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ORIGINAL ARTICLE

Gender and thrombolysis therapy in acute ischemic stroke patients with incidence of obesity

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Abstract

Objective To investigate clinical risk factors that were associated with gender differences in thrombolysis therapy in stroke patients with incidence of obesity.

Method Retrospective data of obese acute ischemic stroke patients were extracted from a stroke registry between January 2010 and June 2016. Gender differences in exclusion from rtPA or thrombolysis therapy were determined following an adjustment for differences in demographics, clinical risk factors using multiple regression analysis. Significant interactions between variables in the regression models were determined using variance inflation factors.

Results A total of 1105 obese stroke patients were admitted, 549 were excluded from rtPA of which 51.7% were males and 48.3% were females. Among obese male stroke patients, age > 80 years (OR = 1.029, 95% CI, 1.005–1.054, $P = 0.016$), a history of peripheral vascular disease (OR = 3.008, 95% CI, 0.989–9.153, $P = 0.052$), and an elevated diastolic blood pressure (OR = 1.018, 95% CI, 1.001–1.035, $P = 0.038$) were associated with exclusion from rtPA therapy. In obese female stroke patients, coronary artery disease was associated with exclusion from rtPA (OR = 2.478, 95% CI, 1.270–4.836, $P = 0.008$) while antihypertensive therapy was associated with inclusion for rtPA (OR = 0.326, 95% CI, 0.139–0.764).

Conclusion Elderly obese male stroke patients with elevated diastolic blood pressure, history of peripheral vascular disease, and obese female stroke patients with a history of coronary artery disease were more likely to be excluded from rtPA.

Keywords Gender · Ischemic stroke · Recombinant tissue-type plasminogen · Activator (rtPA) · Obesity

Introduction

Irrespective of gender, obesity is a major health risk factor for stroke and more than 68% of adults in the USA are classified as overweight or obese [1]. Obesity leads to an estimated average of 238,454 deaths annually [2] and represents a major predictor of morbidity and mortality in both male and female stroke patients [3]. In general, gender and incidence of stroke have been investigated extensively [4–6]. Findings from these studies indicate that the incidence of stroke with age-specific adjustment is greater in men [7], while the overall lifetime risk of stroke is greater in women due to their longer average life expectancy [8–10]. Additionally, worse outcomes have been reported in women [11, 12]. Moreover, the relationship between obesity and the risk for ischemic stroke in both men and women has been investigated [13, 14]. Findings from these studies resulted in the recommendation for the treatment of obesity for primary and secondary prevention of stroke [15], indicating an association of gender and obesity with stroke prevalence and outcome.

While the relationship between obesity and the risk of stroke has been investigated extensively, the effect of clinical risk factors in obese stroke patients undergoing thrombolysis therapy has not been extensively studied. It is not known, for example, whether clinical risk factors in obese stroke patients is associated with the exclusion or inclusion of more obese male or female stroke patients from thrombolysis therapy. Obesity is assessed based on BMI and represents an independent risk factor for stroke [16]. It is the best predictor of stroke in women and the only significant predictor of stroke in men [17]. Although obesity is not an exclusion factor for thrombolysis therapy, specific clinical and demographic factors in obese stroke patients could affect the use of thrombolysis therapy and influence outcomes differently in obese male or

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female stroke population. For example, a combination of BMI, age stroke severity, and several clinical risk factors may act alone or in synergy to exclude more women or men from thrombolysis in stroke patients with obesity.

In an acute ischemic stroke population, women are less likely to receive thrombolysis treatment than men [18, 19]. The severity of stroke is worse in women than in men, but the existing gender difference is attenuated following thrombolysis therapy [20]. This suggests that there is a greater benefit of thrombolytic therapy in women when compared with men [9, 21, 22]. Whether such a benefit also persists for obese stroke women when compared with men is yet to be investigated. If a gender difference also persists within an obese stroke population, one possibility is that the proportion of clinical risk factors in obese male and female stroke patients is different such that more obese male stroke patients are excluded from rtPA when compared with females. This is because more clinical risk factors may be associated with the exclusion of more obese stroke males when compared with females. We tested this hypothesis in a population of obese male acute ischemic stroke patients and compared our results with obese female acute ischemic stroke patients. First, we identified demographic and clinical risk factors that are associated with gender differences in the exclusion of obese male and female stroke patients from thrombolysis therapy. Second, we determined demographic and clinical risk factors that are associated with exclusion of male or female ischemic stroke patients with incidence of obesity from rtPA. An increase in the use of rtPA in obese stroke population will require the identification of specific baseline clinical risk factors in males or females that can be targeted to improve the use of rtPA and treatment outcomes. The current study investigated clinical risk factors that can be managed to eliminate gender differences and improve the use of rtPA in the care of acute ischemic stroke population with obesity.

Methods

Data collection

Retrospective data was collected from the stroke registry of the Greenville Health Care System (GHS) between January 2010 and June 2016. The registry contributes to the Get with The Guidelines (GWTG)–Stroke, a national registry of the American Heart Association and American Stroke Association, which represents a risk model that provides clinicians with a validated and practical bedside instrument for the stratification of mortality risk. The GHS registry has been described in previous studies [4, 9, 23–30]. A stroke neurologist determined whether the patient met the criteria for the description of acute stroke and retrieved. Stroke events were classified as ischemic stroke, transient ischemic attack, intracerebral hemorrhage, or subarachnoid hemorrhage based on the classification of stroke from the Classification of Cerebrovascular Diseases III [31]. In this study, we used data for acute ischemic stroke with incidence of obesity for our data analysis. All data for the patient's demographics, clinical variables that were used for the study was abstracted by a nursing practitioner. Baseline clinical risk factors were extracted from documented patient medical history retrieved from medical records during admission to the GHS stroke unit. Demographic variables including age, race/ethnicity, and gender were collected. Data on admission date, prior medication use history including cholesterol reducers, antihypertensive and diabetes medications, pre-stroke and post-stroke ambulatory statuses, and past medical history were also collected. We abstracted data on clinical risk factors from patients' medical records that include coronary artery disease (CAD), carotid stenosis, diabetes, dyslipidemia, atrial fibrillation/flutter, congestive heart failure (CHF), hypertension, transient ischemic attack (TIA) or previous stroke, smoking history, peripheral vascular disease (PVD), depression, evidence of drug use, chronic renal problems, and history of smoking. Data on laboratory analysis of patients' blood or plasma samples for total serum cholesterol, blood sugar and serum creatinine concentrations, systolic, diastolic pressures, and BMI were also collected. Data were collected for patients within 24 h of stroke onset and 4.5 h rtPA protocol. Collected data were examined under quality control checks using established protocol to ascertain the quality of the data and to ensure against several types of errors including the interpretation or coding of data. Approval for this study was obtained from the ethics committee of the Greenville Health system in 2017. Since this is a retrospective data analysis, all data were de-identified, and the study did not involve patients and no consent was required.

Data analysis

All statistical analyses were performed utilizing SPSS Statistics Software version 24 (Chicago, IL). A univariate analysis was used to determine factors that were associated with receipt of recombinant tissue plasminogen activator (rtPA) in the study population. Descriptive statistics were calculated for the demographic and clinical characteristics of patients. All continuous variables are represented as mean (standard deviation) and comparisons between groups were made using Student's *t* test. All discrete variables are represented as number (percentage) and comparisons between groups were made using Pearson's chi-squared analyses. Univariate analysis was repeated to determine factors associated with receipt of rtPA in the separate rtPA/non-rtPA subgroups and by male and female gender.

Multivariate analysis using a stepwise conditional logistic regression was performed to determine demographic and clinical characteristics associated with exclusion from rtPA

administration in the obese stroke population as well as in the male and female subgroups. The predictor variable for each of our logistic regression model was selected by stepwise regression and variables with $P < 0.05$ were retained in the model. For the goodness of fit test of how well our model fits the data, we used the Hosmer-Lemeshow test that reveals the strength of our prediction models. The discrimination capability for each of our fitted logistic models was determined using the receiver operating characteristic (ROC) curve and quantified by area under the ROC curve (AUC). Multicollinearity and significant interactions between independent variables were examined using variance inflation factors to confirm independence of variables included in the regression models. All statistical analysis was performed using SPSS Statistics Software Version 24.0, and a p value of less than 0.05 was used to determine significance.

Table 1 The overall obese ischemic stroke population by sex

	Male	Female	p value
Number of Patients	571	534	
Age group: no. (%)			
<50 years	70 (12.3)	87 (16.3)	
50–59	145 (25.4)	92 (17.2)	
60–69	152 (26.6)	100 (18.7)	< 0.001*
70–79	129 (22.6)	126 (23.6)	
>80 years	75 (13.1)	129 (24.2)	
Mean ± SD	64.28 ± 13.2	66.52 ± 15.9	< 0.011*
Race: no. (%)			
White	456 (79.9)	414 (77.5)	0.039*
African American	111 (19.4)	106 (19.9)	
Other	4 (0.7)	14 (2.6)	
Medical history: no. (%)			
Atrial fib/flutter	83 (14.5)	95 (17.8)	0.141
Coronary artery disease	197 (34.5)	126 (23.6)	< 0.001*
Carotid artery stenosis	32 (5.6)	23 (4.3)	0.322
Depression	98 (17.2)	148 (27.7)	< 0.001*
Diabetes	219 (38.4)	214 (40.1)	0.558
Drug abuse	65 (11.4)	13 (2.4)	< 0.001*
Dyslipidemia	316 (55.3)	298 (55.8)	0.877
Family history	66 (11.6)	66 (12.4)	0.682
Heart failure	65 (11.4)	72 (13.5)	0.290
Hypertension	458 (80.2)	434 (81.3)	0.654
Previous stroke	141 (24.7)	131 (24.5)	0.950
Previous TIA	52 (9.1)	51 (9.6)	0.800
Peripheral vascular disease	39 (6.8)	53 (9.9)	0.063
Chronic renal	68 (11.9)	60 (11.2)	0.727
History of smoking	166 (29.1)	107 (20.0)	0.001*
Medication history: no. (%)			
Antihypertensive	402 (70.4)	388 (72.7)	0.406
Cholesterol reducer	280 (49.0)	262 (49.1)	0.993
Diabetes medication	173 (30.3)	168 (31.5)	0.676
Initial NIH Stroke Scale			
Group: no. (%)			
0–9	351 (65.2)	307 (60.1)	0.163
10–14	64 (11.9)	64 (12.5)	
15–20	68 (12.6)	69 (13.5)	
21–25	33 ((6.1)	33 (6.5)	
26–42	22 (4.1)	38 (7.4)	
Mean ± SD	8.75 ± 7.8	10.00 ± 8.4	0.013*
Risk of mortality GWTG			
Ischemic stroke			
Mean ± SD	4.8 ± 6.26	6.1 ± 8.84	0.032*
Body mass index			
Mean ± SD	30.8 ± 4.95	32.7 ± 7.20	< 0.001*
Lab values: mean ± SD			
Serum cholesterol (mg/dL)	168.2 ± 48.2	177.6 ± 50.6	0.003*
Blood glucose (mg/dL)	153.8 ± 86.9	156.3 ± 96.4	0.649
Serum creatine (mg/dL)	1.38 ± 1.03	1.21 ± 1.16	0.009*
Systolic blood pressure (mmHg)	153 ± 29	151 ± 29	0.368
Diastolic blood pressure (mmHg)	85 ± 19	82 ± 20	0.011*

Gender differences was determined using Pearson chi-square tests and the Student t test were used. *Significance level was set to $P = 0.05$.(0.05)

Results

Fifty-one percent ($n = 571$) of the obese stroke population ($n = 1105$) were male while 48 % ($n = 534$) were female. The baseline demographic and clinical characteristics of male and obese female stroke patients are presented in Table 1. As shown in Table 1, excluded females were older (66.52 ± 15.9 years vs 64.28 ± 13.2 years, $P = 0.001$) than males and presented with a higher body mass index (BMI: 32.7 ± 7.20 vs 30.8 ± 4.95, $P < 0.001$). Pre-rtPA treatment clinical risk factors including atrial fib/flutter, carotid artery stenosis, diabetes, dyslipidemia, family history of obesity,

Table 2 Demographic and clinical factors of obese stroke patient population characterized by rtPA status and gender

	Patients receiving tPA			Patients excluded from tPA		
	Male	Female	*p* value	Male	Female	*p* value
Number of patients	287	269		284	265	
Age group: no. (%)						
<50 years	43 (15.0)	48 (17.8)	< 0.001*	27 (9.5)	39 (14.7)	0.001*
50–59	85 (29.6)	50 (18.6)		60 (21.1)	42 (15.8)	
60–69	69 (24.0)	52 (19.3)		83 (29.2)	48 (18.1)	
70–79	64 (22.3)	60 (22.3)		65 (22.9)	66 (24.9)	
> 80 years	26 (9.1)	59 (21.9)		49 (17.3)	70 (26.4)	
Mean ± SD	62.4 ± 12.91	65.3 ± 16.03	0.021*	66.2 ± 13.30	67.8 ± 15.72	0.199
Race: no. (%)						
White	223 (77.7)	209 (77.7)	0.656	107 (81.1)	91 (78.4)	0.060
African American	62 (21.6)	56 (20.8)		24 (18.2)	18 (15.5)	
Other	2 (0.7)	4 (1.5)		1 (0.8)	7 (6.0)	
Medical history: no. (%)						
Atrial fib/flutter	28 (9.8)	43 (16.0)	0.028*	55 (19.4)	52 (19.6)	0.940
Coronary artery disease	104 (36.2)	47 (17.5)	< 0.001*	93 (32.7)	79 (29.8)	0.459
Carotid artery stenosis	13 (4.5)	7 (2.6)	0.223	19 (6.7)	16 (6.0)	0.755
Depression	44 (15.3)	73 (27.1)	0.001*	54 (19.0)	75 (28.3)	0.010*
Diabetes	109 (38.0)	92 (34.2)	0.354	110 (38.7)	122 (46.0)	0.083
Drug abuse	30 (10.5)	5 (1.9)	< 0.001*	35 (12.3)	8 (3.0)	< 0.001*
Dyslipidemia	159 (55.4)	150 (55.8)	0.932	157 (55.3)	148 (55.8)	0.894
Family history	34 (11.8)	34 (12.6)	0.776	32 (11.3)	32 (12.1)	0.768
Heart failure	29 (10.1)	30 (11.2)	0.688	36 (12.7)	42 (15.8)	0.287
Hypertension	233 (81.2)	220 (81.8)	0.856	225 (79.2)	214 (80.8)	0.655
Previous stroke	67 (23.3)	51 (19.0)	0.206	74 (26.1)	80 (30.2)	0.281
Previous TIA	27 (9.4)	26 (9.7)	0.918	25 (8.8)	25 (9.4)	0.797
Peripheral vascular disease	11 (3.8)	16 (5.9)	0.246	28 (9.9)	37 (14.0)	0.137
Chron renal	25 (8.7)	22 (8.2)	0.822	43 (15.1)	38 (14.3)	0.791
History of smoking	92 (32.1)	56 (20.8)	0.003*	74 (26.1)	51 (19.2)	0.057
Medication history: no. (%)						
Antihypertensive	205 (71.4)	199 (74.0)	0.500	197 (69.4)	189 (71.3)	0.616
Cholesterol reducer	146 (50.9)	120 (44.6)	0.140	134 (47.2)	142 (53.6)	0.134
Diabetes medication	86 (30.0)	72 (26.8)	0.403	87 (30.6)	96 (36.2)	0.165
Initial NIH Stroke Scale						
Group: no. (%)						
0–9	181 (63.1)	150 (55.8)	0.221	76 (65.5)	67 (64.4)	0.879
10–14	36 (12.5)	38 (14.1)		14 (12.1)	10 (9.6)	
15–20	39 (13.6)	42 (15.6)		15 (12.9)	13 (12.5)	
21–25	20 (7.0)	18 (6.7)		4 (3.4)	6 (5.8)	
26–42	11 (3.8)	21 (7.8)		7 (6.0)	8 (7.7)	
Mean ± SD	9.30 ± 7.7	10.81 ± 8.33	0.026*	8.12 ± 8.0	9.09 ± 8.4	0.190
Risk of mortality GWTG						
Ischemic stroke						
Mean ± SD	5.1 ± 5.84	7.1 ± 9.68	0.020*	4.6 ± 6.67	5.1 ± 7.83	0.518
Body mass index						
Mean ± SD	31.0 ± 5.35	32.9 ± 6.26	<0.001*	30.6 ± 4.52	32.5 ± 8.05	0.001*
Lab values						
Mean ± SD						
Serum cholesterol (mg/dL)	166.9 ± 44.4	178.2 ± 52.1	0.007*	169.7 ± 52.4	176.9 ± 48.9	0.139
Blood glucose (mg/dL)	150.3 ± 80.9	149.4 ± 91.7	0.902	157.3 ± 92.7	163.3 ± 100.7	0.470
Serum creatine (mg/dL)	1.33 ± 1.06	1.09 ± 0.98	0.005*	1.43 ± 1.01	1.32 ± 1.31	0.281
Systolic blood pressure (mmHg)	154 ± 27	152 ± 27	0.455	152 ± 30	150 ± 31	0.588
Diastolic blood pressure (mmHg)	85 ± 17	83 ± 19	0.161	84 ± 22	80 ± 22	0.032*

*Significance level was set to $P < 0.05$

Table 3 The regression model to predict specific clinical factors associated with exclusion or inclusion for rtPA in the obese stroke population without sorting by gender

	B	S.E.	Wald	Sig.	OR	95% C.I. for OR	
Increasing age	0.014	0.008	2.981	0.084	1.014	0.998	1.030
Gender	0.118	0.192	0.377	0.539	1.125	0.772	1.641
Atrial fibrillation	0.456	0.253	3.250	0.071	1.578	0.961	2.592
Coronary artery disease	0.195	0.206	0.890	0.346	1.215	0.811	1.820
Carotid stenosis	0.272	0.413	0.431	0.511	1.312	0.583	2.950
Depression	−0.444	0.252	3.108	0.078	0.642	0.392	1.051
Diabetes	0.237	0.307	0.597	0.440	1.267	0.695	2.312
Drug abuse	0.414	0.350	1.401	0.236	1.513	0.762	3.005
Dyslipidemia	−0.028	0.231	0.015	0.903	0.972	0.618	1.529
Family history of stroke	0.004	0.273	0.000	0.990	1.004	0.587	1.715
Heart failure	0.417	0.264	2.500	0.114	1.518	0.905	2.547
Hypertension	0.063	0.297	0.045	0.831	1.065	0.595	1.906
Previous stroke	0.256	0.210	1.493	0.222	1.292	0.857	1.950
Previous TIA	−0.225	0.315	0.509	0.475	0.798	0.430	1.482
Peripheral vascular disease	0.567	0.355	2.554	0.110	1.763	0.879	3.535
Chronic renal disease	0.493	0.327	2.266	0.132	1.637	0.862	3.110
Smoking history	0.071	0.223	0.101	0.751	1.073	0.694	1.660
NIH Stroke Score, admission	−0.022	0.012	3.560	0.059	0.978	0.956	1.001
Antihypertensive treatment	−0.583	0.269	4.694	0.030*	0.558	0.330	0.946
Cholesterol reducer treatment	0.058	0.244	0.056	0.813	1.060	0.656	1.710
Diabetes treatment	−0.001	0.320	0.000	0.997	0.999	0.533	1.871
Total serum cholesterol	0.000	0.002	0.022	0.881	1.000	0.996	1.003
Blood glucose levels	−0.001	0.001	0.218	0.641	0.999	0.997	1.002
Serum creatinine	−0.106	0.136	0.612	0.434	0.899	0.689	1.174
Systolic blood pressure	−0.001	0.004	0.060	0.806	0.999	0.991	1.007
Diastolic blood pressure	0.003	0.006	0.240	0.624	1.003	0.992	1.014
BMI	0.028	0.014	3.909	0.048*	1.028	1.000	1.057
Race	0.101	0.200	0.254	0.614	1.106	0.748	1.635

Variables associated with rtPA exclusion have positive *B* values (adjusted OR > 1), and variables associated with rtPA inclusion have negative *B* values (adjusted OR < 1)

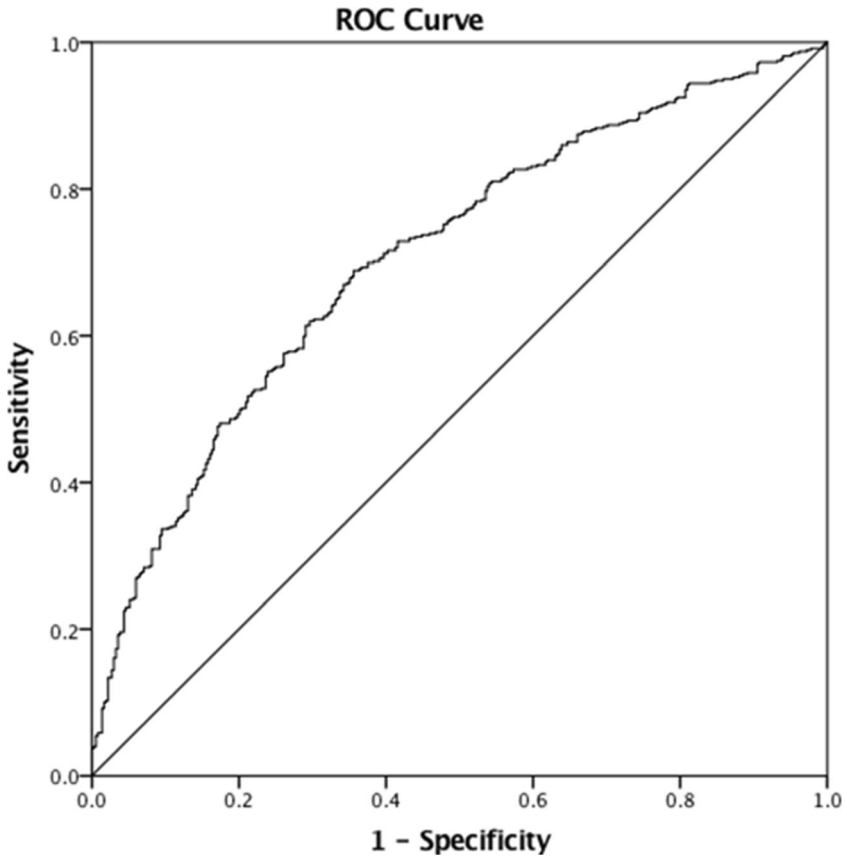

Fig. 1 The area under the ROC curve quantifies the overall ability of the model to discriminate between clinical risk factors with inclusion and those with exclusion from thrombolysis therapy in the whole obese stroke population. The discriminating ability of the model was good with area under the curve (AUROC = 0.648,95% CI, 0.600–0.697, $P < 0.001$). The model shows a strong predictive capability of 64.8% to discriminate variables associated with exclusion or inclusion for rtPA in the obese stroke population

Table 4 The regression model to predict specific clinical factors associated with exclusion or inclusion for rtPA in the obese male stroke patients subgroup

	B	S.E.	Wald	Sig.	OR	95% C.I. for OR	
Age	0.029	0.012	5.759	0.016*	1.029	1.005	1.054
Atrial fibrillation	0.377	0.374	1.016	0.313	1.458	0.700	3.037
Coronary artery disease	− 0.163	0.282	0.335	0.563	0.849	0.489	1.476
Carotid stenosis	0.335	0.564	0.353	0.553	1.398	0.463	4.224
Depression	− 0.328	0.408	0.646	0.422	0.721	0.324	1.602
Diabetes	0.111	0.449	0.061	0.804	1.118	0.463	2.697
Drug abuse	0.497	0.394	1.592	0.207	1.644	0.760	3.558
Dyslipidemia	0.205	0.343	0.360	0.549	1.228	0.628	2.403
Family history of stroke	0.100	0.369	0.074	0.786	1.105	0.537	2.276
Heart failure	0.378	0.393	0.924	0.337	1.459	0.675	3.155
Hypertension	0.014	0.428	0.001	0.974	1.014	0.438	2.346
Previous stroke	0.046	0.307	0.022	0.882	1.047	0.574	1.909
Previous TIA	− 0.254	0.483	0.276	0.600	0.776	0.301	2.000
Peripheral vascular disease	1.101	0.568	3.762	0.052*	3.008	0.989	9.153
Chronic renal disease	0.478	0.475	1.011	0.315	1.613	0.635	4.092
Smoking history	− 0.170	0.302	0.318	0.573	0.844	0.467	1.524
NIH Stroke Score, admission	− 0.016	0.016	1.004	0.316	0.984	0.953	1.016
Antihypertensive treatment	− 0.161	0.380	0.180	0.672	0.851	0.405	1.791
Cholesterol reducer treatment	− 0.369	0.355	1.083	0.298	0.691	0.345	1.386
Diabetes treatment	− 0.247	0.481	0.263	0.608	0.782	0.304	2.006
Total serum cholesterol	0.001	0.003	0.262	0.609	1.001	0.996	1.007
Blood glucose levels	− 0.002	0.002	0.965	0.326	0.998	0.994	1.002
Serum creatinine	− 0.118	0.201	0.348	0.555	0.888	0.599	1.316
Systolic blood pressure	− 0.004	0.006	0.622	0.430	0.996	0.985	1.007
Diastolic blood pressure	0.018	0.008	4.299	0.038*	1.018	1.001	1.035
BMI	0.032	0.025	1.592	0.207	1.032	0.983	1.084
Race	0.095	0.291	0.105	0.746	1.099	0.621	1.945

Variables associated with rtPA exclusion will have positive *B* values (adjusted OR > 1), and variables associated with rtPA inclusion have negative *B* values (adjusted OR < 1)

heart failure, hypertension, previous stroke, previous TIA, peripheral vascular disease, and chronic renal problem were not significantly different between male and obese female stroke patients. Table 1 further reveals that patients taking cholesterol reducer, antihypertensive and diabetic medications were not significantly different between obese male and female stroke patients. The laboratory results indicate that cholesterol level was significantly higher in females (177.6 ± 50.6 mg/dl vs 168.2 ± 48.2 mg/dl, $P = 0.003$), while serum creatinine (1.38 ± 1.03 mg/dl vs 1.21 ± 1.16 mg/dl, $P = 0.009$) and diastolic blood pressure (85 ± 19 mmHg vs 82 ± 20 mmHg, $P = 0.011$) were significantly higher in males. Between females and males, blood glucose (156.3 ± 96.4, g/dl vs 153.8 ± 86.9, $P = 0.649$), and systolic blood pressure (151 ± 29 mmHg vs 153 ± 29 mmHg, $P = 0.368$) were not significantly different. In summary, a significant and higher number of obese stroke females presented with coronary artery disease, depression, a more severe stroke based on NIHSS baseline, whereas more obese stroke males presented with history of drug abuse and smoking.

The characterization of obese stroke patients by rtPA status and gender is shown in Table 2. A total of 284 male and 265 female obese stroke patients were excluded from rtPA. Obese female and male patients acute ischemic stroke patients excluded from rtPA were not significantly different in age (67.8 ± 15.72 vs 66.2 ± 13.30, $P = 0.199$). Females were more likely to present with a history of depression (28.3% vs 19.0%, $P = 0.010$) and a higher BMI (32.5 ± 8.05 vs 30.6 ± 4.52, $P = 0.001$), while males were more likely to have a history of drug abuse (12.3% vs 3.0%, $P < 0.001$) and elevated diastolic blood pressure (84 ± 22 vs. 80 ± 22, $p = 0.032$). Obese female stroke patients included for rtPA were more likely to be depressed (27.1% vs 15.3%, $P = 0.001$), have higher NIH scores (10.81 ± 8.33 vs 9.30 ± 7.7, $P = 0.026$), have a higher risk of mortality (7.1 ± 9.68 vs 5.1 ± 5.84 $P = 0.020$), higher BMI (32.9 ± 6.26 vs 31.0 ± 5.35, $P < 0.001$), and atrial fibrillation (16.0% vs 9.8%, $P = 0.028$) while male patients were more likely to present with coronary artery disease (36.2% vs 17.5%, $P = 0.001$), a history of smoking (32.1% vs 20.8%, $P = 0.003$) and drug abuse (10.5% vs 1.9%, $P < 0.001$). For the laboratory

analysis, female patients were more likely to have elevated serum cholesterol (178.2 ± 52.1 mg/dl vs 166.9 ± 44.4 mg/dl, $P = 0.007$), while male patients were more likely to have elevated serum creatine (1.33 ± 1.06 mg/dL vs 1.09 ± 0.98 mg/dl, $P = 0.005$).

The results of the stepwise conditional logistic regression model for the exclusion or inclusion for rtPA in the obese stroke population without sorting by gender are presented in Table 3. Following adjustment, many of the established significant associations with gender in the univariate analysis were attenuated and became non-significant except for BMI (OR = 1.028, 95% CI, 1.000–1.057, $P = 0.048$), which was associated with exclusion, while antihypertensive medication (OR = 0.558, 95% CI, 0.330–0.946, $P = 0.03$), was significantly associated with inclusion for rtPA. The receiver operating characteristics (ROC) curve for the whole obese stroke population model is presented in Fig. 1. The discriminating capability of the model was good as shown by the ROC curve, with area under the curve (AUROC = 0.648, 95% CI; 0.600–0.697, $P < 0.001$). The ROC curve (Fig. 1) and the corresponding AUC reveal a 64.8% predictive capability of our model to discriminate clinical variables associated with an exclusion or inclusion from rtPA.

Further logistic regression was performed to focus primarily on the obese stroke patient subgroup separately to identify clinical and demographic risk factors that excluded obese male stroke patients from thrombolysis therapy (Table 4). As shown in Table 4, after adjustment, obese male stroke patients who were older (> 80) (OR = 1.029, 95% CI, 1.005–1.054, $P = 0.016$), presented with peripheral vascular disease (OR = 3.008, 95% CI, 0.989–9.153, $P = 0.052$), and had a higher diastolic blood pressure (OR = 1.018, 95% CI, 1.001–1.035, $P = 0.038$), were more likely to be excluded from rtPA. Figure 2 presents the area under the curve (AUROC = 0.675;95% CI, 0.600–0.697, $p < 0.001$), indicating that the discriminating ability of the regression model was good with a 67.5% predictive ability to discriminate clinical risk factors associated with exclusion and inclusion in obese male stroke patients.

Obese female stroke patients (Table 5) were more likely to be excluded if they presented with coronary artery disease (OR = 2.478, 95% CI, 1.270–4.411, $P = 0.008$), and were more likely to receive rtPA if they were taking antihypertensive medications (OR = 0.326, 95% CI, 0.139–0.764, $P = 0.010$). The disseminative ability of our model was very good with a 72.9% predictive ability to discriminate clinical risk factors associated with exclusion and inclusion in obese female stroke patients. The area under the curve (AUROC = 0.729;(95% CI, 0.665–0.6793, $P < 0.001$) is presented in Fig. 3.

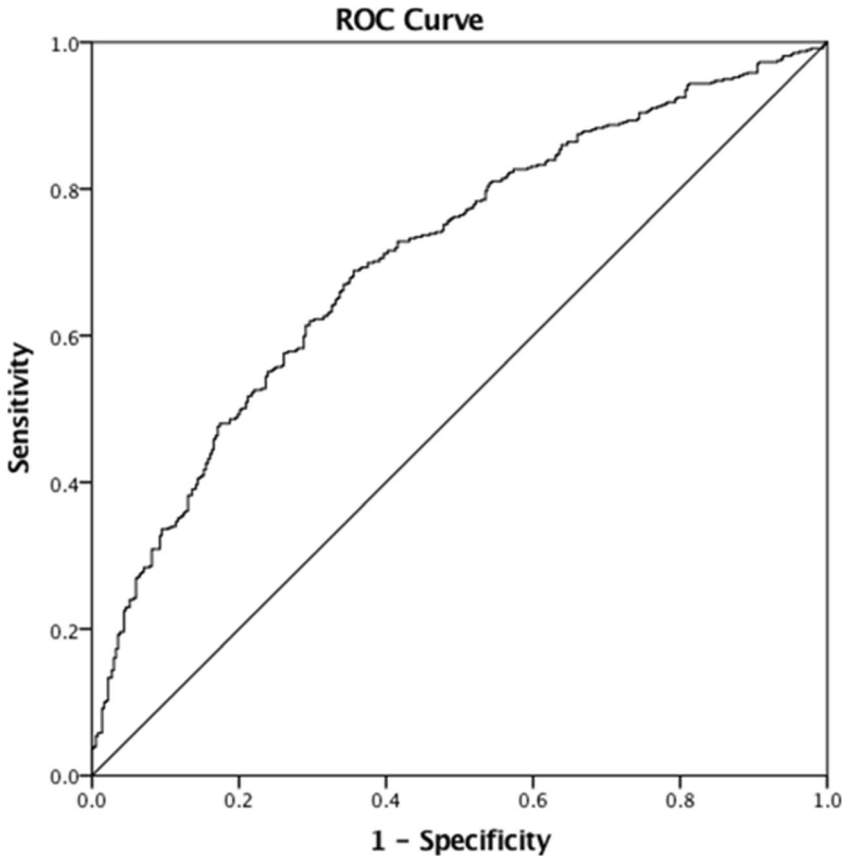

Fig. 2 The area under the ROC curve quantifies the overall ability of the model to discriminate between clinical risk factors with inclusion and those with exclusion from thrombolysis therapy in obese male stroke population. The discriminating ability of the regression model was good (67.5%). Area under the curve (AUROC = 0.675;95% CI, 0.600–0.697)

Discussion

In this study, we found that among obese female stroke patients, coronary artery disease was associated with exclusion from receiving rtPA while being on antihypertensive medication was associated with inclusion for rtPA. After adjusting for age and comorbidities in the whole obese stroke population without sorting by gender, we found that BMI was significantly associated with exclusion from rtPA, while being on antihypertensive medication was significantly associated with inclusion for rtPA treatment. These results changed after we focused the analysis to either the male or female obese stroke population.

In the obese male stroke patients, increasing age, elevated diastolic blood pressure, and the presence of peripheral vascular disease were each associated with exclusion from rtPA; these associations were not shown in the female-only or overall obese stroke populations. In the obese female stroke patients, the association of antihypertensive treatment with inclusion for rtPA that was observed in the obese stroke population did not disappear, but the effect of BMI was attenuated. Moreover, coronary artery disease was the only clinical risk factor that was associated with exclusion from thrombolysis therapy in the female obese stroke patients after the adjusted analysis.

We found that age was significantly different between obese males and females in the group of patients who received rtPA, with women being older on average, but was not significantly different in the no rtPA group in the univariate analysis. In our adjusted analysis, obese male stroke patients increasing were significantly associated with exclusion from rtPA therapy in the obese male-only stroke patient population, but not in the female-only or overall obese stroke patient populations. In stroke studies, a pattern towards a higher rate of exclusion for women has been reported [32–34], while other studies reported similarities in the rates for the administration of rtPA for both men and women stroke patients [35, 36]. Gender differences in pre-treatment risk factors are known to cause treatment delays [37, 38]. Therefore, it is also possible that such delays in obese elderly male stroke patients, especially in the

Table 5 The regression model to predict specific clinical factors associated with exclusion or inclusion for rtPA in obese female acute ischemic stroke patients

	B	S.E.	Wald	Sig.	OR	95% C.I. for OR	
Age	0.005	0.013	0.149	0.700	1.005	0.980	1.030
Atrial fibrillation	0.723	0.388	3.472	0.062	2.061	0.963	4.411
Coronary artery disease	0.908	0.341	7.079	0.008*	2.478	1.270	4.836
Carotid stenosis	0.053	0.719	0.005	0.941	1.055	0.258	4.319
Depression	− 0.606	0.362	2.807	0.094	0.546	0.268	1.108
Diabetes	0.407	0.477	0.727	0.394	1.502	0.590	3.825
Drug abuse	− 0.481	1.243	0.150	0.699	0.618	0.054	7.071
Dyslipidemia	− 0.335	0.358	0.874	0.350	0.715	0.355	1.443
Family history of stroke	− 0.179	0.445	0.162	0.687	0.836	0.350	1.999
Heart failure	0.247	0.405	0.372	0.542	1.280	0.579	2.831
Hypertension	0.165	0.449	0.135	0.713	1.180	0.489	2.844
Previous stroke	0.533	0.317	2.815	0.093	1.703	0.914	3.173
Previous TIA	− 0.392	0.486	0.649	0.421	0.676	0.261	1.753
Peripheral vascular disease	− 0.078	0.541	0.021	0.885	0.925	0.320	2.668
Chronic renal disease	0.589	0.513	1.315	0.251	1.802	0.659	4.927
Smoking history	0.573	0.374	2.352	0.125	1.774	0.853	3.692
NIH Stroke Score, admission	− 0.018	0.018	0.934	0.334	0.982	0.948	1.018
Antihypertensive treatment	− 1.120	0.434	6.653	0.010*	0.326	0.139	0.764
Cholesterol reducer treatment	0.619	0.367	2.843	0.092	1.857	0.904	3.813
Diabetes treatment	0.476	0.482	0.978	0.323	1.610	0.626	4.141
Total serum cholesterol	− 0.001	0.003	0.127	0.721	0.999	0.993	1.005
Blood glucose levels	0.000	0.001	0.003	0.957	1.000	0.997	1.003
Serum creatinine	−0.017	0.208	0.007	0.936	0.983	0.654	1.478
Systolic blood pressure	0.001	0.006	0.050	0.822	1.001	0.989	1.014
Diastolic blood pressure	− 0.014	0.009	2.517	0.113	0.986	0.969	1.003
BMI	0.030	0.019	2.457	0.117	1.030	0.993	1.069
Race	− 0.070	0.304	0.053	0.818	0.932	0.513	1.693

Variables associated with rtPA exclusion will have positive *B* values (adjusted OR > 1), and variables associated with rtPA inclusion have negative *B* values (adjusted OR < 1)

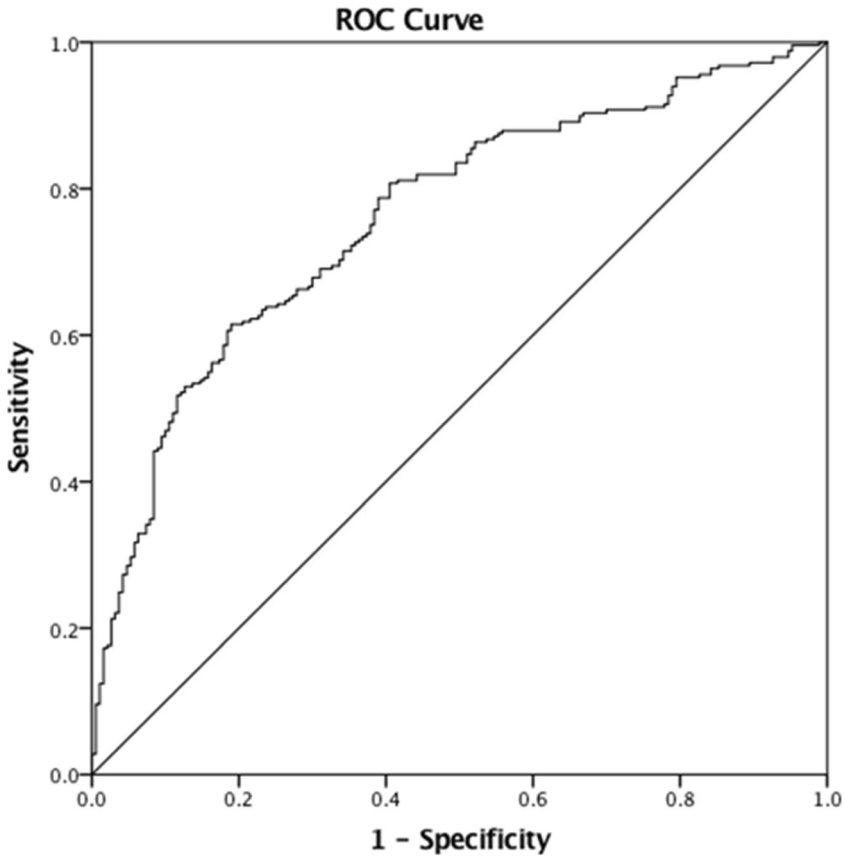

Fig. 3 The area under the ROC curve quantifies the overall ability of the model to discriminate between clinical risk factors with inclusion and those with exclusion from thrombolysis therapy in the obese female stroke population model. The discriminating ability of the regression model was very good (72.9%) with area under the curve (AUROC = 0.729;95% CI, 0.665–0.6793, $P < 0.001$)

pretreatment management of comorbidities such as diastolic blood pressure and peripheral vascular disease, could account for the higher exclusion rate of obese male stroke patients in the current study.

In general, obesity is evaluated on the basis of BMI values; it is an independent risk factor for stroke [16], a prominent predictor of stroke in women and a sole predictor of stroke in men [17]. In our adjusted analysis, the effect of BMI disappeared while the effect of older age significantly excluded more obese male stroke patients than females from thrombolysis therapy. While obesity itself is not an exclusion factor for thrombolysis therapy, our results reveal that a demographic factor such as age and specific baseline clinical risk factors including diastolic blood pressure and peripheral vascular disease in obese stroke patients, rather than obesity alone could exclude more obese male stroke patients than females from thrombolysis therapy. These findings suggest that the synergy between age as a demographic variable and clinical risk factors in obese stroke patients may act to exclude more men than women from thrombolysis therapy. Our findings suggest age-associated differences in pretreatment comorbidities between obese male and female stroke patients.

The established gender difference in this study is comparable with other studies that investigated gender differences in stroke [4, 10, 24, 39–41]. We found that more obese male than female stroke patients were excluded from thrombolysis therapy. In obese stroke patients, we did not find a significant gender difference in race or medical history of dyslipidemia, heart failure, hypertension, previous stroke, previous TIA, and chronic renal problem. Other studies reported that men stroke patients are more likely to present with a history of heart disease [41], prevalence of smoking [42], and incidence of dyslipidemia [43], while women are more likely to present with atrial fibrillation [44]. In our study, increasing age, an elevated diastolic blood pressure and a history of peripheral vascular disease were associated with exclusion from rtPA therapy in obese males, while a history of coronary artery disease was associated with exclusion from rtPA in obese females.

Several limitations should be considered in interpreting the findings of this study. This is a retrospective data analysis with a tendency of bias in selection. Moreover, there is a potential of incorrect categorization of obesity which could inaccurately affect the relationship between obesity and stroke in our data analysis. Additionally, our study is from one institution which may inhibit the generalization of the results because of the possibility of a selection bias. Data for anthropometric measures including body fat distribution and abdominal obesity should have been included in a study that evaluates obesity and stroke but was not available in our dataset. However, in this study, we determined whether clinical risk factors that excluded men and women from thrombolysis therapy differ

in a stroke population with obesity. Our findings indicate that adjusted odds ratios established gender differences in demographic and pretreatment risk factors that excluded more men than women from thrombolysis therapy in a stroke population with obesity.

Conclusion

The current study reveals that more clinical risk factors excluded more obese male stroke patients than females. Increasing age, history of peripheral vascular disease, and elevated diastolic blood pressure were significantly associated with exclusion from thrombolysis in obese males, while coronary artery disease was associated with exclusion from thrombolysis in obese females. More research is necessary to develop measures for identified clinical risk factors associated with exclusion from rtPA in order to improve the use of thrombolysis therapy for obese stroke patients irrespective of gender.

Compliance with ethical standard

Approval for this study was obtained from the ethics committee of the Greenville Health system in 2017. Since this is a retrospective data analysis, all data were de-identified, and the study did not involve patients and no consent was required.

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