358	1 versus 3: 0.671
				1 versus 2: 0.329
				2 versus 3: 0.305
Edema volume, mm³‡	69,950 ± 90,664	41,783 ± 42,640	75,940 ± 113,286	1 versus 3: 0.813
				1 versus 2: 0.266
				2 versus 3: 0.289

Values are presented as mean ± SD or number (%).
BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; TICI, Thrombolysis In Cerebral Infarction; LKN, last known normal.
*Statistically significant.
†Data missing for 3 patients (*n* = 87).
‡Data missing for 4 patients (*n* = 86).

stroke, although one study did find that women who smoke have a 17% increase in incidence of hemorrhagic stroke.[6] Therefore, in the current study, we aimed to determine the sex-based effects of smoking on short-term outcomes after MT using our previously published Blood And Clot Thrombectomy Registry And Collaboration (BACTRAC) stroke tissue bank (ClinicalTrials.gov Identifier: NCT03153683).[7] We evaluated percent change in National Institutes of Health Stroke Scale (NIHSS) score from admission to discharge, infarct volume, and cerebral edema volume following MT for large vessel occlusion in the context of smoking.

MATERIALS AND METHODS

Patients undergoing MT as standard treatment for a large vessel occlusion were registered in our continuously enrolling tissue

bank (institutional review board number 48831). Briefly, intracranial arterial blood distal to the thrombus, systemic arterial blood proximal to the thrombus, and the thrombus itself are collected and banked separately.[7] Inclusion criteria were as follows: adults ≥18 years old, nonpregnant, nonprisoner, emergent large vessel occlusive ischemic stroke suspected, and qualifying for standard MT. Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Kentucky.[8,9]

For analysis, after providing consent, subjects were divided into 3 self-reported groups: current smoker, previous smoker (defined as having quit >6 months before the ischemic event), and nonsmoker. NIHSS scores were recorded on admission and at discharge. The percent change in NIHSS score was defined as score at admission minus score at discharge divided by score at

Table 2. Male Versus Female Smokers

	Male	Female		P Value
Sex	11 (48%)	12 (52%)		
Age, years	60.6 ± 12.9	63.1 ± 13.4		0.660
BMI	27.4 ± 6.1	28.7 ± 8.5		0.698
Comorbidities				
Hypertension	6 (55%)	9 (75%)		0.400
Diabetes mellitus type 2	2 (18%)	5 (42%)		0.371
Hyperlipidemia	5 (45%)	4 (33%)		0.680
Previous stroke	1 (9%)	2 (17%)		>0.999
Previous myocardial infarction	1 (9%)	3 (25%)		0.590
NIHSS score on admission				
Minor (1—4)	0 (0%)	0 (0%)		
Moderate (5—15)	5 (45%)	4 (33%)		0.543
Moderate/severe (16—20)	4 (36%)	7 (58%)		
Severe (≥21)	2 (19%)	1 (9%)		
NIHSS score at discharge*				
Minor (1—4)	4 (57%)	4 (40%)		
Moderate (5—15)	3 (43%)	4 (40%)		0.645
Moderate/severe (16—20)	0 (0%)	1 (10%)		
Severe (≥21)	0 (0%)	1 (10%)		
TICI score				
1/2A: <50% perfusion	1 (9%)	1 (8%)		
2B: >50% perfusion	3 (27%)	3 (25%)		>0.999
3: full perfusion	7 (64%)	8 (67%)		
LKN to thrombectomy completion time, minutes	510 ± 469	479 ± 224		0.839
Infarct volume, mm³	75,439 ± 110,607	74,096 ± 121,086		0.980
Edema volume, mm³	74,781 ± 111,280	75,839 ± 116,819		0.899

Values are presented as mean ± SD or number (%).
BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; TICI, Thrombolysis In Cerebral Infarction; LKN, last known normal.
*Data missing for males (n = 7) and 10 females (n = 10).

admission × 100. Percent change of NIHSS score was found to be a better prognosticator over delta NIHSS score of functional outcome at 3 months for patients who received reperfusion therapy.[10] Infarct volume and cerebral edema volume were measured on postoperative magnetic resonance imaging or computed tomography by a single neuroradiologist who was blinded to the subject groups (D.E.L.) as previously reported.[11] Linear regression analysis was performed using GraphPad Prism 8.2 (GraphPad Software, San Diego, California, USA) based on infarct or edema volume versus the percent change in NIHSS score. Groups were evaluated based on sex and smoking status, and a P value <0.05 was considered significant. Demographic

tables were constructed via appropriate unpaired t tests and Fisher exact tests using GraphPad Prism 8.2.

RESULTS

The study included 90 adults (>18 years old); 49 (54%) were female. Median age was 69 years (range, 25–101 years). Of patients, 23 (25.5%) were active smokers, 14 (15.5%) were previous smokers, and 53 (59%) were nonsmokers. Mean infarct time (time from last known normal to recanalization) was 501 ± 345 minutes. Mean infarct volume was 64,757 ± 87,643 mm³. Mean edema volume was 66,978 ± 90,676 mm³. Mean NIHSS score on admission was

Table 3. Male Versus Female Nonsmoker Summary			
	Male	**Female**	**P Value**
Sex	24 (45%)	29 (55%)	
Age, years	72.5 ± 16.2	73.4 ± 15.5	0.839
BMI	27.8 ± 5.9	28.6 ± 6.6	0.671
Comorbidities			
Hypertension	15 (63%)	20 (69%)	0.772
Diabetes mellitus type 2	5 (21%)	12 (41%)	0.145
Hyperlipidemia	4 (17%)	5 (17%)	>0.999
Previous stroke	2 (8%)	6 (21%)	0.269
Myocardial infarction	0 (0%)	2 (7%)	0.495
NIHSS score on admission			
Minor (1–4)	2 (8%)	1 (3%)	
Moderate (5–15)	7 (29%)	14 (48%)	0.077
Moderate/severe (16–20)	2 (8%)	7 (24%)	
Severe (≥21)	13 (54%)	7 (24%)	
NIHSS score at discharge†			
Minor (1–4)	8 (40%)	8 (42%)	
Moderate (5–15)	4 (20%)	7 (37%)	0.434
Moderate/severe (16–20)	4 (20%)	1 (5%)	
Severe (≥21)	4 (20%)	3 (16%)	
TICI score			
1/2A: <50% perfusion	2 (8%)	0 (0%)	
2B: >50% perfusion	6 (5%)	13 (45%)	0.416
3: full perfusion	16 (67%)	16 (55%)	
LKN to thrombectomy completion time, minutes	479 ± 339	501 ± 270	0.793
Infarct volume, mm³‡	93,525 ± 103,965	41,636 ± 53,827	0.031*
Edema volume, mm³‡	97,151 ± 113,597	45,888 ± 56,068	0.047*

Values are presented as mean ± SD or number (%).
BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; TICI, Thrombolysis In Cerebral Infarction; LKN, last known normal.
*Statistically significant.
†Data missing for males (n = 20) and females (n = 19).
‡Data missing for 1 male (n = 23) and 3 females (n = 26).

16.9 ± 7.6, and mean NIHSS score at discharge was 9.3 ± 8.6. Mean age at time of infarct for the current smoking patients was 10 years earlier when compared with the nonsmokers (61.9 years vs. 72.9 years, P = 0.004) (Table 1). No significant demographic differences were found between sexes based on smoking status (Tables 2−4). Infarct volume and edema volume were evaluated based on sex and smoking status (Tables 1−4). Significantly smaller infarct and edema volumes were found in female patients who were nonsmokers (P < 0.05) and previous smokers (P = 0.12) relative to their male counterparts. Infarct volume for currently smoking female patients was not significantly different from currently smoking male patients (P = 0.980) (Tables 2−4). Percent change in NIHSS score with infarct volume (P < 0.0001, r^2 = 0.691) or edema volume (P < 0.0001, r^2 = 0.751) was correlated only in smokers (Figure 1A−D). When further evaluated based on sex,

only female smokers showed a significant correlation for infarct volume (P = 0.0002, r^2 = 0.848) or edema volume (P < 0.0001, r^2 = 0.889) versus percent change in NIHSS score; male smokers were not correlated (P = 0.44, r^2 = 0.124; P = 0.26, r^2 = 0.248) (Figure 2A−D).
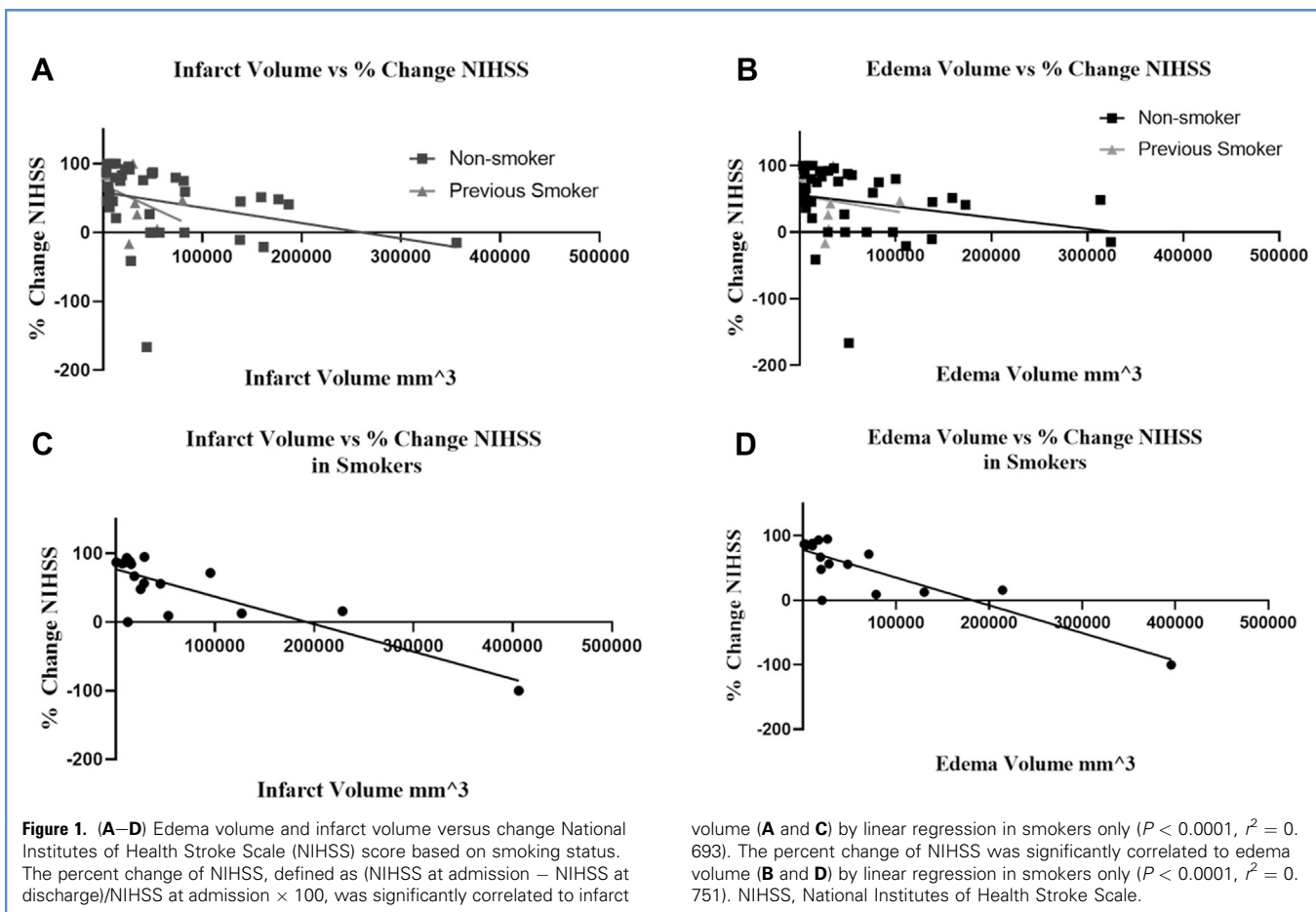
DISCUSSION

On average, smokers experienced a stroke 10 years earlier than nonsmokers, which is consistent with previously published findings.[4,12] Female former smokers and nonsmokers had significantly smaller infarct and edema volumes compared with male counterparts. Statistically significant regressions existed between infarct or edema volume in relation to worsening change in NIHSS score in smokers only. Female smokers were the most at

Table 4. Male Versus Female Previous Smokers

	Male	Female	P Value
Sex	6 (43%)	8 (57%)	
Age, years	61.5 ± 14.4	68.9 ± 11.5	0.308
BMI	28.6 ± 6.0	28.3 ± 8.5	0.936
Comorbidities			
Hypertension	4 (67%)	6 (75%)	>0.999
Diabetes mellitus type 2	1 (17%)	2 (25%)	>0.999
Hyperlipidemia	3 (50%)	3 (38%)	>0.999
Previous stroke	1 (17%)	3 (38%)	0.580
Previous myocardial infarction	1 (17%)	0 (0%)	0.429
NIHSS score on admission)			
Minor (1−4)	0 (0%)	0 (0%)	
Moderate (5−15)	2 (33.3%)	4 (50%)	0.627
Moderate/severe (16−20)	2 (33.3%)	1 (12.5%)	
Severe (≥21)	2 (33.3%)	3 (37.5%)	
NIHSS score at discharge*			
Minor (1−4)	0 (0%)	2 (40%)	
Moderate (5−15)	3 (100%)	2 (40%)	0.237
Moderate/severe (16−20)	0 (0%)	1 (20%)	
Severe (≥21)	0 (0%)	0 (0%)	
TICI score			
1/2A: <50% perfusion	0 (0%)	2 (25%)	
2B: >50% perfusion	3 (50%)	3 (37.5%)	0.417
3: full perfusion	3 (50%)	3 (37.5%)	
LKN to thrombectomy completion time, minutes	348 ± 190	701 ± 602	0.195
Infarct volume, mm³	62,324 ± 48,339	28,449 ± 26,557	0.118
Edema volume, mm³	61,274 ± 48,101	27,164 ± 33,973	0.145

Values are presented as mean ± SD or number (%).
BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; TICI, Thrombolysis In Cerebral Infarction; LKN, last known normal.

Figure 1. (**A**–**D**) Edema volume and infarct volume versus change National Institutes of Health Stroke Scale (NIHSS) score based on smoking status. The percent change of NIHSS, defined as (NIHSS at admission − NIHSS at discharge)/NIHSS at admission × 100, was significantly correlated to infarct volume (**A** and **C**) by linear regression in smokers only ($P < 0.0001$, $r^2 = 0.693$). The percent change of NIHSS was significantly correlated to edema volume (**B** and **D**) by linear regression in smokers only ($P < 0.0001$, $r^2 = 0.751$). NIHSS, National Institutes of Health Stroke Scale.
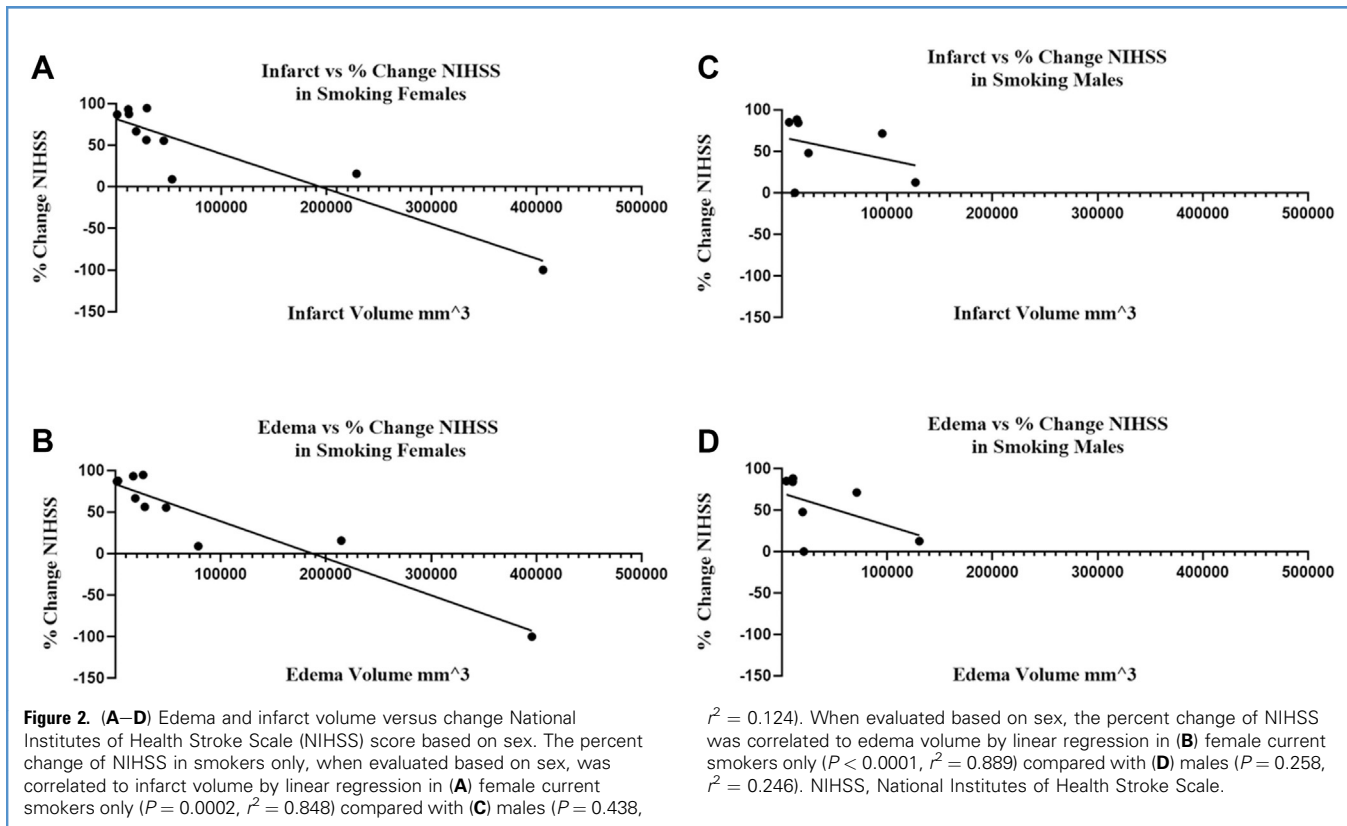
risk of higher infarct and edema volumes, which correlated with worse functional outcomes as detailed in the correlation with change in NIHSS score. Clinically these findings should be considered when counseling patients before and after stroke to aid in smoking cessation.

Advanced age has a known negative correlation with stroke outcome.[13] As others have reported,[5] we found that smokers experience stroke on average 10 years earlier compared with nonsmokers. This significantly earlier onset may account for the controversial smoking paradox, as younger patients may recover more easily from stroke. While one study of patients receiving intravenous thrombolysis treatment found a favorable outcome for smokers attributed to higher recanalization rates in smokers over nonsmokers,[2] a meta-analysis study found no difference in prognostic outcome of smokers with ischemic stroke.[4] In contrast, our study focusing on large vessel occlusion demonstrates that female smokers experience larger infarct volumes than female nonsmokers and previous smokers and does not support the smoking paradox.

Another interesting finding is that infarct volume and edema were significantly correlated with NIHSS score functional outcomes in only female smokers. Early neurological improvement is a recently adopted method to help account for the effect of MT on recovery.[14] As cited in more recent studies, percent change of NIHSS score as a predictive method of stroke outcome is being used to improve the early neurological improvement calculation.[10,15,16] Recent literature demonstrates that percent change of NIHSS score as an early neurological improvement better correlates with functional outcomes at 3 months over the traditional delta NIHSS score measure for patients receiving alteplase and thrombectomy.[10,16] Percent change permits capture of patients who may have had a small delta but recovered fully. For instance, a patient who presents with an NIHSS score of 30 and is discharged with a score of 24 has a delta NIHSS score of 6 but improved only 20%, whereas a patient presenting with a score of 10 and leaving with a score of 4 also has a delta NIHSS score of 6 but had 60% improvement. Evaluating percent change of NIHSS score with infarct volume and edema volume after thrombectomy predicts early clinical outcome in a straightforward way for female smokers undergoing thrombectomy. It is increasingly recognized that men and women have some unique pathophysiologic mechanisms in

Figure 2. (**A**–**D**) Edema and infarct volume versus change National Institutes of Health Stroke Scale (NIHSS) score based on sex. The percent change of NIHSS in smokers only, when evaluated based on sex, was correlated to infarct volume by linear regression in (**A**) female current smokers only ($P = 0.0002$, $r^2 = 0.848$) compared with (**C**) males ($P = 0.438$, $r^2 = 0.124$). When evaluated based on sex, the percent change of NIHSS was correlated to edema volume by linear regression in (**B**) female current smokers only ($P < 0.0001$, $r^2 = 0.889$) compared with (**D**) males ($P = 0.258$, $r^2 = 0.246$). NIHSS, National Institutes of Health Stroke Scale.

risks, evolution, and recovery from stroke, including varying effects of sex hormones.[17] More studies are needed to explore the source of this high correlation present only in female smokers.

One limitation of this study is that selection bias is present with all patients in the BACTRAC registry being enrolled from only the University of Kentucky. Our population is >80% Caucasian residing in mostly rural areas; therefore, a more diverse population is needed to validate these findings to determine that these observations are not unique to this area of Kentucky. However, some of our findings confirm previously published data, suggesting that our results may reflect the greater population. The BACTRAC study continues to enroll more patients, and we plan to re-evaluate our findings for validation and expansion of our results.

CONCLUSIONS

Patients who continue to smoke are more likely to have a stroke earlier in life with potentially more significant disability and worse prognosis. However, smoking is more detrimental for female patients, strongly suggesting more rigorous counseling on smoking cessation for women. Further research is needed to identify the link between increased infarct volume and edema volume in female smokers and the strong correlation to worsening prognosis with increased infarct volume and edema volume.

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