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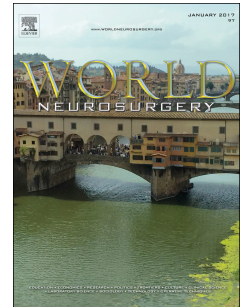
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Credit Author Statement

Jacqueline A. Frank: Methodology, Formal Analysis, Investigation, Writing-original draft.
Kara Jo Swafford: Writing-review and editing, visualization. **Jill M. Roberts:** Writing-review and editing. **Amanda L. Trout:** Writing-review and editing. **Ann M. Stowe:** Writing-review and editing. **Douglas E. Lukins:** Methodology, Formal Analysis, Writing-review and editing. **Stephen Grupke:** Investigation. **Keith R. Pennypacker:** Writing-original draft, Writing-review and editing, Project administration. **Justin F. Fraser:** Writing-original draft, Writing-review and editing, Project administration, Investigation, Supervision, Data Curation.

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¹Department of Neurology, University of Kentucky, Lexington, Kentucky, USA

²Department of Neurosurgery, University of Kentucky, Lexington, Kentucky, USA

³Department of Radiology, University of Kentucky, Lexington, Kentucky, USA

⁴Department of Neuroscience, University of Kentucky, Lexington, Kentucky, USA

⁵Center for Advanced Translational Stroke Science, University of Kentucky, Lexington, Kentucky, USA

Corresponding Author:

Justin F. Fraser, MD, FAANS, FAHA
Associate Professor of Cerebrovascular, Endovascular, and Skull Base Surgery
Director, Cerebrovascular Surgery and NeuroInterventional Radiology
Departments of Neurological Surgery, Neurology, Radiology, and Neuroscience
Center for Advanced Translational Stroke Science
University of Kentucky
E-mail: jfr235@uky.edu

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¹Department of Neurology, University of Kentucky, Lexington, Kentucky, USA

²Department of Neurosurgery, University of Kentucky, Lexington, Kentucky, USA

³Department of Radiology, University of Kentucky, Lexington, Kentucky, USA

⁴Department of Neuroscience, University of Kentucky, Lexington, Kentucky, USA

⁵Center for Advanced Translational Stroke Science, University of Kentucky, Lexington, Kentucky, USA

Corresponding Author:

Justin F. Fraser, MD, FAANS, FAHA
Associate Professor of Cerebrovascular, Endovascular, and Skull Base Surgery
Director, Cerebrovascular Surgery and NeuroInterventional Radiology
Departments of Neurological Surgery, Neurology, Radiology, and Neuroscience
Center for Advanced Translational Stroke Science
University of Kentucky
E-mail: jfr235@uky.edu

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Abstract

Objective:

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

Methods

Ninety subjects (>18 years) were divided into three groups based on smoking status: current, previous (defined as having quit greater than 6 months prior to the ischemic event), and non-smokers. Percent change in NIHSS score was defined as score at admission minus the score at discharge divided by the score at admission, and was used as a predictor of functional outcome. Linear regression analysis was performed based on infarct or edema volume versus the percent change in NIHSS score and separated by sex.

Results

Consistent with previous findings, smokers suffered a stroke ten years earlier than non-smokers ($p=.004$). 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 MRI or CT, is predictive of functional recovery only in female smokers.

Conclusions

These findings are valuable for patient counseling, particularly for females, for smoking cessation.

Clinical Trial Registration

<https://clinicaltrials.gov>. Unique Identifier: NCT03153683.

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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, attributing 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. evaluated how smoking affects prognosis following intravenous thrombolysis treatment (IVT) and found a favorable outcome for smokers attributed to higher recanalization rates in smokers over non-smokers ². However, a recent meta-analysis including 21 different studies performed by Li et al. found no difference in prognostic outcome of smokers and ischemic stroke ⁴. 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. The only study of its kind 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 non-smokers experiencing stroke ⁵. Few studies incorporated sex-based differences in the context of smoking and stroke, although one study did find that women who smoke have a 17% increase in incidence of hemorrhagic stroke ⁶. Therefore, in this 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: 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.

Methods

Patients undergoing a mechanical thrombectomy (MT) as standard treatment for a large vessel occlusion were registered in our continuously enrolling tissue bank (IRB 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/exclusion criteria were as follows: adults 18 years and older, non-pregnant, non-prisoner, suspected of emergent large vessel occlusive ischemic stroke, qualifying for standard mechanical thrombectomy. Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Kentucky ^{8,9}.

For analysis, consented subjects were divided into three self-reported groups: current smoker, previous smoker (defined as having quit greater than 6 months prior to the ischemic event), and non-smoker. NIHSS scores were recorded upon admission and at discharge. The percent change in NIHSS score was defined as score at admission minus the score at discharge divided by the score at admission times one hundred. Percent change of NIHSS was found to be a better prognosticator over delta NIHSS of functional outcome at 3 months for reperfusion therapy patients¹⁰. Infarct and cerebral edema volumes were measured on postoperative MRI or CT by a single neuro-radiologist who was blinded to the subject groups (DL) as previously reported ¹¹. Linear regression analysis was performed using GraphPad Prism version 8.2 (GraphPad Software, San Diego CA) based on infarct or edema volume versus the percent change in NIHSS score. Groups were evaluated based on sex and smoking status, a p value of less than 0.05 was considered significant. Demographic tables were constructed via appropriate unpaired T-tests and Fisher's exact tests using GraphPad Prism 8.2 software.

Results

Ninety adult subjects (>18 years) were included in the study, of which 49 (54%) were female. Median age was 69 years (25-101). Twenty-three (25.5%) were active smokers, 14 (15.5%) were previous smokers, and 53 (59%) were non-smokers. Mean infarct time (time from last known normal (LKN) to recanalization) was 501 ± 345 minutes. Mean infarct volume was $64,757 \pm 87,643 \text{ mm}^3$. Mean edema volume was $66,978 \pm 90,676 \text{ mm}^3$. Mean NIHSS score on admission was 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 population was 10 years earlier when compared to the non-smoking population, 61.9 versus 72.9 years ($p=0.004$) (Table 1). No significant demographic differences were found between sexes based on smoking status (Tables 2-4). Infarct and edema volume were evaluated based on sex and smoking status (Tables 1-4). Females had significantly smaller infarct and edema volumes as non-smokers ($p<0.05$) and previous smokers ($p=0.12$) relative to their male counterparts. Infarct volume for currently smoking females was not significantly different than currently smoking males ($p=0.980$) (Tables 2-4). Percent change in NIHSS with infarct ($p<0.0001$, $r^2=0.691$) or edema ($p<0.0001$, $r^2=0.751$) volume was only correlated in smokers (Figure 1a-d). When further evaluated based on sex, only female smokers showed a significant correlation for infarct ($p=0.0002$, $r^2=0.848$) or edema ($p<0.0001$, $r^2=0.889$) volume versus percent change in NIHSS, males were not correlated ($p=0.44$, $r^2=0.124$) ($p=0.26$, $r^2=0.248$) (Figures 2a-d).

Discussion

On average, smokers suffered a stroke ten years earlier than non-smokers, which is consistent with previously published findings^{4,12}. Female former and non-smokers had significantly smaller infarct and edema volumes as compared to 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 risk of higher infarct and edema volumes which correlated to worse functional outcomes as detailed in the correlation with change in NIHSS score. Clinically these findings should be considered when counseling patients prior to and following stroke to aid in smoking cessation.

Advanced age is a known negative correlate of stroke outcome¹³. We found, as others have reported⁵, that smokers experience stroke on average ten years earlier compared to non-smokers. This significantly earlier onset may account for the controversial smoking paradox, as younger patients may recover more easily from stroke. While one study of IVT patients found a favorable outcome for smokers attributed to higher recanalization rates in smokers over non-smokers², a meta-analysis study found no difference in prognostic outcome of smokers and ischemic stroke⁴. In contrast, our study focusing on ELVO demonstrates that female smokers experience larger infarct volumes than female non- 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 (EIN) is a method recently adopted to help account for the effect of mechanical thrombectomy on recovery¹⁴. As cited in more recent studies, percent change of NIHSS score as a predictive method of stroke outcome is being used to improve the EIN calculation^{10,15,16}. Recent literature demonstrates that percent change of NIHSS as an EIN better correlates with functional outcomes

at 3 months over the traditional delta NIHSS measure for patients receiving alteplase and thrombectomy^{10,16}. Percent change permits capture of the patients that may have had a small delta but recovered fully. For instance, a patient that presents with a NIHSS score of 30 and is discharged at a score of 24 has a delta NIHSS of 6 but only got 20% better, where as a patient presenting with a score of 10 and leaving at a score of 4 also has a delta NIHSS of 6 but had 60% improvement. Evaluating percent change of NIHSS score with infarct volume/edema after thrombectomy predicts early clinical outcome in a straightforward way for female smokers undergoing thrombectomy. There is an increasing recognition, that men and women have some unique pathophysiologic mechanisms in risks, evolution, and recovery from stroke, including varying effects of sex hormones¹⁷. 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 would be 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 our results may reflect the greater population. The BACTRAC study continues to enroll more patients and we will re-evaluate our findings for validation and expansion of our results.

Summary/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 females.

Further research is needed to identify the link between increased infarct and edema in our female smoking population as well as the strong correlation to worsening prognosis with increase infarct and edema volume.

Disclosures

Drs. Keith Pennypacker, Justin Fraser, and Ann Stowe are co-owners of Cerelux, LLC. Dr. Fraser is a consultant with Stream Biomedical, Penumbra, and Medtronic. Dr. Fraser is an equity holder of Fawkes Biotechnology.

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Abbreviations

National Institutes of Health Stroke Scale (NIHSS)

mechanical thrombectomy (MT)

large vessel occlusion (ELVO)

intravenous thrombolysis treatment (IVT)

Blood And Clot Thrombectomy Registry And Collaboration (BACTRAC)

Early neurological improvement (EIN)

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Table 1: Overall Demographics

	(1) Non-smoker	(2) Previous Smoker	(3) Current Smoker	p-value
Sex- n (%)	M 24 (45)	M 6 (43)	M 11 (48)	p>0.999
Age	72.9 ± 15.7	65.7 ± 12.9	61.9 ± 12.9	1 v 3: 0.004 1 v 2: 0.118 2 v 3: 0.391
BMI	28.2 ± 6.3	28.4 ± 7.2	28.2 ± 7.3	1 v 3: 0.941 1 v 2: 0.916 2 v 3: 0.895
Comorbidities- n (%)				
Hypertension	35 (66)	10 (71)	15 (65)	p= 0.917
Diabetes Mellitus II	17 (32)	3 (21)	7 (30)	p= 0.891
Hyperlipidemia	9 (17)	6 (43)	9 (39)	p= 0.014
Previous Stroke	8 (15)	4 (29)	3 (13)	p= 0.419
Myocardial Infarction	1 (2)	3 (21)	4 (17)	p= 0.019
NIHSS on Admission- n (%)				
Minor Stroke (1-4)	3 (6)	0 (0)	0 (0)	0.075
Moderate Stroke (5-15)	21 (40)	6 (43)	9 (39)	
Moderate/Severe (16-20)	9 (17)	3 (21)	11 (48)	
Severe Stroke (≥ 21)	20 (37)	5 (36)	3 (13)	
NIHSS at Discharge*-n (%)				
Minor Stroke (1-4)	16 (41)	2 (25)	8 (47)	0.496
Moderate Stroke (5-15)	12 (31)	5 (62)	7 (41)	
Moderate/Severe (16-20)	4 (10)	1 (13)	1 (6)	
Severe Stroke (≥ 21)	7 (18)	0 (0)	1 (6)	
TICI Score- n (%)				
1/2A = < 50% Perfusion	2 (4)	2 (14)	2 (9)	0.463
2B = > 50% Perfusion	19 (36)	6 (43)	6 (26)	
3 = Full Perfusion	32 (60)	6 (43)	15 (65)	
LKN to Thrombectomy Completion Time (minutes)*	491 ± 299	550 ± 492	492 ± 347	1 v 3: 0.983 1 v 2: 0.583 2 v 3: 0.687
Infarct Volume (mm³)**	65992 ± 84544	42967 ± 39764	76383 ± 115358	1 v 3: 0.671 1 v 2: 0.329 2 v 3: 0.305
Edema Volume (mm³)**	69950 ± 90664	41783 ± 42640	75940 + 113286	1 v 3: 0.813 1 v 2: 0.266 2 v 3: 0.289

Values are, mean \pm SD or (%). *3 patient's data were missing (n=87); **4 patient's data were missing (n=86).

Table 2: Male vs Female Smoker Summary

	Male	Female	p-value
Sex-n (%)	11 (48)	12 (52)	
Age	60.6 \pm 12.9	63.1 \pm 13.4	p=0.660
BMI	27.4 \pm 6.1	28.7 \pm 8.5	p=0.698
Comorbidities- n (%)			
Hypertension	6 (55)	9 (75)	p=0.400
Diabetes Mellitus II	2 (18)	5 (42)	p=0.371
Hyperlipidemia	5 (45)	4 (33)	p=0.680
Previous Stroke	1 (9)	2 (17)	p>0.999
Previous MI	1 (9)	3 (25)	p=0.590
NIHSS on Admission-n (%)			
Minor Stroke (1-4)	0 (0)	0 (0)	p=0.543
Moderate Stroke (5-15)	5 (45)	4 (33)	
Moderate/Severe (16-20)	4 (36)	7 (58)	
Severe Stroke (\geq 21)	2 (19)	1 (9)	
NIHSS at Discharge*-n (%)			
Minor Stroke (1-4)	4 (57)	4 (40)	p=0.645
Moderate Stroke (5-15)	3 (43)	4 (40)	
Moderate/Severe (16-20)	0 (0)	1 (10)	
Severe Stroke (\geq 21)	0 (0)	1 (10)	
TICI Score-n (%)			
1/2A = < 50% Perfusion	1 (9)	1 (8)	p>0.999
2B = > 50% Perfusion	3 (27)	3 (25)	
3 = Full Perfusion	7 (64)	8 (67)	
LKN to Thrombectomy Completion Time (minutes)	510 \pm 469	479 \pm 224	p=0.839
Infarct Volume (mm³)	75,439 \pm 110,607	74,096 \pm 121,086	p=0.980
Edema Volume (mm³)	74,781 \pm 111,280	75,839 \pm 116,819	p=0.899

Values are, mean \pm SD or (%). *patient's data were missing for males (n=7), females (n=10).

Table 3: Male vs Female Non-smoker Summary

	Male	Female	p value
Sex-n (%)	24 (45)	29 (55)	
Age	72.5 \pm 16.2	73.4 \pm 15.5	p=0.839
BMI	27.8 \pm 5.9	28.6 \pm 6.6	p=0.671
Comorbidities-n (%)			
Hypertension	15 (63)	20 (69)	p=0.772
Diabetes Mellitus II	5 (21)	12 (41)	p=0.145
Hyperlipidemia	4 (17)	5 (17)	p>0.999
Previous Stroke	2 (8)	6 (21)	p=0.269
Myocardial Infarction	0 (0)	2 (7)	p=0.495
NIHSS on Admission-n (%)			
Minor Stroke (1-4)	2 (8)	1 (3)	p=0.077
Moderate Stroke (5-15)	7 (29)	14 (48)	
Moderate/Severe (16-20)	2 (8)	7 (24)	
Severe Stroke (\geq 21)	13 (54)	7 (24)	
NIHSS at Discharge*-n (%)			
Minor Stroke (1-4)	8 (40)	8 (42)	p=0.434
Moderate Stroke (5-15)	4 (20)	7 (37)	
Moderate/Severe (16-20)	4 (20)	1 (5)	
Severe Stroke (\geq 21)	4 (20)	3 (16)	
TICI Score- n (%)			
1/2A = < 50% Perfusion	2 (8)	0 (0)	p=0.416
2B = > 50% Perfusion	6 (5)	13 (45)	
3 = Full Perfusion	16 (67)	16 (55)	
LKN to Thrombectomy Completion Time (minutes)	479 \pm 339	501 \pm 270	p=0.793
Infarct Volume (mm³)**	93,525 \pm 103,965	41,636 \pm 53,827	p=0.031
Edema Volume (mm³)**	97,151 \pm 113,597	45,888 \pm 56,068	p=0.047

Values are, mean \pm SD or (%). *patient's data were missing for males (n=20), females (n=19);

**1 patient's data were missing for males (n=23), 3 patients data missing for females (n=26).

Table 4: Male vs Female Previous-Smoker Summary

	Male	Female	value
Sex- n (%)	6 (43)	8 (57)	
Age	61.5 ± 14.4	68.9 ± 11.5	p=0.308
BMI	28.6 ± 6.0	28.3 ± 8.5	p=0.936
Comorbidities- n (%)			
Hypertension	4 (67)	6 (75)	p>0.999
Diabetes Mellitus II	1 (17)	2 (25)	p>0.999
Hyperlipidemia	3 (50)	3 (38)	p>0.999
Previous Stroke	1 (17)	3 (38)	p=0.580
Previous MI	1 (17)	0 (0)	p=0.429
NIHSS on Admission-n (%)			
Minor Stroke (1-4)	0 (0)	0 (0)	p=0.627
Moderate Stroke (5-15)	2 (33.3)	4 (50)	
Moderate/Severe (16-20)	2 (33.3)	1 (12.5)	
Severe Stroke (≥ 21)	2 (33.3)	3 (37.5)	
NIHSS at Discharge*-n (%)			
Minor Stroke (1-4)	0 (0)	2 (40)	p=0.237
Moderate Stroke (5-15)	3 (100)	2 (40)	
Moderate/Severe (16-20)	0 (0)	1 (20)	
Severe Stroke (≥ 21)	0 (0)	0 (0)	
TICI Score- (n,%)			
1/2A = < 50% Perfusion	0 (0)	2 (25)	p=0.417
2B = > 50% Perfusion	3 (50)	3 (37.5)	
3 = Full Perfusion	3 (50)	3 (37.5)	
LKN to Thrombectomy Completion Time (minutes)	348 ± 190	701 ± 602	p=0.195
Infarct Volume (mm³)	62,324 ± 48,339	28,449 ± 26,557	p=0.118
Edema Volume (mm³)	61,274 ± 48,101	27,164 ± 33,973	p=0.145

Values are, mean ± SD or (%).

Figures

Figure 1: Edema and Infarct Volume vs Change NIHSS Score in Smoking Status

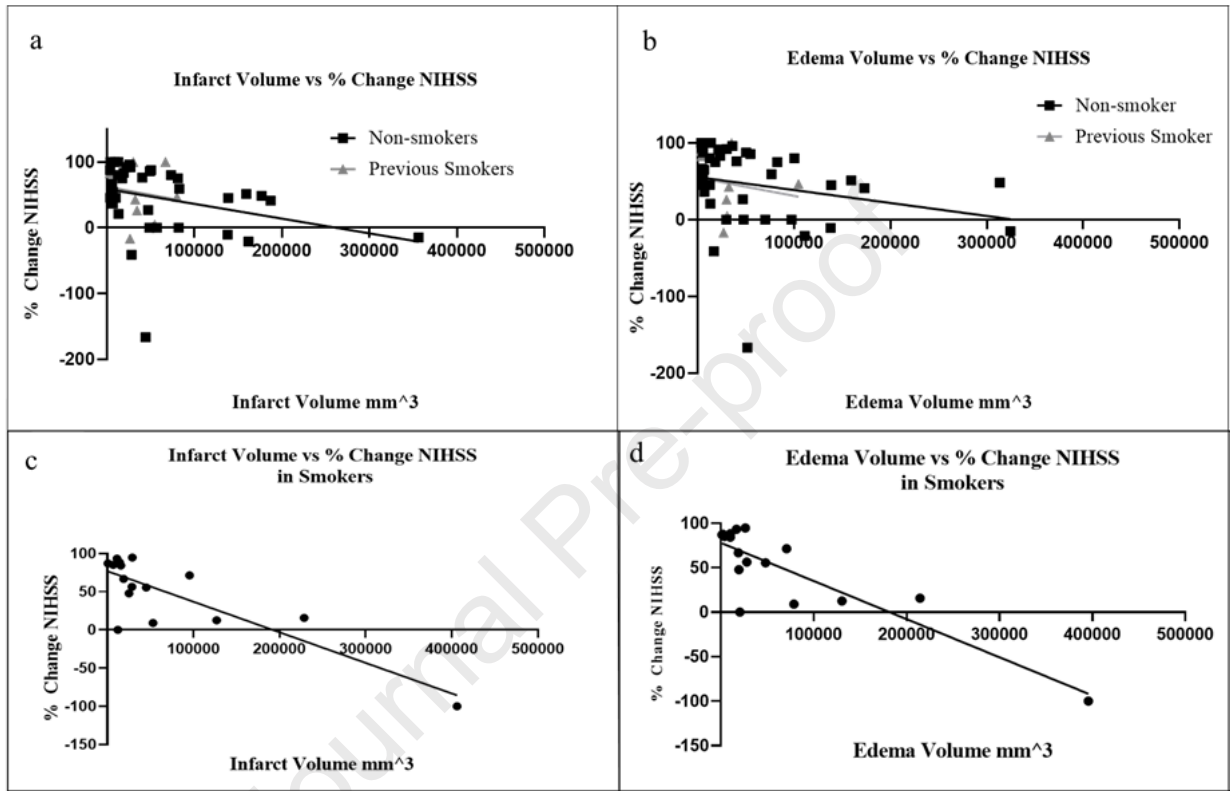


Figure 1: The percent change of NIHSS defined as $((\text{NIHSS at admission} - \text{NIHSS at discharge}) / \text{NIHSS at admission} \times 100)$ was significantly correlated to infarct volume (a,c) by linear regression in smokers only ($p < 0.0001$, $r^2 = 0.693$). The percent change of NIHSS was significantly correlated to edema volume (b,d) by linear regression in smokers only ($p < 0.0001$, $r^2 = 0.751$).

Figure 2: Edema and Infarct Volume vs Change NIHSS Score, sex difference

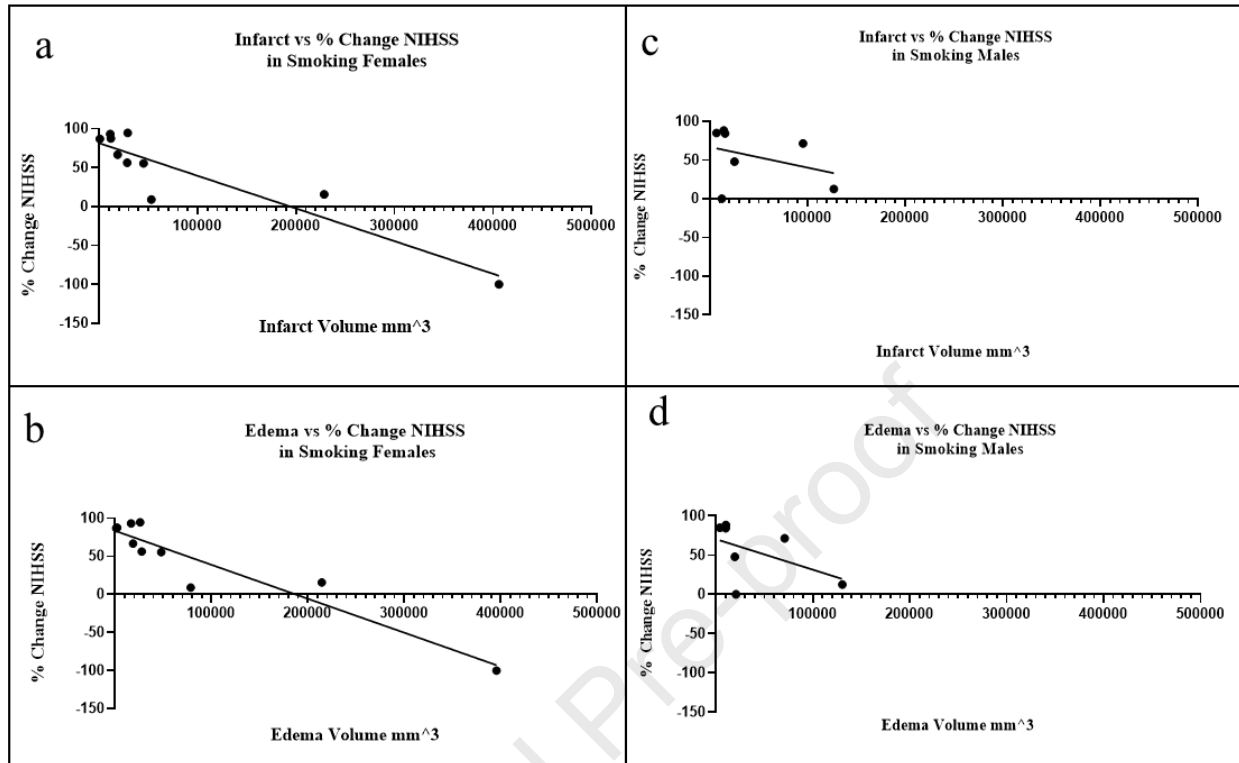


Figure 2: The percent change of NIHSS in smokers only, when evaluated based on sex, the percent change of NIHSS was correlated to infarct volume by linear regression in (a) female current smokers only ($p=0.0002$, $r^2=0.848$) compared to (c) males ($p=.438$, $r^2=0.124$). When evaluated based on sex, 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 to (d) males ($p=0.258$, $r^2=0.246$).

Table 1: Overall Demographics

	(1) Non-smoker	(2) Previous Smoker	(3) Current Smoker	p-value
Sex- n (%)	M 24 (45)	M 6 (43)	M 11 (48)	p>0.999
Age	72.9 ± 15.7	65.7 ± 12.9	61.9 ± 12.9	1 v 3: 0.004 1 v 2: 0.118 2 v 3: 0.391
BMI	28.2 ± 6.3	28.4 ± 7.2	28.2 ± 7.3	1 v 3: 0.941 1 v 2: 0.916 2 v 3: 0.895
Comorbidities- n (%)				
Hypertension	35 (66)	10 (71)	15 (65)	p= 0.917
Diabetes Mellitus II	17 (32)	3 (21)	7 (30)	p= 0.891
Hyperlipidemia	9 (17)	6 (43)	9 (39)	p= 0.014
Previous Stroke	8 (15)	4 (29)	3 (13)	p= 0.419
Myocardial Infarction	1 (2)	3 (21)	4 (17)	p= 0.019
NIHSS on Admission- n (%)				
Minor Stroke (1-4)	3 (6)	0 (0)	0 (0)	0.075
Moderate Stroke (5-15)	21 (40)	6 (43)	9 (39)	
Moderate/Severe (16-20)	9 (17)	3 (21)	11 (48)	
Severe Stroke (≥ 21)	20 (37)	5 (36)	3 (13)	
NIHSS at Discharge*-n (%)				
Minor Stroke (1-4)	16 (41)	2 (25)	8 (47)	0.496
Moderate Stroke (5-15)	12 (31)	5 (62)	7 (41)	
Moderate/Severe (16-20)	4 (10)	1 (13)	1 (6)	
Severe Stroke (≥ 21)	7 (18)	0 (0)	1 (6)	
TICI Score- n (%)				
1/2A = < 50% Perfusion	2 (4)	2 (14)	2 (9)	0.463
2B = > 50% Perfusion	19 (36)	6 (43)	6 (26)	
3 = Full Perfusion	32 (60)	6 (43)	15 (65)	
LKN to Thrombectomy Completion Time (minutes)*	491 ± 299	550 ± 492	492 ± 347	1 v 3: 0.983 1 v 2: 0.583 2 v 3: 0.687
Infarct Volume (mm³)**	65992 ± 84544	42967 ± 39764	76383 ± 115358	1 v 3: 0.671 1 v 2: 0.329 2 v 3: 0.305
Edema Volume (mm³)**	69950 ± 90664	41783 ± 42640	75940 + 113286	1 v 3: 0.813 1 v 2: 0.266 2 v 3: 0.289

Values are, mean \pm SD or (%). *3 patient's data were missing (n=87); **4 patient's data were missing (n=86).

Table 2: Male vs Female Smoker Summary

	Male	Female	p-value
Sex-n (%)	11 (48)	12 (52)	
Age	60.6 \pm 12.9	63.1 \pm 13.4	p=0.660
BMI	27.4 \pm 6.1	28.7 \pm 8.5	p=0.698
Comorbidities- n (%)			
Hypertension	6 (55)	9 (75)	p=0.400
Diabetes Mellitus II	2 (18)	5 (42)	p=0.371
Hyperlipidemia	5 (45)	4 (33)	p=0.680
Previous Stroke	1 (9)	2 (17)	p>0.999
Previous MI	1 (9)	3 (25)	p=0.590
NIHSS on Admission-n (%)			
Minor Stroke (1-4)	0 (0)	0 (0)	p=0.543
Moderate Stroke (5-15)	5 (45)	4 (33)	
Moderate/Severe (16-20)	4 (36)	7 (58)	
Severe Stroke (\geq 21)	2 (19)	1 (9)	
NIHSS at Discharge*-n (%)			
Minor Stroke (1-4)	4 (57)	4 (40)	p=0.645
Moderate Stroke (5-15)	3 (43)	4 (40)	
Moderate/Severe (16-20)	0 (0)	1 (10)	
Severe Stroke (\geq 21)	0 (0)	1 (10)	
TICI Score-n (%)			
1/2A = < 50% Perfusion	1 (9)	1 (8)	p>0.999
2B = > 50% Perfusion	3 (27)	3 (25)	
3 = Full Perfusion	7 (64)	8 (67)	
LKN to Thrombectomy Completion Time (minutes)	510 \pm 469	479 \pm 224	p=0.839
Infarct Volume (mm³)	75,439 \pm 110,607	74,096 \pm 121,086	p=0.980
Edema Volume (mm³)	74,781 \pm 111,280	75,839 \pm 116,819	p=0.899

Values are, mean \pm SD or (%). *patient's data were missing for males (n=7), females (n=10).

Table 3: Male vs Female Non-smoker Summary

	Male	Female	p value
Sex-n (%)	24 (45)	29 (55)	
Age	72.5 \pm 16.2	73.4 \pm 15.5	p=0.839
BMI	27.8 \pm 5.9	28.6 \pm 6.6	p=0.671
Comorbidities-n (%)			
Hypertension	15 (63)	20 (69)	p=0.772
Diabetes Mellitus II	5 (21)	12 (41)	p=0.145
Hyperlipidemia	4 (17)	5 (17)	p>0.999
Previous Stroke	2 (8)	6 (21)	p=0.269
Myocardial Infarction	0 (0)	2 (7)	p=0.495
NIHSS on Admission-n (%)			
Minor Stroke (1-4)	2 (8)	1 (3)	p=0.077
Moderate Stroke (5-15)	7 (29)	14 (48)	
Moderate/Severe (16-20)	2 (8)	7 (24)	
Severe Stroke (\geq 21)	13 (54)	7 (24)	
NIHSS at Discharge*-n (%)			
Minor Stroke (1-4)	8 (40)	8 (42)	p=0.434
Moderate Stroke (5-15)	4 (20)	7 (37)	
Moderate/Severe (16-20)	4 (20)	1 (5)	
Severe Stroke (\geq 21)	4 (20)	3 (16)	
TICI Score- n (%)			
1/2A = < 50% Perfusion	2 (8)	0 (0)	p=0.416
2B = > 50% Perfusion	6 (5)	13 (45)	
3 = Full Perfusion	16 (67)	16 (55)	
LKN to Thrombectomy Completion Time (minutes)	479 \pm 339	501 \pm 270	p=0.793
Infarct Volume (mm³)**	93,525 \pm 103,965	41,636 \pm 53,827	p=0.031
Edema Volume (mm³)**	97,151 \pm 113,597	45,888 \pm 56,068	p=0.047

Values are, mean \pm SD or (%). *patient's data were missing for males (n=20), females (n=19);

**1 patient's data were missing for males (n=23), 3 patients data missing for females (n=26).

Table 4: Male vs Female Previous-Smoker Summary

	Male	Female	value
Sex- n (%)	6 (43)	8 (57)	
Age	61.5 ± 14.4	68.9 ± 11.5	p=0.308
BMI	28.6 ± 6.0	28.3 ± 8.5	p=0.936
Comorbidities- n (%)			
Hypertension	4 (67)	6 (75)	p>0.999
Diabetes Mellitus II	1 (17)	2 (25)	p>0.999
Hyperlipidemia	3 (50)	3 (38)	p>0.999
Previous Stroke	1 (17)	3 (38)	p=0.580
Previous MI	1 (17)	0 (0)	p=0.429
NIHSS on Admission-n (%)			
Minor Stroke (1-4)	0 (0)	0 (0)	p=0.627
Moderate Stroke (5-15)	2 (33.3)	4 (50)	
Moderate/Severe (16-20)	2 (33.3)	1 (12.5)	
Severe Stroke (≥ 21)	2 (33.3)	3 (37.5)	
NIHSS at Discharge*-n (%)			
Minor Stroke (1-4)	0 (0)	2 (40)	p=0.237
Moderate Stroke (5-15)	3 (100)	2 (40)	
Moderate/Severe (16-20)	0 (0)	1 (20)	
Severe Stroke (≥ 21)	0 (0)	0 (0)	
TICI Score- (n,%)			
1/2A = < 50% Perfusion	0 (0)	2 (25)	p=0.417
2B = > 50% Perfusion	3 (50)	3 (37.5)	
3 = Full Perfusion	3 (50)	3 (37.5)	
LKN to Thrombectomy Completion Time (minutes)	348 ± 190	701 ± 602	p=0.195
Infarct Volume (mm³)	62,324 ± 48,339	28,449 ± 26,557	p=0.118
Edema Volume (mm³)	61,274 ± 48,101	27,164 ± 33,973	p=0.145

Values are, mean ± SD or (%).

Figures

Figure 1: Edema and Infarct Volume vs Change NIHSS Score in Smoking Status

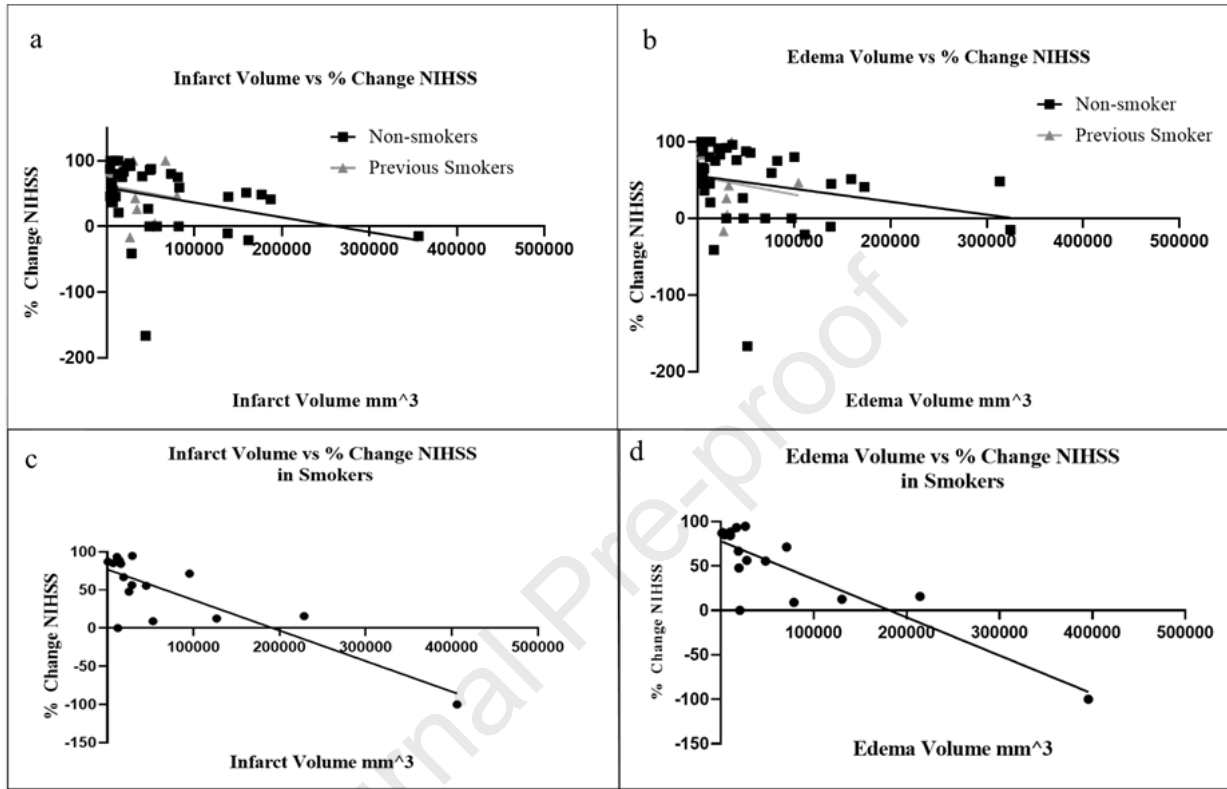


Figure 1: The percent change of NIHSS defined as $((\text{NIHSS at admission} - \text{NIHSS at discharge}) / \text{NIHSS at admission} \times 100)$ was significantly correlated to infarct volume (a,c) by linear regression in smokers only ($p < 0.0001$, $r^2 = 0.693$). The percent change of NIHSS was significantly correlated to edema volume (b,d) by linear regression in smokers only ($p < 0.0001$, $r^2 = 0.751$).

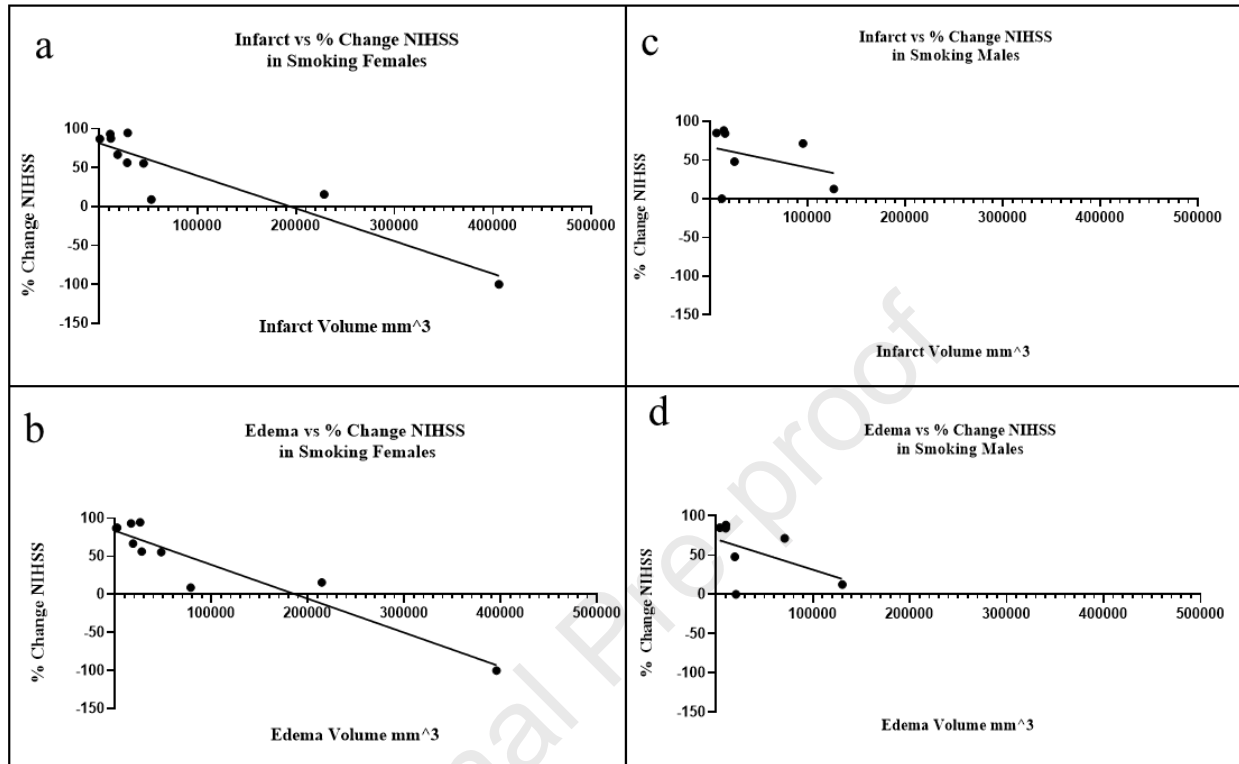
Figure 2: Edema and Infarct Volume vs Change NIHSS Score, sex difference

Figure 2: The percent change of NIHSS in smokers only, when evaluated based on sex, the percent change of NIHSS was correlated to infarct volume by linear regression in (a) female current smokers only ($p=0.0002$, $r^2=0.848$) compared to (c) males ($p=.438$, $r^2=0.124$). 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 to (d) males ($p=0.258$, $r^2=0.246$).

Figures

Figure 1: Age vs Smoking Status

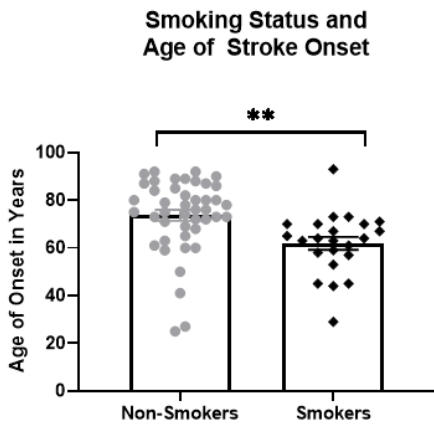


Figure 1: Average age of stroke onset for non-smokers (72.9 ± 15.7) versus smokers (61.9 ± 12.9) ($p = 0.004$).

Figure 2: Smoking Status vs Infarct and Edema

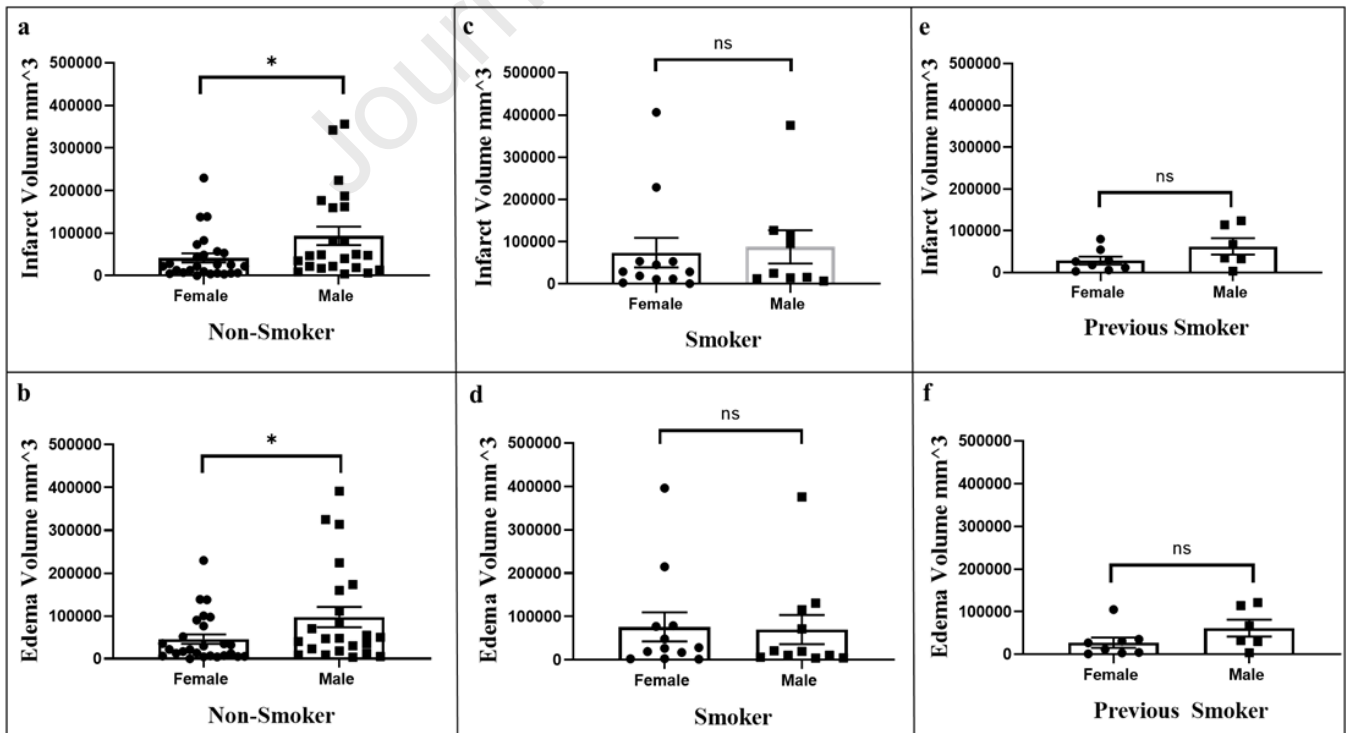


Figure 2: a: Infarct volume in mm^3 of non-smoking females ($41,636 \pm 53,827$) versus non-smoking males ($93,525 \pm 103,965$) ($p=0.031$). b: Edema volume in mm^3 of non-smoking females ($45,888 \pm 56,068$) versus non-smoking males ($97,151 \pm 113,597$) ($p=0.047$). c: Infarct volume in mm^3 of smoking females ($74,096 \pm 121,086$) versus smoking males ($74,436 \pm 110,607$) ($p=0.980$). d: Edema volume in mm^3 of smoking females ($75,839 \pm 121,086$) versus smoking males ($74,781 \pm 111,280$) ($p=0.899$). e: Infarct volume in mm^3 of previously smoking females ($28,449 \pm 26,557$) versus previously smoking males ($62,324 \pm 48,339$) ($p=0.118$). f: Edema volume in mm^3 of previously smoking females ($27,164 \pm 33,973$) versus previously smoking males ($61,274 \pm 48,101$) ($p=0.145$).

Figure 3: Edema and Infarct Volume vs Change NIHSS Score in Smoking Status

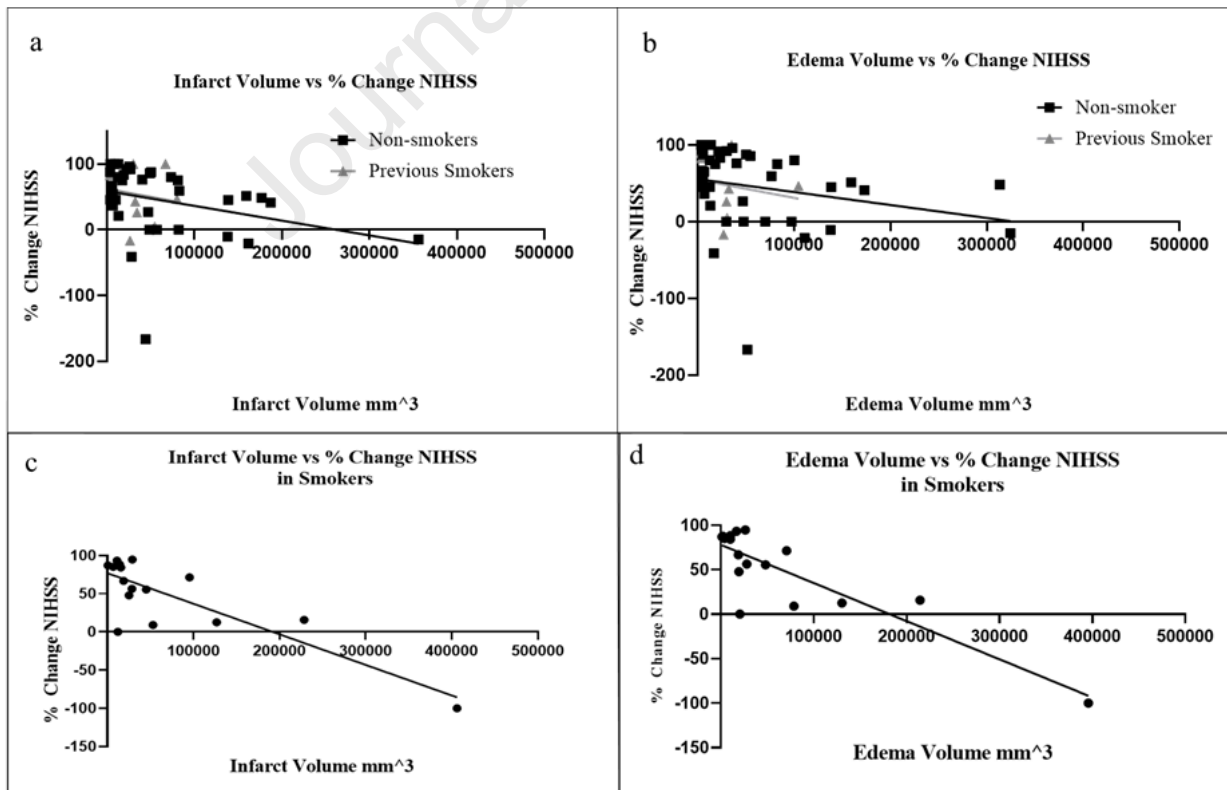


Figure 3: The percent change of NIHSS defined as $((\text{NIHSS at admission} - \text{NIHSS at discharge}) / \text{NIHSS at admission} \times 100)$ was significantly correlated to infarct volume (a,c) by linear regression in smokers only ($p < 0.0001$, $r^2 = 0.693$). The percent change of NIHSS was significantly correlated to edema volume (b,d) by linear regression in smokers only ($p < 0.0001$, $r^2 = 0.751$).

Figure 4: Edema and Infarct Volume vs Change NIHSS Score, sex difference

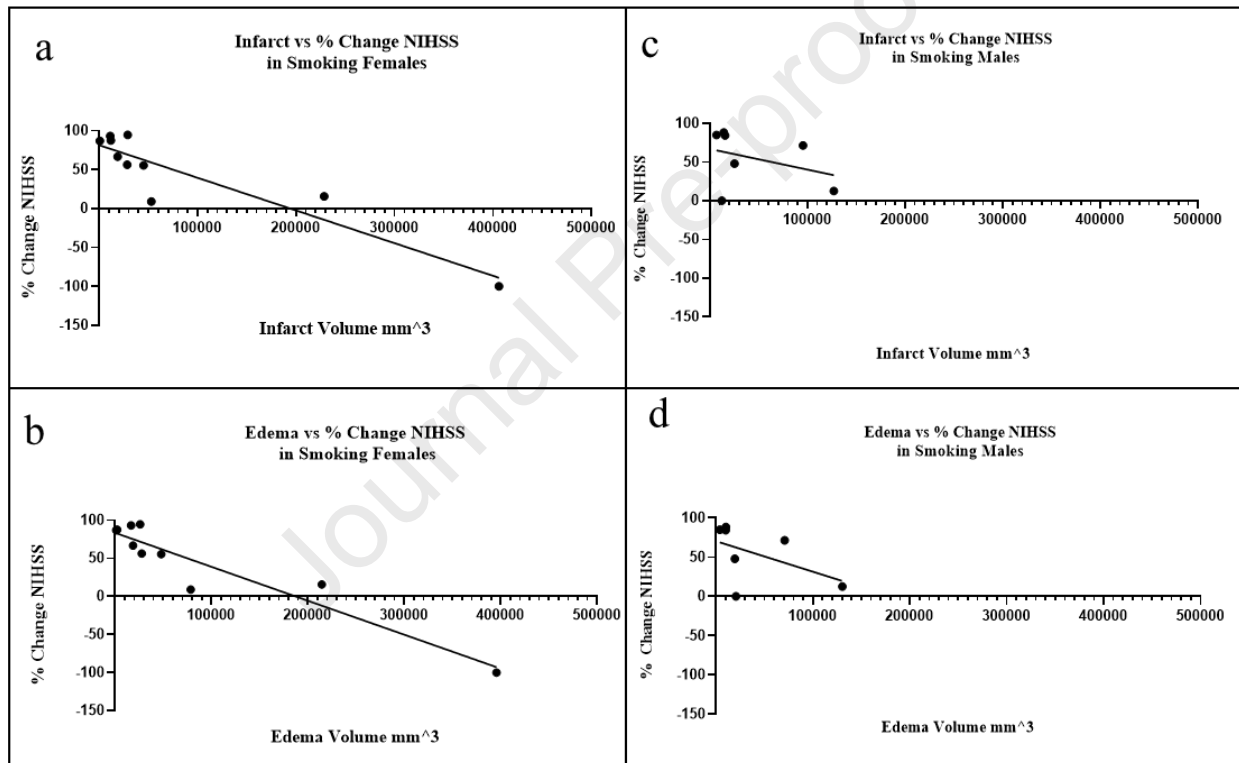


Figure 4: The percent change of NIHSS in smokers only, when evaluated based on sex, the percent change of NIHSS was correlated to infarct volume by linear regression in (a) female current smokers only ($p = 0.0002$, $r^2 = 0.848$) compared to (c) males ($p = .438$, $r^2 = 0.124$). When evaluated based 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 to (d) males ($p = 0.258$, $r^2 = 0.246$).

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Abbreviations

National Institutes of Health Stroke Scale (NIHSS)

mechanical thrombectomy (MT)

large vessel occlusion (ELVO)

intravenous thrombolysis treatment (IVT)

Blood And Clot Thrombectomy Registry And Collaboration (BACTRAC)

Early neurological improvement (EIN)

Disclosures

Drs. Keith Pennypacker, Justin Fraser, and Ann Stowe are co-owners of Cerelux, LLC. Dr.

Fraser is a consultant with Stream Biomedical, Penumbra, and Medtronic. Dr. Fraser is an equity holder of Fawkes Biotechnology.