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Acute Ischemic Stroke and Heart Failure: Stroke Risk Factors Associated with Exclusion from Thrombolytic Therapy

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Abstract

Objective: Acute ischemic stroke (AIS) patients with congestive heart failure (HF) that present with various risk factors are less likely to receive recombinant tissue plasminogen activator (rtPA). The risk factors associated with excluding AIS patients with congestive heart failure (AIS-HF) from rtPA therapy have not been fully established. **Methods:** Retrospective data for 5469 AIS patients comprised of 590 AIS patients with HF and 4879 AIS patients without HF were collected from a regional stroke registry between January 2010 and June 2016. Baseline risk factors were analyzed using logistic regression analysis to determine the risk factors associated with rtPA exclusion in AIS-HF patients. **Results:** In the adjusted analysis, AIS-HF patients that that did not receive rtPA were more likely to be older (OR = 0.982, 95% CI, 0.966-1, $P = .020$), presented with coronary artery disease (OR = 0.618, 95% CI, 0.391-0.98, $P = .040$), and with an elevated INR (OR = 0.326, 95% CI, 0.129-0.82, $P = .018$). AIS-HF patients that were included for rtPA therapy were more likely to show improvement in ambulatory status (OR = 1.69, 95% CI, 1.058-2.7, $P = .028$). The discriminating power of the model was strong with an area under the curve (AUROC) = 0.668 (95% CI, 0.611-0.724, $P < .001$). **Conclusion:** Our study establishes the associations between stroke risk factors and exclusion from rtPA therapy. This finding suggests the need to develop management strategies for older HF patients with carotid artery disease and an elevated INR to improve their eligibility for rtPA treatment following an acute ischemic stroke.

Keywords

acute ischemic stroke, congestive heart failure, exclusion, recombinant tissue plasminogen activator

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Introduction

Acute ischemic stroke (AIS) remains a global health burden as it represents the second leading cause of a significant morbidity.[1] Several nonmodifiable risk factors such as age and gender and modifiable risk factors such as hypertension and heart failure are known to represent major contributors to the incidence of stroke.[2] While it is difficult to control the effect of nonmodifiable risk factors, major public health efforts have focused on managing modifiable risk factors, such as congestive heart failure (HF) to decrease the stroke burden.[3]

Heart failure is a complicated clinical condition caused by structural or functional cardiac distress, resulting in decreased cardiac output or increased intracardiac pressures.[4] More than 15% of AIS patients present with HF, and AIS is reported to be caused by HF in at least 9% of stroke cases.[4,5] Moreover, HF constitutes the source of various damaging pathophysiologic mechanisms in AIS, including the release of prothrombotic and proinflammatory mediators and poor cerebral tissue oxygenation.[6] Therefore, HF may affect the safety and efficacy of acute recanalization stroke therapies, including the use of recombinant tissue plasminogen activator (rtPA).[7]

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The standard treatment for ischemic stroke is rtPA. Since its approval by the FDA in 1996, rtPA has resulted in significantly better clinical outcomes in patients with symptomatic stroke,[7] such that more than 30% of patients who meet inclusion criteria experience only minimal or no disability following treatment with rtPA.[8] When treated with rtPA, the clinical response in AIS-HF patients is the same as in AIS patients without HF.[2] This finding indicates the efficacy and safety of rtPA for AIS-HF patients.[9] Moreover, there is no evidence of an increased risk of symptomatic intracerebral hemorrhage (sICH) after intravenous rtPA in AIS-HF patients.[10] However, despite the safety of rtPA, many AIS-HF patients are less likely to be treated with rtPA and more likely to present with higher rates of mortality and long-term deficits compared to a similar cohort without HF.[11,12]

Safety of rtPA implies that ischemic stroke patients treated with rtPA are not associated with complications related to intravenous r-tPA including symptomatic intracranial hemorrhage, and major systemic hemorrhage.[11,12] One possibility that many AIS-HF patients are less likely to be treated with rtPA could be that AIS-HF patients may present with risk factors that worsen outcomes following rtPA therapy and are therefore unable to benefit from the demonstrated advantage of rtPA reperfusion therapy. This study aims to identify risk factors associated with exclusion from rtPA therapy in AIS patients with HF. Our results may help identify specific stroke risk factors that could explain why some cohorts of AIS-HF patients are less likely to receive rtPA. Knowledge of these factors will provide further insight into specific risk factors that can be managed to improve the care of AIS patients with heart failure.

Methods

Study Population

This is a retrospective cohort study using data obtained from a regional stroke registry of Prisma Health Upstate. The registry includes all patients aged >18 admitted to Prisma Health stroke unit between January 2010 and January 2016. The description of the registry is provided in previous studies.[13,14] Our study was approved by the Prisma Health ethics committee. We extracted data from all AIS patients with and without HF who underwent a series of blood tests and brain imaging to confirm ischemic stroke at admission. All data were obtained from electronic records. Patients with a prior diagnosis of primary intracerebral, intraventricular, or subarachnoid hemorrhage or those unable to complete coronal vascular imaging were not included in our data analysis. The inclusion criteria included patients' data for strokes diagnosed and confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) within 7 days of the appearance of symptoms or clinical signs. We focused on data for AIS patients with and without a history of HF for this study and collected patients' demographics, laboratory values, medical history, and medications. The demographic variables included age, race, gender, ethnicity, and Body mass index (BMI). In addition, data for NIH stroke severity (NIHSS) were collected. Data on risk factors were collected, including atrial fibrillation/atrial flutter, coronary artery disease (CAD), carotid stenosis, depression, diabetes, drug or alcohol use, dyslipidemia, family history of stroke, congestive heart failure (CHF), hormonal replacement therapy, hypertension, migraine, obesity, prior stroke, prior transient ischemic attack (TIA), prosthetic heart valve, peripheral vascular disease, chronic renal disease, sleep apnea, and history of smoking. Data on ambulatory status were recorded at different times during the entire clinical encounter: on admission, during admission, and after discharge. Scoring ambulatory data was performed in this fashion: 0 (not documented); 1 (patient not able to ambulate); 2: (ambulate with assistance) 3: (ambulate independently). Improvement in ambulation was quantified by taking their score at discharge and subtracting their ambulation score on admission, with greater than zero being an improvement in ambulation.

Statistical Analysis

All statistical analyses were determined using the Statistical Package for Social Sciences version 26.0 for Windows (SPSS, Chicago, IL), and $P < .05$ was considered statistically significant. Univariate analysis was used to determine differences in risk factors in AIS with or without a previous diagnosis of HF, and AIS patients with or without HF stratified by receipt or no receipt of rtPA. Univariate analysis was used to evaluate differences in continuous and categorical variables. For all continuous variables, the mean, standard deviation, and range were calculated using the Student's T-tests, while discrete variables were analyzed using Pearson's Chi-Squared analyses. The univariate analysis was used to identify demographics and risk factors for acute ischemic stroke patients stratified by receipt or no receipt of rtPA for Table 1, while Table 2, compares risk factors of acute ischemic stroke patients with or without heart failure stratified by receipt or no receipt of rtPA

For the multivariate analysis, significant associations in the univariate comparisons were entered into a binary multivariable logistic regression model. The adjusted odds ratios (ORs) for risk factors were calculated from their respective coefficients in the logistic regression models. We used a backward stepwise logistic regression analysis approach and considered a statistical variable removal level of $P < .10$. Potential risk factors associated with inclusion or exclusion from rtPA were calculated. We performed subgroup analyses for AIS patients with HF while AIS patients without HF served as the control. We determined our models' sensitivity, specificity, and accuracy by using the area under the Receiver Operating Curve (ROC). The Hosmer Lemeshow test determined multicollinearity and interactions among the independent variables.

Results

A total of 5469 AIS were identified. Of these, 4142 patients did not receive rtPA, while 1327 patients received rtPA. Table 1 presents the risk factors of AIS patients stratified by treatment

Table 1. Demographic and Factors for Acute Ischemic Stroke Patients Stratified by Absence or Presence of rtPA use Among Acute Ischemic Stroke Patients.

Characteristics	No rtPA	rtPA	*P* value
Number of patients	4142	1327	
Age Group: No. (%)			
<50	467 (11.3)	191 (14.4)	.001*[a]
50-59	736 (17.8)	260 (19.6)	
60-69	981 (23.7)	318 (24.0)	
70-79	942 (22.7)	289 (21.8)	
>=80	1016 (24.5)	269 (20.3)	
Mean ± SD	67.73 ± 14.69	65.76 ± 14.78	<.001*[b]
Race: No (%)			
White	3228 (77.9)	1060 (79.9)	.313
Black	774 (18.7)	228 (17.2)	
Other	140 (3.4)	39 (2.9)	
Gender: No. (%)			
Female	2148 (51.9)	659 (49.7)	.163
Male	1994 (48.1)	668 (50.3)	
Hispanic Ethnicity: No. (%)	55 (1.3)	30 (2.3)	.017*[a]
BMI: Mean ± SD	28.18 ± 7.01	28.84 ± 6.84	.003*
Medical History: No. (%)			
Atrial Fib	713 (17.2)	211 (15.9)	.266
Coronary Artery Disease	1262 (30.5)	399 (30.1)	.782
Carotid Artery Stenosis	278 (6.7)	56 (4.2)	.001*[a]
Depression	516 (12.5)	205 (15.4)	.005*[a]
Diabetes	1520 (36.7)	415 (31.3)	<.001*[a]
Drugs or Alcohol	260 (6.3)	77 (5.8)	.532
Dyslipidemia	2055 (49.6)	700 (52.8)	.047*[a]
Stroke Family History	364 (8.8)	130 (9.8)	.265
Heart Failure	453 (10.9)	137 (10.3)	.531
Hormone Replacement Therapy	48 (1.2)	31 (2.3)	.002*[a]
Hypertension	3262 (78.8)	1044 (78.7)	.95
Migraine	89 (2.1)	45 (3.4)	.011*[a]
Obesity	1633 (39.4)	678 (51.1)	<.001*[a]
Previous Stroke	1134 (27.4)	290 (21.9)	<.001*[a]
Previous TIA (> 24 h)	334 (8.1)	143 (10.8)	.002*[a]
Prosthetic Heart Valve	52 (1.3)	10 (0.8)	.133
Peripheral Vascular Disease	321 (7.7)	79 (6.0)	.029*[a]
Chronic Renal Disease	368 (8.9)	79 (6.0)	.001*
Sleep Apnea	125 (3.0)	45 (3.4)	.495
Smoker	1098 (26.5)	388 (29.2)	.052
Medication History: No (%)			
HTN medication	2851 (68.8)	943 (71.1)	.125
Cholesterol Reducer	1796 (43.4)	632 (47.6)	.006*[a]
Diabetic Medication	1164 (28.1)	331 (24.9)	.025*[a]
Antidepressant	865 (11.5)	110 (45.3)	<.001*[a]
Initial NIHSS Score: No (%)			
0-9	2556 (76.3)	733 (59.4)	<.001*[a]
10-14	308 (9.2)	199 (16.1)	
15-20	308 (9.2)	193 (15.6)	
21-25	180 (5.4)	110 (8.9)	
Mean ± SD	8.40 ± 8.79	7.35 ± 8.03	.055
Lab values: Mean ± SD			
Total cholesterol	173.01 ± 53.60	168.66 ± 46.47	.006*[b]
Triglycerides	139.25 ± 104.13	140.71 ± 107.94	.674
HDL	41.77 ± 13.91	41.80 ± 13.65	.946
LDL	105.39 ± 42.06	102.52 ± 39.07	.029*[b]
Lipids	6.64 ± 2.83	6.25 ± 1.60	<.001*[b]
Blood Glucose	149.22 ± 82.86	141.29 ± 74.84	.001*[b]
Serum Creatinine	1.34 ± 1.27	1.14 ± 0.75	<.001*[b]

(continued)

Table 1. (continued)

Characteristics	No rtPA	rtPA	*P* value
INR	1.17 ± 0.57	1.06 ± 0.15	<.001*[b]
Vital Signs: Mean ± SD			
Heart Rate	82.07 ± 18.94	81.81 ± 17.18	.644
Blood Pressure Systolic	151.99 ± 30.04	151.31 ± 26.92	.439
Blood Pressure Diastolic	82.29 ± 19.38	82.92 ± 18.30	.277
Ambulation Status Prior to Event: No. (%)			
Ambulate Independently	3628 (87.6)	1259 (94.9)	<.001*[a]
Ambulate with Assistance	180 (4.3)	23 (1.7)	
Unable to Ambulate	193 (4.7)	20 (1.5)	
Not Documented	140 (3.4)	25 (1.9)	
Ambulation Status on Admission: No. (%)			
Ambulate Independently	1099 (26.5)	232 (17.5)	<.001*[a]
Ambulate with Assistance	1320 (31.9)	306 (23.1)	
Unable to Ambulate	1249 (30.2)	479 (36.1)	
Not Documented	474 (11.4)	310 (23.4)	
Ambulation Status on Discharge: No. (%)			
Ambulate Independently	1516 (36.6)	658 (49.6)	<.001*[a]
Ambulate with Assistance	847 (20.4)	222 (19.7)	
Unable to Ambulate	1466 (35.4)	354 (26.7)	
Not Documented	313 (7.6)	93 (7.0)	
First Care Received: No. (%)			
Emergency Department	3285 (80.1)	1012 (76.6)	.006*[a]
Direct Admission	815 (19.9)	309 (23.4)	
Improved Ambulation: No. (%) 1110 (29.7)		663 (55.5)	<.001* [a]
NIHSS > 7: No. (%)	1177 (33.5)	690 (52.4)	<.001*[a]
Diastolic Blood Pressure ≥ 80 mm Hg	2167 (52.4)	721 (54.5)	.188

[a]Pearson's Chi-Squared test.
[b]Student's T test.
* *P*-value < .05.

with or without rtPA while Table 2 presents risk factors, demographics, and laboratory characteristics of AIS patients with or without HF stratified by rtPA treatment. Compared with the AIS-HF group without rtPA, AIS-HF patients that received rtPA were more likely to be Hispanics, younger, and have a higher BMI, obese with a history of elevated INR, ambulate independently prior to the stroke event and demonstrate improvement in ambulation status after discharge. They were less likely to be females, treated in the emergency department, and less likely to present with a history of previous stroke and an elevated INR.

AIS patients without HF that received rtPA were younger, with higher BMI, more likely to present with a history of depression, dyslipidemia, migraine, obesity, history of previous stroke, TIA, taking hormone replacement therapy, cholesterol reducers, antidepressants and more likely to present with higher diastolic blood pressure. They were less likely to present with peripheral vascular disease, chronic renal disease, higher total cholesterol, LDL, and lipids. AIS patients without HF that received rtPA were less likely to present with higher blood glucose, serum creatine, elevated INR, take diabetic medication, treated in the emergency department, ambulate independently prior to the stroke event, during admission or after discharge.

The results for the adjusted analysis for risk factors associated with rtPA in the AIS population of patients without HF are presented in Table 3. AIS patients without HF that did not receive rtPA therapy were more likely to be Hispanic, have coronary artery stenosis, a previous history of stroke, and present with elevated heart rate, INR, lipid levels, and serum creatinine. AIS patients without HF treated with rtPA were more likely to present with a history of a previous TIA, high total cholesterol, and direct admission for treatment. The discriminating power of the model was strong, as shown by the ROC curve (Figure 1), with the area under the curve (AUROC) = 0.698 (95% CI, 0.678-0.718 $P < .001$).

The risk factors associated with rtPA therapy in AIS patients with HF are presented in Table 4. Patients with increasing age that presented with coronary artery disease and a high INR level were more likely to not to receive rtPA. In contrast, AIS-HF patients with improved ambulation were more likely to be treated with rtPA. The discriminating power of the model was strong, as shown by the ROC curve (Figure 2), with the AUROC = 0.668 (95% CI, 0.611-0.724, $P < .001$).

Discussion

Patients with HF are reportedly to recurrently not treated with rtPA in stroke clinical trials, either due to their poor premorbid functional status.[15] Notwithstanding, most of the evidence regarding treatment outcomes in AIS-HF patients are mainly

Table 2. Comparison of Demographics and Risk Factors of Acute Ischemic Stroke Patients with or Without Heart Failure Dependent on rtPA Administration.

	No Heart Failure			Heart Failure		
Characteristic	no rtPA	rtPA		no rtPA	rtPA	
Number of patients	3689	1190	*P*-value	453	137	*P*-value
Age Group: No. (%)						
<50 years	441 (12.0)	179 (15.0)	.013*[a]	26 (5.7)	12 (8.8)	.086*[a]
50-59	688 (18.7)	237 (19.9)		48 (10.6)	23 (16.8)	
60-69	896 (24.3)	289 (24.3)		85 (18.8)	29 (21.2)	
70-79	830 (22.5)	257 (21.6)		112 (24.7)	32 (23.4)	
>=80	834 (22.6)	228 (19.2)		182 (40.2)	41 (29.9)	
Age Mean ± SD	66.97 ± 14.64	65.35 ± 14.76	.001*[b]	73.89 ± 13.53	69.31 ± 14.55	.001*[b]
Race: No (%)						
White	2889 (78.3)	963 (80.9)	.156	339 (74.8)	97 (70.8)	.622
Black	673 (18.2)	192 (16.1)		101 (22.3)	36 (26.3)	
Other	127 (3.4)	35 (2.9)		13 (2.9)	4 (2.9)	
Gender: No. (%)						
Female	1866 (50.6)	596 (50.1)	.765	282 (62.3)	63 (46.0)	.001*[a]
Male	1823 (49.4)	594 (49.9)		171 (37.7)	74 (54.0)	
Hispanic Ethnicity: No. (%)	55 (1.5)	27 (2.3)	.069	0 (0)	3 (2.2)	.002*[a]
BMI: Mean ± SD	28.18 ± 6.92	28.70 ± 6.69	.023*[b]	28.21 ± 7.72	29.97 ± 7.92	.021*[b]
Medical History: No. (%)						
Atrial Fib	516 (14.0)	161 (13.5)	.691	197 (43.5)	50 (36.5)	.146
Coronary Artery Disease	999 (27.1)	328 (27.6)	.745	263 (58.1)	71 (51.8)	.197
Carotid Artery Stenosis	242 (6.6)	50 (4.2)	.003*[a]	36 (7.9)	6 (4.4)	.155
Depression	443 (12.0)	179 (15.0)	.006*[a]	73 (16.1)	26 (19.0)	.432
Diabetes	1294 (35.1)	351 (29.5)	<.001*[a]	226 (49.9)	64 (46.7)	.515
Drugs or Alcohol	238 (6.5)	68 (5.7)	.362	22 (4.9)	9 (6.6)	.431
Dyslipidemia	1783 (48.3)	620 (52.1)	.024*[a]	272 (60.0)	80 (58.4)	.73
Stroke Family History	337 (9.1)	117 (9.8)	.472	27 (6.0)	13 (9.5)	.15
Hormone Replacement Therapy	44 (1.2)	29 (2.4)	.002*[a]	4 (0.9)	2 (1.5)	.555
Hypertension	2866 (77.7)	918 (77.1)	.694	396 (87.4)	126 (92.0)	.144
Migraine	84 (2.3)	45 (3.8)	.005*[a]	5 (1.1)	0 (0)	.217
Obesity	1456 (39.5)	607 (51.0)	<.001*[a]	177 (39.1)	71 (51.8)	.008*[a]
Previous Stroke	298 (8.1)	129 (10.8)	.003*[a]	162 (35.8)	33 (24.1)	.011*[a]
Previous TIA (>24 h)	298 (8.1)	129 (10.8)	.003*[a]	36 (7.9)	14 (10.2)	.402
Prosthetic Heart Valve	41 (1.1)	8 (0.7)	.186	11 (2.4)	2 (1.5)	.499
Peripheral Vascular Disease	276 (7.5)	66 (5.5)	.023*[a]	45 (9.9)	13 (9.5)	.878
Chronic Renal Disease	276 (7.5)	61 (5.1)	.005*[a]	92 (20.3)	18 (13.1)	.059
Sleep Apnea	102 (2.8)	34 (2.9)	.867	23 (5.1)	11 (8.0)	.194
Smoker	1021 (27.7)	359 (30.2)	.097	77 (17.0)	29 (21.2)	.265
Medication History: No (%)						
HTN medication	2450 (66.4)	820 (68.9)	.112	401 (88.5)	123 (89.8)	.682
Cholesterol Reducer	1533 (41.6)	553 (46.5)	.003*[a]	268 (58.1)	79 (57.7)	.935
Diabetic Medication	991 (29.6)	279 (23.4)	.019*[a]	173 (38.2)	52 (38.0)	.961
Antidepressant	416 (11.3)	192 (16.1)	<.001*[a]	73 (16.1)	30 (21.9)	.118
Lab values: Mean ± SD						
Total cholesterol	174.4 ± 54.08	169.45 ± 45.78	.003*[b]	160.70 ± 47.46	161.69 ± 51.88	.844
Triglycerides	140.0 ± 102.90	141.71 ± 109.46	.637	132.66 ± 114.40	131.84 ± 93.37	.942
HDL	41.92 ± 13.87	42.10 ± 13.59	.702	40.51 ± 14.23	39.20 ± 13.85	.37
LDL	106.44 ± 42.46	102.86 ± 38.26	.009*[b]	96.13 ± 37.02	99.52 ± 45.59	.405
Lipids	6.63 ± 2.91	6.22 ± 1.58	<.001*[b]	6.714 ± 1.91	6.52 ± 1.78	.324
Blood Glucose	148.75 ± 83.02	139.27 ± 71.77	<.001*[b]	153.06 ± 81.49	158.86 ± 96.02	.486
Serum Creatinine	1.32 ± 1.29	1.11 ± 0.719	<.001*[b]	1.49 ± 1.06	1.411 ± 0.96	.441
INR	1.15 ± 0.53	1.04 ± 0.14	<.001*[b]	1.31 ± 0.76	1.14 ± 0.171	.013*[b]
Vital Signs: Mean ± SD						
Heart Rate	82.07 ± 18.87	81.59 ± 17.16	.167	82.05 ± 19.48	83.70 ± 17.26	.373
Blood Pressure Systolic	152.48 ± 30.11	151.19 ± 26.96	.496	148.0 ± 29.21	152.3 ± 26.55	.122
Blood Pressure Diastolic	82.55 ± 19.21	82.96 ± 18.12	.023*[b]	80.17 ± 20.54	82.58 ± 19.81	.226

(continued)

Table 2. (continued)

Characteristic	No Heart Failure			Heart Failure		
	no rtPA	rtPA		no rtPA	rtPA	
Number of patients	3689	1190	*P*-value	453	137	*P*-value
Ambulation Status Prior to Event: No. (%)						
Ambulate Independently	3288 (89.1)	1137 (95.5)	<.001*[a]	340 (75.1)	122 (89.1)	.008*[a]
Ambulate with Assistance	143 (3.9)	18 (1.5)		37 (8.2)	5 (3.6)	
Unable to Ambulate	153 (4.1)	12 (1.0)		40 (8.8)	8 (5.8)	
Not Documented	105 (2.8)	23 (1.9)		35 (7.7)	2 (1.5)	
Ambulation Status on Admission: No. (%)						
Ambulate Independently	1023 (27.7)	219 (18.4)	<.001*[a]	76 (16.8)	13 (9.5)	.024*[a]
Ambulate with Assistance	1206 (32.7)	278 (23.4)		114 (25.2)	28 (20.4)	
Unable to Ambulate	1046 (28.4)	412 (34.6)		203 (44.8)	67 (48.6)	
Not Documented	414 (11.2)	281 (23.6)		60 (13.2)	29 (21.2)	
Ambulation Status on Discharge: No. (%)						
Ambulate Independently	1403 (38.0)	615 (51.7)	<.001*[a]	113 (24.9)	43 (31.4)	.334
Ambulate with Assistance	1306 (35.4)	315 (26.5)		160 (35.3)	39 (28.5)	
Unable to Ambulate	716 (19.4)	180 (15.1)		131 (28.9)	42 (30.7)	
Not Documented	264 (7.2)	80 (6.7)		49 (10.8)	13 (9.5)	
First Care Received: No. (%)						
Emergency Department	2901 (79.4)	906 (76.5)	.029*[a]	387 (85.4)	106 (77.4)	.002*[a]
Direct Admission	751 (20.6)	279 (23.5)		24 (5.3)	18 (13.1)	
Improved Ambulation: No (%)	1012 (29.4)	627 (56.3)	<.001*[a]	129 (31.8)	57 (45.6)	.005*[a]

[a]Pearson's Chi-Squared test.
[b]Student's T test.
* *P*-value < .05.

Table 3. Clinical Factors that were Associated with rtPA Treatment for Acute Ischemic Stroke Patients Without Heart Failure. Adjusted OR<1 Indicates Factors Associated with Exclusion from rtPA While OR>1 Indicates Factors Associated with Getting rtPA Treatment. Hosmer-Lemeshow Test ($P = .742$), Cox & Snell ($R^2 = 0.105$). The Overall Classified Percentage of 68.8% was Applied to Check for Fitness of the Logistic Regression Model. *Indicates Statistical Significance ($P < .05$) with a 95% Confidence Interval.

Variables	B Value	Wald	Odds Ratio	95% C.I.		*P*-value
				Lower	Upper	
Increasing Age	−0.005	2.871	0.995	0.989	1	.090
Hispanic Ethnicity	−0.769	5.698	0.464	0.247	0.87	.017*
Coronary Artery Stenosis	−0.597	8.192	0.55	0.366	0.83	.004*
Previous Stroke	−0.294	8.169	0.745	0.609	0.91	.004*
Previous TIA	0.37	6.723	1.447	1.094	1.91	.010*
Anti-HTN medication	0.167	2.713	1.182	0.969	1.44	.100
Anti-Depressant	0.185	3.551	1.203	0.993	1.46	.060
Total Cholesterol	0.397	10.872	1.487	1.175	1.88	.001*
Lipids	−0.002	4.311	0.998	0.996	1	.038*
Serum Creatinine	−0.106	16.041	0.899	0.854	0.95	<.001*
INR	−0.192	9.487	0.825	0.73	0.93	.002*
Heart Rate	−2.041	43.743	0.13	0.071	0.24	<.001*
Ambulation Improvement	0.004	3.066	1.004	0.999	1.01	.080
Direct admission	1.054	155.259	2.87	2.432	3.39	<.001*

Backward Stepwise model based on Likelihood Ratio was applied.
Model assumptions were fulfilled.
Multicollinearity and interactions among independent variables were checked and no significant interactions were found.
Hosmer-Lemeshow test ($P = .742$), Cox & Snell ($R^2 = 0.105$).

from observational studies.[16,17] Findings reveal that HF is an independent predictor of unfavorable outcomes.[18,19] While a lower fraction of higher mortality risks linked to HF in AIS have been reported,[6] it has also been observed that there was no difference in the rate of successful vessel recanalization after intravenous rtPA between patients who had a stroke

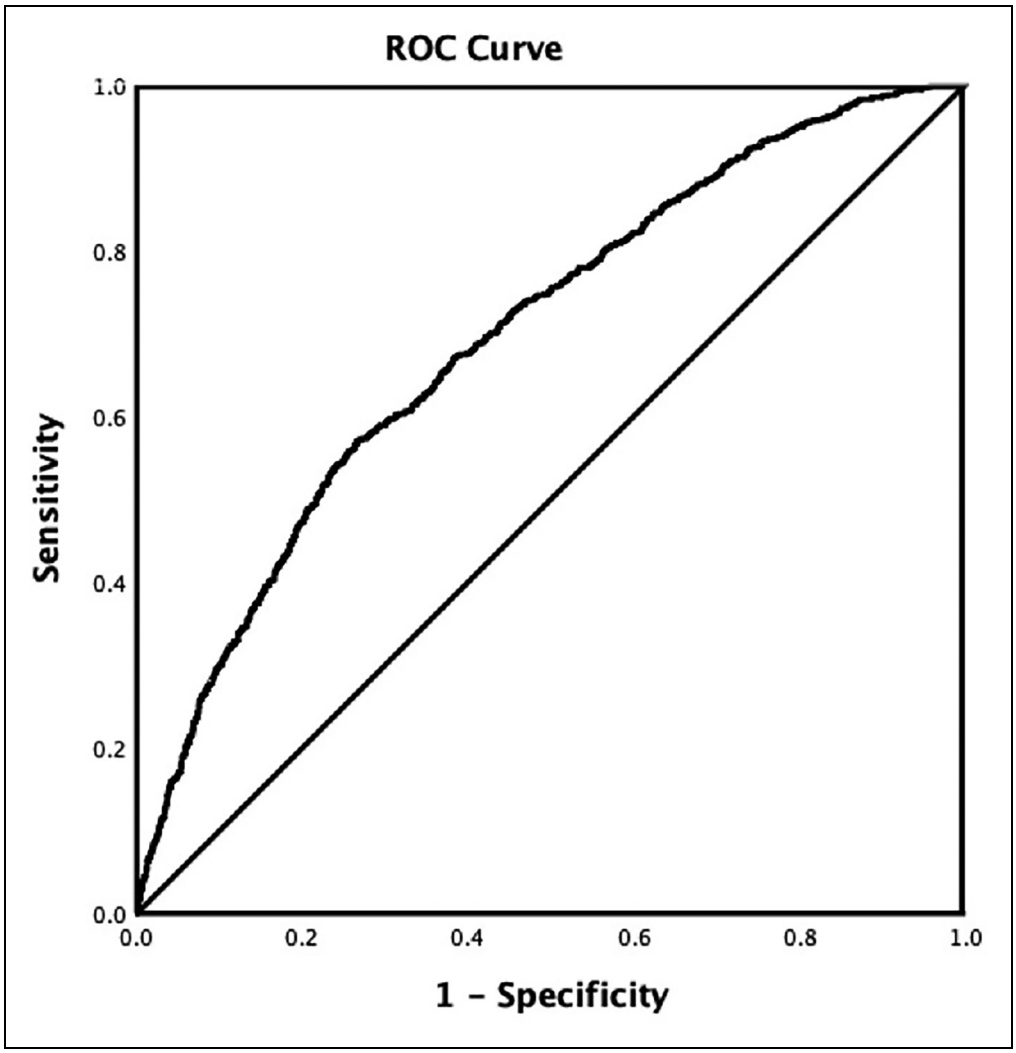

Figure 1. ROC curve for acute ischemic stroke patients without heart failure treated with rtPA. Area under the curve (AUC) values for the ROC analysis indicates a better discriminative capability of the model (AUC = 0.698, 95% CI, $P < .001$).

Table 4. Clinical Factors Associated with rtPA Treatment for Ischemic Stroke Patients with Heart Failure. Adjusted OR<1 Indicates Factors that are Associated with Exclusion from rtPA While OR>1 Indicates Factors that are Associated with Treatment with rtPA. Hosmer-Lemeshow Test ($P = .800$), Cox & Snell ($R^2 = 0.780$). The Overall Classified Percentage of 75.4% was Applied to Check for Fitness of the Logistic Regression Model. *Indicates Statistical Significance ($P < .05$) with a 95% Confidence Interval.

				95% C.I.		
Variables	B Value	Wald	Odds Ratio	Lower	Upper	*P*-value
Increasing Age	−0.019	5.387	0.982	0.966	1	.020*
Previous Stroke	−0.464	3.255	0.629	0.38	1.04	.071
Coronary Artery Disease	−0.481	4.215	0.618	0.391	0.98	.040*
Hypertension	0.674	2.641	1.962	0.87	4.42	.104
Chronic Renal Disease	−0.547	3.028	0.579	0.312	1.07	.082
INR	−1.12	5.64	0.326	0.129	0.82	.018*
Ambulation Improvement	0.525	4.829	1.69	1.058	2.7	.028*

Backward Stepwise model based on Likelihood Ratio was applied.
Model assumptions were fulfilled.
Multicollinearity and interactions among independent variables were checked and no significant interactions were found.
Hosmer-Lemeshow test ($P = .800$), Cox & Snell ($R^2 = 0.780$).

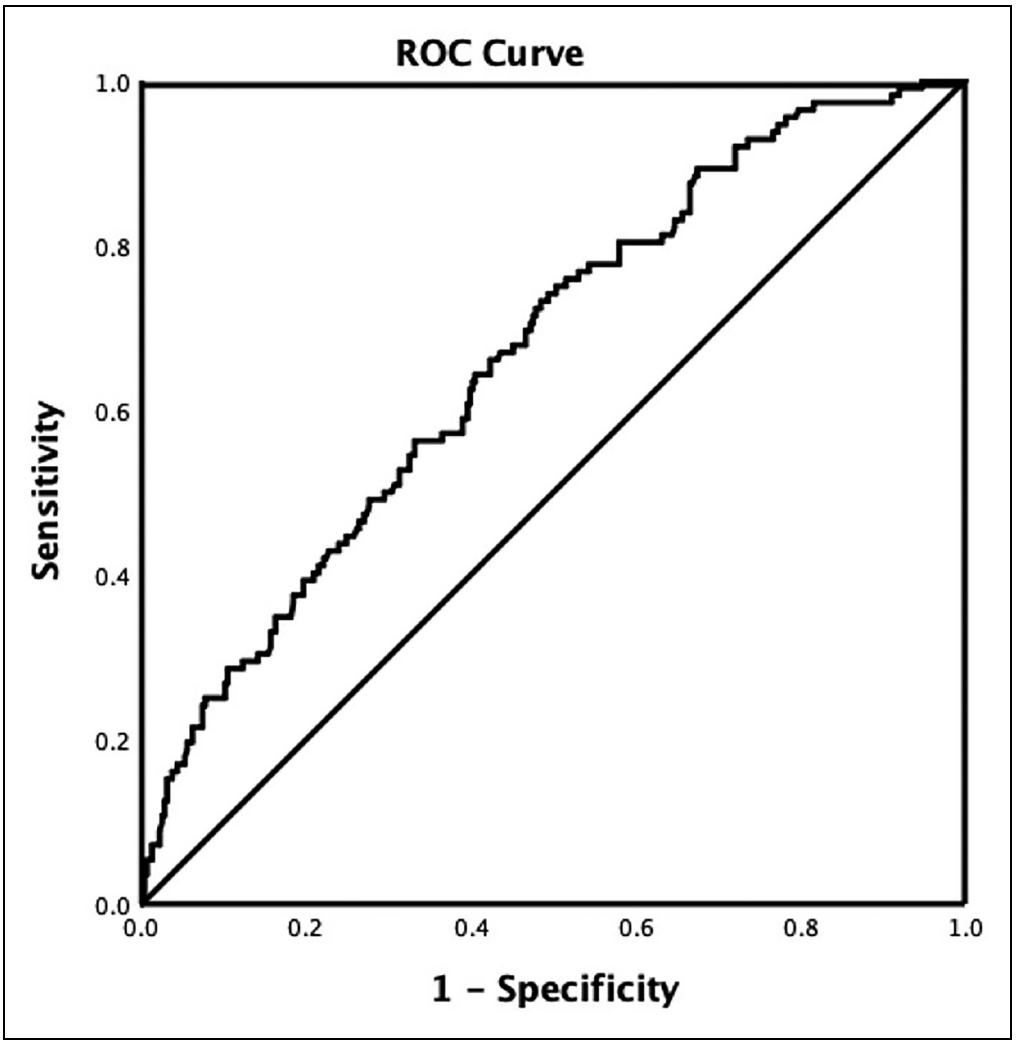

Figure 2. ROC for acute ischemic stroke patients treated with heart failure. Area under the curve (AUC) values in ROC analysis indicates a better discriminative capability of the model with the area under the ROC curve (AUC) = 0.668, 95% CI, $P < .001$.

with and without HF.[6,9] Furthermore, there was also no difference in the rate of intracranial bleeding.

While existing studies[10,20] suggest that AIS-HF patients present with specific risk factors that worsen outcomes, the current study investigated the specific risk factors that may contribute to the reason that AIS-HF patients are less likely to receive rtPA and are therefore unable to benefit from the demonstrated advantage of thrombolytic therapy. In the adjusted analysis for AIS patients without HF, we observed that patients that received rtPA presented with a history of previous TIA, elevated cholesterol levels, and direct admission to a primary stroke center for treatment. Similar findings have been reported for AIS patients with histories of previous TIA,[21–23] elevated cholesterol levels,[13,24] and direct admission.[25,26] We also observed that AIS patients without HF who did not receive rtPA were more likely to be Hispanic and present with coronary artery stenosis, previous stroke, and elevated lipid level, creatinine, INR, and heart rate. Our finding that Hispanic AIS patients without HF were more likely not to be treated with rtPA is supported by prior studies showing lower rates of rtPA use among the Hispanic population.[27]

In addition, our finding that AIS patients without HF that present with coronary artery stenosis, history of previous stroke, and elevated lipid levels, INR, creatinine, and heart rate was more likely not to receive rtPA is consistent with other studies demonstrating the association between rtPA and elevated heart rate,[28] lipid levels,[29] INR,[30] creatinine,[31] coronary artery stenosis,[32] and previous stroke.[29] Estimates of eligibility for rtPA in the AIS population are reported to range from 6% to 8% of all strokes.[33,34] While the most common exclusion factor for rtPA is the delay in presentation for treatment, comorbidities such as history of coronary artery stenosis,[35,36] previous stroke,[29,37] elevated lipids,[38] INR,[39] creatinine,[31] and heart rate[21] have been reported to contribute to the low eligibility rate for rtPA.

In the AIS cohort with HF, we observed that older and present with coronary artery disease and elevated INR levels were more likely not to be treated with rtPA. Age is one of the critical factors influencing the treatment outcome of

stroke.[40] The gap in clinical outcomes between those <80 and >80 years of age is significant when comparing long-term outcomes.[21,41] Therefore, it is not surprising that some of the major, randomized, controlled trials testing the efficacy of thrombolytic agents excluded older patients.[42] While age is not an exclusion criterion for rtPA,[29] studies[43,44] have found that patients over 80 did not receive rtPA due to a higher risk of intracranial hemorrhage or hemorrhagic conversion. Therefore, the fear of bleeding in addition to the increased burden of comorbidities in the HF population, and the association with poor neurologic outcomes and higher mortality rates[45–47] may contribute to our finding that older AIS-HF patients were more likely not to be treated rtPA therapy.

Moreover, we found that AIS-HF patients with a history of CAD were more likely not to be treated with rtPA. CAD is a major contributor to HF and is associated with high morbidity and mortality.[45,48] Approximately 65% of patients admitted for HF present with a history of CAD.[49] Stroke severity among AIS patients with CAD is reported to be comparable to that of AIS patients with HF.[49] This finding indicates that CAD and HF are associated with worse outcomes in AIS patients.[50,51] Our finding that AIS-HF patients with CAD did not receive rtPA therapy suggests the need for a future study to distinguish CAD status by clinical history from the underlying etiology of HF in AIS patients. Such a study will provide the basis for other studies to test novel therapeutic strategies targeting CAD in the AIS-HF patient population.

We also found that AIS patients with HF that presented with an elevated International Ratio (INR) were less likely to receive rtPA. INR is used to evaluate coagulopathies associated with rtPA therapy.[52] In the current guideline,[53] an INR > 1.7 is considered as an exclusion criterion for rtPA. However, whether it is safe to administer rtPA at INR levels lower than 1.7 is controversial, especially as rising INR indicates a risk of bleeding.[54] The INR level in our AIS-HF patient cohort was 1.14, indicating that the presence of HF and an elevated INR may pose a risk of bleeding and thus lead to exclusion from rtPA.

Our finding that an improvement in ambulatory status during admission was associated with rtPA therapy in AIS-HF patients was not surprising. Improvement in ambulatory status is a quantitative metric based on a patient's stroke recovery during hospitalization. This variable has been previously documented as a predictor of long-term stroke recovery after rtPA administration.[55] This finding supports our current result that AIS-HF patients treated with rtPA were more likely to be associated with an improvement in ambulatory status.

Limitations

This was a retrospective analysis of data from a regional stroke registry. Since this is not a prospective, randomized, controlled study, it is difficult to determine cause-and-effect relationships for rtPA in AIS-HF patients. Also, the patients' records did not define HF status, which could misclassify those with subclinical HF. Moreover, previous coronary revascularization has been shown to reduce the association between CAD and poor HF outcomes. Our results in a population with a significant revascularization history may underestimate the impact of CAD. Finally, several other factors such as heavy episodic alcohol consumption, hyperlipidemia, hypercholesterolemia, metabolomic syndrome, cardiomyopathy hypoglycemic medications not present in our stroke data base may affect the use of rtPA for AIS-HF patients. Future studies on the effect of such risk factors on the use rtPA therapy for will help to improve the care of AIS patients with or without HF.

Conclusion

Heart failure is highly prevalent in patients hospitalized for AIS. In this study, AIS patients with heart failure who presented increased age, coronary artery disease, and an elevated INR were more likely not to be treated with rtPA therapy. Our findings identify specific risk factors that can be managed to improve the use of rtPA therapy for AIS-HF patients.

Abbreviations

Adjusted OR-	Adjusted odd ratio
Afib	atrial fibrillation
CI	confidence interval
HRT	Hormone Therapy
BMI	Body mass index
CHF	Congestive heart failure
CI	Confidence interval
IRB	Institutional Review Board
INR	International normalized ratio
LDL-C	Low-density lipoprotein cholesterol
HDL-C	high-density lipoprotein cholesterol
rtPA	Recombinant tissue plasminogen
TC	Total cholesterol
TG	Triglyceride
AIS	Acute ischemic stroke
NIHSS	National Institute of Health Stroke Scale
MRI	Magnetic Resonance Imaging
CT	Computer Tomography
MCA	middle cerebral artery
CAD	coronary artery disease
HRT	hormone replacement therapy
TIA	transient ischemic attack
PVD	Peripheral vascular disease
ROC	Receiver Operating Curve
INR	International Normalized Ratio
HRV	heart rate variability
TP	total power
VLF	very low frequency
LF	low frequency
HF	high-frequency domains.

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Authors' Contribution

CBS, KK, NP, CR, CE and TIN designed the concept, experiment, and data analysis. MS, MGE and TIN critically revised the drafts, interpreted the results, read and approved the last version of this manuscript. All authors have provided the corresponding author with permission to be named in the manuscript and approved the submission of this manuscript.

Declaration of Conflicting Interests

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Ethics Approval and Consent to Participate

This is a retrospective data collection. The institutional review board approved this study of PRISMA Health institutional committee for ethics (approval number: 00052571).

Availability of Data and Materials

The retrospective datasets are available by request from the corresponding author of this manuscript, respectively.

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References

1. Haeusler KG, Laufs U, Endres M. Chronic heart failure and ischemic stroke. *Stroke*. 2011;42(10):2977-2982.
2. Liu Y, Ma J, Shi Q, et al. Quantitatively monitoring acute ischemic stroke patients post recombinant tissue plasminogen activator treatment. *Health Sci Rep*. 2021;4(1):e218.
3. Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. *J Am Coll Cardiol.* 2020;76(25):2982-3021.
4. Lee VH, Conners JJ, Cutting S, Song SY, Bernstein RA, Prabhakaran S. Elevated international normalized ratio as a manifestation of post-thrombolytic coagulopathy in acute ischemic stroke. *J Stroke Cerebrovasc Dis.* 2014;23(8):2139-2144.
5. Vandelli L, Marietta M, Gambini M, et al. Fibrinogen decrease after intravenous thrombolysis in ischemic stroke patients is a risk factor for intracerebral hemorrhage. *J Stroke Cerebrovasc Dis.* 2015;24(2):394-400.
6. Siedler G, Sommer K, Macha K, et al. Heart failure in ischemic stroke: relevance for acute care and outcome. *Stroke*. 2019;50(11):3051-3056.
7. Hui W, Wu C, Zhao W, et al. Efficacy and safety of recanalization therapy for acute ischemic stroke with large vessel occlusion: a systematic review. *Stroke*. 2020;51(7):2026-2035.
8. Muruet W, Rudd A, Wolfe CDA, Douiri A. Long-term survival after intravenous thrombolysis for ischemic stroke: a propensity score-matched cohort with up to 10-year follow-up. *Stroke*. 2018;49(3):607-613.
9. Siedler G, Sommer K, Macha K, et al. Heart failure in ischemic stroke. 2019;50(11):3051-3056. doi:10.1161/STROKEAHA.119.026139.
10. Chen BJ, Daneshvari NO, Johansen MC. Bleeding risk in patients with cardiac disease from ischaemic stroke reperfusion therapy: an update. *BMJ Neurol Open*. 2021;3(2):e000156.
11. Savarese G, Lund LH. Global public health burden of heart failure. *Card Fail Rev*. 2017;3(1):7-11.
12. Mene-Afejuku TO, Pernia M, Ibebuogu UN, et al. Heart failure and cognitive impairment: clinical relevance and therapeutic considerations. *Curr Cardiol Rev.* 2019;15(4):291-303.
13. Brechtel L, Poupore N, Stoikov T, Roley LT, Emerson JF, Nathaniel T. Comorbidities associated with different levels of total cholesterol in male and female acute ischemic stroke patients. *Medicine (Baltimore).* 2020;99(52):e23870.
14. Poupore N, Strat D, Mackey T, Brown K, Snell A, Nathaniel IT. Thrombolytic therapy in ischemic stroke patients with a preceding transient ischemic attack (TIA) in a telestroke and non-telestroke setting. *Neurol Clin Neurosci.* 2020;5:34-39.
15. Bhaskar S, Stanwell P, Cordato D, Attia J, Levi C. Reperfusion therapy in acute ischemic stroke: dawn of a new era? *BMC Neurol.* 2018;18(1):8.
16. Lin N-T, Cao Y-C, Cheng Z-Z, Wang Y, Xu P-Y. Thrombolysis lead to better long-term outcome in Chinese stroke patients. *Neuroimmunol Neuroinflamm.* 2016;3(4):98-101.
17. Sobolewski P, Kozera G, Szczuchniak W, et al. Cerebral thrombolysis in patients with ischemic stroke and heart failure. *Neurol Neurochir Pol*. 2018;52(5):593-598.
18. Nogueira RG, Gupta R, Jovin TG, et al. Predictors and clinical relevance of hemorrhagic transformation after endovascular therapy for anterior circulation large vessel occlusion strokes: a multicenter retrospective analysis of 1122 patients. *J Neurointerv Surg*. 2015;7(1):16-21.
19. Palumbo V, Baldasseroni S, Nencini P, et al. The coexistence of heart failure predicts short term mortality, but not disability, in patients with acute ischemic stroke treated with thrombolysis: the Florence area Registry. *Eur J Intern Med*. 2012;23(6):552-557.
20. Cuadrado-Godia E, Ois A, Roquer J. Heart failure in acute ischemic stroke. *Curr Cardiol Rev.* 2010;6(3):202-213.
21. Poupore N, Strat D, Mackey T, Snell A, Nathaniel T. Ischemic stroke with a preceding trans ischemic attack (TIA) less than 24 hours and thrombolytic therapy. *BMC Neurol.* 2020;20(1):197.
22. Poupore N, Strat D, Mackey T, Nathaniel TI. The association between an antecedent of transient ischemic attack prior to onset of stroke and functional ambulatory outcome. *Clin Appl Thromb Hemost.* 2020;26:1076029620906867. doi:10.1177/1076029620906867.
23. Poupore N, Strat D, Mackey T, Nathaniel IT. The association between an antecedent of transient ischemic attack prior to onset of stroke and functional ambulatory outcome. *Clin Appl Thromb Hemost.* 2020;26:1-11.
24. Brechtel L, Poupore N, Monroe M, et al. Role of dyslipidemia in ischemic stroke patients treated in the telestroke network. *Adv Med Sci*. 2021;66(2):254-261.

25. Poupore N, Strat D, Mackey T, Brown K, Snell A, Nathaniel TI. Cholesterol reducer and thrombolytic therapy in acute ischemic stroke patients. *Lipids Health Dis*. 2020;19(1):84.
26. Rathfoot C, Edrissi C, Sanders CB, Knisely K, Poupore N, Nathaniel T. Gender differences in comorbidities and risk factors in ischemic stroke patients with a history of atrial fibrillation. *BMC Neurol.* 2021;21(1):209.
27. Aparicio HJ, Carr BG, Kasner SE, et al. Racial disparities in intravenous recombinant tissue plasminogen activator use persist at primary stroke centers. *J Am Heart Assoc*. 2015;4(10):e001877.
28. Tomii Y, Toyoda K, Nakashima T, et al. Effects of hyperacute blood pressure and heart rate on stroke outcomes after intravenous tissue plasminogen activator. *J Hypertens*. 2011;29(10):1980-1987.
29. Fugate JE, Rabinstein AA. Absolute and relative contraindications to IV rt-PA for acute ischemic stroke. *Neurohospitalist*. 2015;5(3):110-121.
30. Erdman MJ, Davidson KE, Haller JT, et al. Effect of alteplase administration on international normalized ratio in patients with acute ischemic stroke. *Neurohospitalist*. 2020;10(3):176-180.
31. Marsh EB, Gottesman RF, Hillis AE, Urrutia VC, Llinas RH. Serum creatinine may indicate risk of symptomatic intracranial hemorrhage after intravenous tissue plasminogen activator (IV tPA). *Medicine (Baltimore)*. 2013;92(6):317-323.
32. Tomkins AJ, Hood RJ, Pepperall D, Null CL, Levi CR, Spratt NJ. Thrombolytic recanalization of carotid arteries is highly dependent on degree of stenosis, despite sonothrombolysis. *J Am Heart Assoc.* 2016;5(2), doi:10.1161/jaha.115.002716.
33. de los Ríos la Rosa F, Khoury J, Kissela BM, et al. Eligibility for intravenous recombinant tissue-type plasminogen activator within a population: the effect of the European Cooperative Acute Stroke Study (ECASS) III trial. *Stroke*. 2012;43(6):1591-1595.
34. Eissa A, Krass I, Levi C, Sturm J, Ibrahim R, Bajorek B. Understanding the reasons behind the low utilisation of thrombolysis in stroke. *Australas Med J.* 2013;6(3):152-167.
35. Blum B, Brechtel L, Nathaniel T. Thrombolysis therapy in specialized and non-specialized stroke units. *Arch Med Res.* 2018;49(8):588-597.
36. Poupore N, Strat D, Mackey T, Snell A, Nathaniel T. Ischemic stroke with a preceding Trans ischemic attack(TIA) less than 24 hours: Predicting clinical risk factors for thrombolytic therapy. Research Square; 2019.
37. Fugate JE, Rabinstein AA. Update on intravenous recombinant tissue plasminogen activator for acute ischemic stroke. *Mayo Clin Proc.* 2014;89(7):960-972.
38. Gainey J, Blum B, Bowie B, et al. Stroke and dyslipidemia: clinical risk factors in the telestroke versus non-telestroke. *Lipids Health Dis.* 2018;17(1):226.
39. Aggarwal HR, Hassan AE, Rodriguez GJ, Suri MF, Taylor RA, Qureshi AI. Use of intravenous recombinant tissue plasminogen activator in patients with borderline elevation of international normalized ratio. *J Vasc Interv Neurol*. 2013;6(2):1-8.
40. Furie KL, Kasner SE, Adams RJ, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. *Stroke*. 2011;42(1):227-276.
41. IST-3 Collaborative Group. Effect of thrombolysis with alteplase within 6h of acute ischaemic stroke on long-term outcomes (the third International Stroke Trial [IST-3]): 18-month follow-up of a randomised controlled trial. *Lancet Neurol*. 2013;12(8):768-776.
42. Albers GW, Clark WM, Madden KP, Hamilton SA. ATLANTIS Trial: results for patients treated within 3hours of stroke onset. *Stroke*. 2002;33(2):493-496.
43. Engelter ST, Reichhart M, Sekoranja L, et al. Thrombolysis in stroke patients aged 80 years and older: Swiss survey of IV thrombolysis. *Neurology*. 2005;65(11):1795-1798.
44. Engelter ST, Bonati LH, Lyrer PA. Intravenous thrombolysis in stroke patients of ≥80 versus <80 years of age—a systematic review across cohort studies. *Age Ageing.* 2006;35(6):572-580.
45. Nathaniel IT, Gainey J, Blum B, Montgomery C, Ervin L, Madeline L. Clinical risk factors in thrombolysis therapy: telestroke versus nontelestroke. *J Stroke Cerebrovasc Dis*. 2018;27(9):2524-2533.
46. Nathaniel TI, Ubah C, Wormack L, Gainey J. The telestroke and thrombolysis therapy in diabetic stroke patients. *Diabetol Metab Syndr.* 2019;11(1):36.
47. Nathaniel TI, Williams JA, Fazzone B, et al. Contraindications and exclusion criteria in guidelines for rt-pa in acute ischemic stroke: can the new aha/asa guideline expand the use of rt-pa? *Hypertension*. 2016;68(Suppl 1):3-6.
48. Heart Failure Society of America. Executive summary: HFSA 2006 comprehensive heart failure practice guideline. *J Card Fail.* 2006;12(1):10-38.
49. Gheorghiade M, Sopko G, De Luca L, et al. Navigating the crossroads of coronary artery disease and heart failure. *Circulation*. 2006;114(11):1202-1213.
50. Manzano L, Babalis D, Roughton M, et al. Predictors of clinical outcomes in elderly patients with heart failure. *Eur J Heart Fail*. 2011;13(5):528-536.
51. Nathaniel TI, Cochran T, Chaves J, et al. Co-morbid conditions in use of recombinant tissue plasminogen activator (rt-PA) for the treatment of acute ischaemic stroke. *Brain Inj.* 2016;30(10):1261-1265.
52. Rost NS, Masrur S, Pervez MA, Viswanathan A, Schwamm LH. Unsuspected coagulopathy rarely prevents IV thrombolysis in acute ischemic stroke. *Neurology*. 2009;73(23):1957-1962.
53. Kitchen S, Preston FE. Standardization of prothrombin time for laboratory control of oral anticoagulant therapy. *Semin Thromb Hemost*. 1999;25(1):17-25.
54. Shikdar S, Vashisht R, Bhattacharya PT. *International Normalized Ratio (INR)*. StatPearls Publishing; 2022.
55. Lawson TR, Brown IE, Westerkam DL, et al. Tissue plasminogen activator (rt-PA) in acute ischemic stroke: outcomes associated with ambulation. *Restor Neurol Neurosci.* 2015;33(3):301-308.