Cholesterol reducer and Thrombolytic therapy in acute ischemic stroke

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Research

Abstract

Background

Specific clinical risk factors may contribute to worsening or improving neurological functions in an acute ischemic stroke (AIS) patient pre-treated with a cholesterol reducer with a subsequent recombinant tissue plasminogen activator (rtPA) treatment. We investigated clinical risk factors associated with good or poor presenting neurological symptoms in ischemic stroke patients with prior cholesterol reducer use, specifically a statin and rtPA therapy.

Methods

We retrospectively analyzed baseline clinical and demographic data of 630 patients with AIS taking cholesterol reducers prior to rtPA treatment from January 2010 to June 2016 in a regional stroke center. Progressing (NIHSS ≤ 7) or worsening (NIHSS > 7) scores for neurologic improvement determined measures for treatment outcome. Multivariate logistic regression models identified demographic and clinical factors associated with worsening or progressing neurologic functions.

Results

Adjusted multivariate analysis showed that in an ischemic stroke population with a combined rtPA and cholesterol reducer medication history, increasing age (OR = 1.032, 95% CI, 1.015-1.048, P < 0.001) and atrial fibrillation (OR = 1.859, 95% CI, 1.098-3.149, P = 0.021) demonstrated a likely association with worsening neurologic functions, while direct admission (OR = 0.411, 95% CI, 0.246-0.686, P = 0.001) and being Caucasian (OR = 0.496, 95% CI, 0.297-0.827, P = 0.007) showed an association with improving or progressing neurologic functions.

Conclusion

A prior cholesterol reducer, namely a statin, plus rtPA combination may be associated with worsening neurological function for elderly AIS patients with atrial fibrillation, while Caucasians directly admitted to a neurology unit are more likely to show an association with progress or improvements in neurologic functions.

Introduction

The function of cholesterol reducer, such as statins in primary and secondary prevention of stroke in patients at risk of cerebrovascular events is well established[1–3]. Findings reveal that statins reduce the risk of first and recurrent ischemic stroke[4, 5], and statin treatment may also improve treatment outcome through pleiotropic non-statin-associated effects[6]. In general, several studies[7–10] report the relationship between statin use and stroke, including related favorable outcome. Some studies[11, 12] also report contradictory evidence that cholesterol reducers, including statins, do not reduce initial stroke severity in rtPA treated ischemic patients. In general, several studies[13–15] report favorable outcome

associated with statin use and stroke while some studies[11, 12, 16] also report contradictory evidence that cholesterol reducers, including statins, do not reduce initial stroke severity in rtPA treated ischemic patients. While most of the findings have been linked to the effects of clinical risk factors, however, the effect of specific clinical risk factors that may contribute to the favorable or unfavorable outcome is not clear.

Patients with a National Institute of Health Stroke Scale (NIHSS) score of equal to or less than 7 at the time of admission demonstrate a higher likelihood of making progress after an AIS, while scores greater than 7 on admission demonstrated a higher probability of worsening neurological function in hemispheric stroke[17, 18]. Therefore, the baseline NIHSS, stratified by NIHSS scores of ≥ 7 for worsening neurologic functions and ≤ 7 for neurologic improvement can be used to assess improvement or non-improvement following thrombolytic therapy [19, 20]. In another study [21], NIHSS scores turned out to be predictive for any vessel occlusions in the anterior circulation, and cut-off values of NIHSS scores ≥ 7 of 3 to 6 hours of stroke onset provided a predictive value of 84.4%[21]. In another study [20], major neurological improvements were observed below NIHSS of 8 within 24 hours of stroke onset, while a score of < or = 6 forecasts a good recovery [22]. While low and high NIHSS cut-off points are effective predictors for good and poor outcomes, the NIHSS is heavily weighted towards hemispheric stroke[23]. Therefore, the current study is focused on clinical risk factors associated with good or poor presenting neurological symptoms in hemispheric ischemic stroke patients with prior cholesterol reducer use, specifically a statin and rtPA therapy.

Eligibility for rtPA within a population of patients with acute ischemic stroke ranges from 6–8% [12, 13], suggesting that specific clinical risk factors may contribute to stroke severity and affect treatment outcome following thrombolytic therapy with or without cholesterol reduction therapy (statin). However, clinical risk factors associated with improving or worsening neurologic functions in ischemic stroke patients with prior cholesterol reduction therapy treated with rtPA are not well understood. The proportion of ischemic stroke patients with prior cholesterol reduction therapy at the time of admission and treated with rtPA may be different from those with rtPA lacking prior cholesterol reduction therapy. This could be possible if more clinical risk factors are associated with improving or worsening neurologic functions following rtPA in patients' prior cholesterol reducer vs. patients without the cholesterol reducer. In this study, we tested the hypothesis that specific clinical risk factors may contribute to improving or worsening neurologic functions in AIS patients with previous cholesterol reducer users who were treated with rtPA, such that some patients are more likely to present with worsening neurologic functions while some may present with improvements following thrombolytic therapy. Understanding the specific clinical risk factors associated with worsening neurologic functions associated with previous cholesterol reduction therapy plus rtPA will provide information about the measurable and qualitative risks of rtPA and cholesterol reducer use in ischemic stroke patients. In turn, this could help identify future potential research areas to investigate to increase eligibility for rtPA and improve ischemic stroke treatment outcomes.

Methods

Study Population

This IRB approved, retrospective study, analyzed patients with an acute ischemic stroke, admitted to the health system of Prisma Health-Upstate in Greenville, South Carolina, USA between January 2010 and June 2016. The analysis included patients that within 24 hours of symptom onset initially presented with an acute ischemic stroke based on brain magnetic resonance image(MRI) or computer tomography (CT) findings demonstrating early signs of ischemia (loss of gray/white matter distinction, hypodensity, or sulcal swelling) or middle cerebral artery (MCA) hyper density. Cholesterol reducer use, specifically a statin in this study, includes an active use at the time of admission, while patients that were not receiving a cholesterol reducer at the time of admission were considered as non-cholesterol reducer use. The stroke registry provided the data on demographics, clinical characteristics, and laboratory values and our previous studies have described the stroke registry[24–26]. Clinical characteristics of the patients included: atrial fibrillation/atrial flutter, coronary artery disease (CAD), carotid stenosis, depression, diabetes, drug or alcohol abuse, dyslipidemia, family history of stroke, congestive heart failure (CHF), hormone replacement therapy (HRT), hypertension, migraine, obesity, prior stroke, prior trans ischemic attack(TIA), prosthetic heart valve, peripheral vascular disease (PVD), chronic renal disease, sickle cell, sleep apnea, and history of smoking. This study also analyzed patients' ambulatory data. The scores ranged from 0 to 3 in this fashion: undocumented (0), patients not able to ambulate (1), able to ambulate with assistance (2), and able to ambulate independently (3). The validity of the scoring has been described in a previous study[27]. Each patients' ambulatory status was tracked and collected on admission, during admission, and after discharge. From this, we analyzed ambulation and compared patients' ambulation status at discharge to their ambulation status on admission to discern any patient improvement in ambulation. In addition, we collected patient demographic variables, including race, gender, ethnicity, BMI, medical history, medication history, and stroke severity (NIHSS) score.

Statistical Analysis

We performed all statistical analyses using the Statistical Package for Social Sciences v 26.0 for Windows (SPSS, Chicago, IL). We examined differences between the 2 groups stratified according to cholesterol reducer use in the acute phase of stroke and by stroke severity (NIHSS scores ≤ 7 and NIHSS scores ≥ 7). We then performed univariate statistical analysis of the factors associated with neurologic improvement or worsening stratified by rtPA with or without prior cholesterol reducer use. In the univariate analysis, the Pearson $\chi 2$ test analyzed discrete variables while the Student's t test analyzed data for all continuous variables. To identify independent predictors of neurologic improvement or worsening, we performed multivariate analysis including the analysis of the established predictors (demographic and clinical variables) with a probability value < 0.2 in the univariate analysis[28]. Because of the nonrandomized design of our study, we performed a post hoc adjusted analysis (logistic regression) of demographic and clinical risk factors associated with neurologic improvement or worsening as major outcomes using the backward selection method. This approach allowed all the variables which were

approaching significance to be selected. This selection then removes a variable if it does not add to the significance of the model overall. Odds ratios (ORs) predicted the odds of having a higher NIHSS score in association with thrombolysis treatment in cholesterol reduction therapy status.

In the regression model, the dependent variable, the NIHSS score stratification, assessed the degree of stroke severity. The primary independent variables in the regression model for the entire AIS population included all the demographic and clinical risk factors for the rtPA with prior cholesterol reducer use group and rtPA without prior cholesterol reducer use group. The odds of developing worsening neurological function (NIHSS $\leq$ 7) and for making progress or improvements(NIHSS $\geq$ 7) were analyzed separately for the group who received rtPA (independent of cholesterol reducer use status), rtPA without cholesterol reducer use, and rtPA with cholesterol reducer use. We checked for multicollinearity and interactions among independent variables using the Hosmer-Lemeshow test. Overall correct classification percentage and area under the Receiver Operating Curve (ROC) determine the sensitivity, specificity, and accuracy of the logistic regression model. Logistic regression determined odd ratios and 95% confidence intervals (95% CIs) of outcome measures were considered. These odds ratios predicted which independent variables positively influenced a patient with an AIS who made progress or improvement or those with worsened neurological functions.

Results

A total of 5,469 acute ischemic stroke (AIS) patients were identified. In this population, 1,608 patients were eligible for rtPA and 1,327 of these received rtPA (Table 1). Of the patients treated with rtPA, 630 were taking a cholesterol reducer prior to the event, whereas 687 were not. As presented in Table 1, the rtPA treated subset of patients was younger (65.8 ± 14.8 vs 67.7 ± 14.7), more likely to be Hispanic (2.3% vs. 1.3%) and have a higher BMI (28.18 ± 7.01 vs. 28.84 ± 6.84). This group presented with lower rates of carotid stenosis (4.2% vs 6.7%) and diabetes (31.3% vs 36.7%) but had higher rates of depression (15.4% vs 12.5%) and dyslipidemia (52.8% vs 49.6%). Further, the rtPA group was more likely to be on HRT (2.3% vs. 1.2%), suffer from migraines (3.4% vs. 2.1%), and be obese (51.1% vs. 39.4). They presented with fewer prior strokes (21.9% vs. 27.4%), but a greater history of TIAs (10.8% vs. 8.1%). They were less likely to have PVD (6.0% vs. 7.7%) and chronic renal disease (6.0% vs. 8.9%) but were more likely to be taking cholesterol reducing agents (47.6% vs. 43.4%) and antidepressants (16.7% vs. 11.8%). The rtPA group was taking fewer antidiabetic medications (24.9% vs. 28.1%) and presented with higher NIHSS scores (9.95 ± 6.6 vs 7.82 ± 6.8), lower levels of serum cholesterol (168.7 ± 46.5 mg/dL vs 173.0 ± 53.6 mg/dL), creatinine concentrations (1.14 ± 0.75 mg/dL vs 1.34 ± 1.27 mg/dL), and blood glucose (141.3 ± 74.8 mg/dL vs 149.2 ± 82.9 mg/dL) when compared to the no rtPA group. Moreover, the rtPA group differed significantly on ambulation classification prior to stroke, on admission, and on discharge. Patients in the rtPA group were more likely to be directly admitted to the hospital (23.4% vs. 19.9%) and have an improved ambulatory status (55.3% s. 29.7%).

Table 2 shows the clinical and demographic characteristics associated with improving or worsening neurologic functions for patients who received rtPA and previously used cholesterol reducers versus those

who didn't have a history of cholesterol reducer usage. In the rtPA with prior cholesterol reducer use group, patients with worsening neurologic functions were older (70.83 ± 13.26 vs. 65.95 ± 12.09), less likely to be Caucasian (86.3% vs. 79.0%), and more likely to be female (51.5% vs. 40.5%), with higher rates of atrial fibrillation (23.9% vs. 11.5%), and heart failure (15.2% vs. 9.7%). This group presented with lower rates of a family history of stroke (7.1% vs. 14.0%) and obesity (47.2% vs. 58.3%). For lab values, the group with worsening neurologic functions who received rtPA presented with higher blood glucose levels (147.04 ± 73.66 vs. 136.22 ± 63.35), higher INR (1.07 ± 0.12 vs. 1.04 ± 0.12) and were more likely to be directly admitted to the hospital (84.5% vs. 67.3%). For the rtPA without prior cholesterol reducer use group, the patients with worsening neurologic functions were older (66.31 ± 15.82 vs. 59.67 ± 15.47), presented with lower BMI (27.83 ± 6.24 vs. 29.07 ± 6.72), higher rates of heart failure (10.8% vs. 5.2%), hypertension (71.1% vs. 59.5%), and were more likely to be taking anti-HTN medications (56.7% vs. 49.0%). This group presented with lower rates of a family history of stroke (6.3% vs. 12.7%), migraines (2.1% vs. 6.2%), obesity (45.4% vs. 56.2%) and smoking history (29.1% vs. 38.2%), higher serum creatinine (1.16 ± 1.04 vs. 1.04 ± 0.4) and higher INR (1.07 ± 0.18 vs. 1.04 ± 0.15), but had lower triglycerides (128.33 ± 95.18 vs. 153.54 ± 119.4). In addition, this group presented with a higher heart rate (84.98 ± 18.94 vs. 80.71 ± 16.21) and were more likely to be directly admitted to the hospital (82.2% vs. 72.2%).

The forest plot demonstrating clinical factors that were associated with the severity of stroke for the total ischemic stroke population (Fig. 1). In the adjusted analysis, increasing age (OR = 1.03, 95% CI, 1.019–10.4, P < 0.001) and being female (OR = 1.369, 95% CI, 1.048–1.787, P = 0.021) were variables associated with worsening neurologic functions, while dyslipidemia (OR = 0.709, 95% CI, 0.541-0.927, P = 0.012), obesity (OR = 0.745, 95% CI, 0.572-0.971, P = 0.029), direct admission (OR = 0.466, 95% CI, 0.324-0.670, P < 0.001), and Caucasian race (OR = 0.589, 95% CI, 0.42-0.828, P = 0.002) were associated with improving neurologic functions. The discriminating capability of the model was moderately strong as shown by the ROC curve (Fig. 2), with area under the curve (AUROC) = 0.677 (95% CI, 0.646–0.707, P < 0.001). In the rtPA group without prior cholesterol reducer use (Fig. 3) increasing age (OR = 1.027, 95% CI, 1.014-1.041, P < 0.0.01), a higher heart rate (OR = 1.016, 95% CI, 1.005–1.027, P = 0.005), and ambulation (OR = 1.571, 95% CI, 1.078–2.289, P = 0.019) were associated with neurologic deterioration or worsening neurologic functions. Patients with a family history of stroke (OR = 0.511, 95% CI, 0.264–0.99, P = 0.047), migraines (OR = 0.250, 95% CI, 0.130–0.943, P = 0.038), obesity (OR = 0.685, 95% CI, 0.473-0.992, P = 0.045), direct admission (OR = 0.512, 95% CI, 0.303–0.866, P = 0.013), and Caucasian race (OR = 0.604, 95% CI, 0.381-0.957, P = 0.032) were more likely to be associated with a neurologic improvement. As presented in Fig. 4, the predictive power of the logistic regression was moderately strong, as the area under the curve (AUROC) was 0.681 (95% CI, 0.637–0.724, P < 0.001). For the rtPA group with prior cholesterol reducer use (Fig. 5), increasing age (OR = 1.032, 95% CI, 1.015–1.048, P < 0.001) and atrial fibrillation (OR = 1.859, 95% CI, 1.098–3.149, P = 0.021) were more likely to be associated with worsening neurologic function. Direct admission (OR = 0.411, 95% CI, 0.246–0.686, P = 0.001) and Caucasian race (OR = 0.496, 95% CI, 0.297–0.827, P = 0.007) were associated with greater neurologic improvement. The ROC curve for the predictive power of the regression model as presented in Fig. 6 shows that the discriminating capability

of the model was moderately strong, with the area under the curve (AUROC) = 0.680 (95% CI, 0.639–0.722, P < 0.001).

Discussion

While clinical trials have shown inconsistent results, with either improved outcomes[29] or no effect[30] when combining cholesterol reduction therapy with rtPA in acute stroke patients, several studies have shown the beneficial effect of cholesterol reducers, including statin pre-treatment[31]. Despite this, the question that involves specific baseline clinical risk factors that could lead to neurologic improvement or worsen neurologic function has yet to be fully investigated by observational studies[32]. To assess whether specific clinical risk factors may influence cholesterol reducer-rtPA treated ischemic stroke patients, such that some patients are more likely to present with neurologic improvement or worsening functions following thrombolytic therapy, we conducted a retrospective data analysis in which data from AIS patients with prior cholesterol reducer use who were treated with thrombolytic therapy were analyzed.

In the univariate analysis, AIS patients without prior cholesterol reduction therapy who received rtPA were more likely to present with worsening neurological functions (NIHSS greater than 7) if they were older, had a lower BMI, had a history of heart failure, hypertension, or used anti-HTN medications. This group also presented with lower rates of a family history of stroke, migraine, obesity, smoking history. These patients had higher serum creatinine, International Normalized Ratio (INR), and heart rates, but presented with lower triglyceride levels and were associated with non-improvement in ambulation. After adjusting for the effect of confounding variables, AIS patients with increasing age and higher heart rate were not likely to improve neurologically, while those with a history of stroke, migraines, obesity, direct admission, and Caucasian ethnicity were more likely to exhibit neurologic improvement following thrombolytic therapy. These findings are consistent with a single-center study involving small cohorts which shows that a history of stroke[33, 34], migraines[35], obesity[36, 37] and direct admission into the neurological unit [38] were associated with improved functional outcomes following thrombolytic therapy. In addition, our finding that AIS patients without prior cholesterol reducer use who presented with increased age[39] and higher heart rate had a likelihood of worsening neurological function following thrombolytic shows consistency with previous studies[9, 31, 40, 41].

In the rtPA with prior cholesterol reducer use cohort, AIS patients more likely to develop worsening neurological function in the univariate analysis were older, less likely to be of Caucasian ethnicity, and more likely to be female. This group had higher rates of atrial fibrillation, heart failure, and increased blood glucose levels, but had lower rates of a family history of stroke and obesity. Following the adjusted analysis, the effect of increasing age and atrial fibrillation, which were significant for diminished neurological function in the univariate analysis, were sustained and significant for a worsening neurological function in the AIS with prior cholesterol reducer use group treated with rtPA. Elderly patients have been shown to do well with statins, which can reduce mortality from all types of vascular events[42]. Moreover, studies have shown that rtPA works as effectively in the elderly as in younger patients[43]. It has also been shown that age may influence the outcome and risk of hemorrhage after rtPA therapy[44–

46]. Therefore, increasing age is associated with an increased number of comorbidities and worse outcomes regardless of rtPA-related complications[47]. While studies have not shown age alone to negate the beneficial effects of rtPA, the association between cholesterol reducers and age in rtPA-treated AIS patients' needs further evaluation to generate evidence on how the interactions between cholesterol reducers and rtPA may promote poor outcomes in elderly AIS patients taking both. Findings from such studies may explain why elderly patients in the current study with combined prior cholesterol reducer use and rtPA developed worsening neurologic deficits.

Our observed worsening neurologic function in AIS patients with prior cholesterol reducer use and rtPA is not surprising as atrial fibrillation is associated with worse initial outcomes in patients with ischemic strokes[48]. Statins are known to be effective at reducing the incidence of atrial fibrillation after coronary surgery, but the effectiveness of statins on management of atrial fibrillation is not clear[49]. Although research on animal models has shown that the development of atrial fibrillation can be due to a NO-redox imbalance in the atria[50]. However, there are two different mechanisms that have been reported to determine whether atrial fibrillation is acute or chronic[50]. Statins in this study[50] were shown to be effective providing protection from the development of acute atrial fibrillation, but once atrial fibrillation sets in, statins were not effective in the long-term management of chronic atrial fibrillation. This finding may suggest that cholesterol reducers, and more specifically statins, may be ineffective in the long-term management of atrial fibrillation.

One of the main strengths of our study is the ability to use a logistic regression model to identify baseline demographic and clinical risk factors that may determine whether AIS patients with prior cholesterol reduction therapy and rtPA therapy with baseline stroke severity are more likely to exhibit neurological improvement or develop worsening neurologic function. Our findings indicate that prior cholesterol reducer usage, namely a statin, in addition to rtPA therapy may be associated with worsening neurologic function for elderly AIS patients with atrial fibrillation, while the statin and rtPA combination in Caucasians and those directly admitted to a neurology unit are more likely to be associated with improvement in neurologic function. This study also presents some limitations. This study is a retrospective study; therefore, bias should always be considered when trying to draw conclusions. Moreover, while the stroke registry did record date for patients that take statins versus, but information about other cholesterol reducers were not included. Therefore, it is difficult to compare the effects that may be due to another type of cholesterol reducer apart from statins, or due to the potential heterogenous pool of cholesterol reduction therapy used. Finally, since our stroke registry was only obtained from one hospital, it is challenging to make conclusions about the entire population. However, in this study, we have shown specifically that prior statin use in combination with rtPA therapy in patients with acute ischemic stroke is a promising therapy that necessitates more clinical trials in the near future.

Conclusion

After controlling for demographic and clinical risk factors, older patients with atrial fibrillation who presented with an acute ischemic stroke on pre-stroke cholesterol reduction therapy namely statin, and

received rtPA were more likely to develop worsening neurologic functions, while Caucasian patients directly admitted to a neurology unit were more likely to develop improving neurologic functions.

Abbreviations

Adjusted OR-:Adjusted odd ratio; BMI: Body mass index; CHF: Congestive heart failure; CI: Confidence interval; INR: International normalized ratio; LDL-C: Low-density lipoprotein; rtPA: Recombinant tissue plasminogen; TC: Total cholesterol; TG: Total glyceride, 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: trans ischemic attack; PVD: Peripheral vascular disease; ROC: Receiver Operating Curve; INR: International Normalized Ratio.

Declarations

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Tables

Table 1. Demographic and clinical characteristics of ischemic stroke patients receiving rtPA or not receiving rtPA. Results for continuous variables are presented as Mean ± SD, while discrete data are presented as percentage frequency. Pearson's Chi-Square is used to compare differences between demographic and clinical characteristics in rtPA treated groups.

Characteristic	No rtPA group	rtPA group	
Number of patients	4142	1327	*P*-value
Age Group: No. (%)			
<50	467 (11.3)	191 (14.4)	0.001*[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	67.7±14.7	65.8±14.8	<.001*[b]
Race: No (%)			
White	3228 (77.9)	1060 (79.9)	0.313
Black	774 (18.7)	228 (17.2)	
Other	140 (3.4)	39 (2.9)	
Gender: No. (%)			
Female	1994 (48.1)	668 (50.3)	0.163
Male	2148 (51.9)	659 (49.7)	
Hispanic Ethnicity: No. (%)	55 (1.3)	30 (2.3)	0.017*[a]
BMI: Mean ± SD	28.18 ± 7.01	28.84 ± 6.84	0.003*[b]
Medical History: No. (%)			
Atrial Fib	713 (17.2)	211 (15.9)	0.266
Coronary Artery Disease	1262 (30.5)	399 (30.1)	0.782
Carotid Artery Stenosis	278 (6.7)	56 (4.2)	0.001*[a]
Depression	516 (12.5)	205 (15.4)	0.005*[a]
Diabetes	1520 (36.7)	415 (31.3)	<0.001*[a]
Drugs or Alcohol	260 (6.3)	77 (5.8)	0.532

Dyslipidemia	2055 (49.6)	700 (52.8)	0.047*[a]
Stroke Family History	364 (8.8)	130 (9.8)	0.265
Heart Failure	453 (10.9)	137 (10.3)	0.531
Hormonal Replacement Therapy	48 (1.2)	31 (2.3)	0.002*[a]
Hypertension	3262 (78.8)	1044 (78.7)	0.95
Migraine	89 (2.1)	45 (3.4)	0.011*[a]
Obesity	1633 (39.4)	678 (51.1)	<0.001*[a]
Previous Stroke	1134 (27.4)	290 (21.9)	<0.001*[a]
Previous TIA (> 24 hours)	334 (8.1)	143 (10.8)	0.002*[a]
Prosthetic Heart Valve	52 (1.3)	10 (0.8)	0.133
Peripheral Vascular Disease	321 (7.7)	79 (6.0)	0.029*[a]
Chronic Renal Disease	368 (8.9)	79 (6.0)	0.001*[a]
Sickle Cell	4 (0.1)	0 (0.0)	0.257
Sleep Apnea	125 (3.0)	45 (3.4)	0.495
Smoker	1098 (26.5)	388 (29.2)	0.052
Medication History: No (%)			
HTN medication	2851 (68.8)	943 (71.1)	0.125
Cholesterol Reducer	1796 (43.4)	632 (47.6)	0.006*[a]
Diabetes medication	1164 (28.1)	331 (24.9)	0.025*[a]
Antidepressant	489 (11.8)	222 (16.7)	<0.001*[a]
Initial NIHSS Score: No (%)			
0-9	2556 (76.3)	733 (59.4)	<0.001*[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	7.43 ± 8.11	10.55 ± 8.18	<0.001*[b]
Lab values: Mean ± SD			

Total cholesterol	173.01 ± 53.6	168.66 ± 46.48	0.006*[b]
Triglycerides	139.25 ± 104.13	140.71 ± 107.94	0.674
HDL	41.77 ± 13.91	41.8 ± 13.65	0.946
LDL	105.39 ± 42.06	102.52 ± 39.07	0.029*[b]
Lipids	6.64 ± 2.83	6.25 ± 1.6	<0.001*[b]
Blood Glucose	149.22 ± 82.86	141.29 ± 74.84	0.001*[b]
Serum Creatinine	1.34 ± 1.27	1.14 ± 0.75	<0.001*[b]
Initial Platelet Count	36527.8 ± 87310.62	174859.69 ± 128632.87	<0.001*[b]
INR	1.17 ± 0.57	1.06 ± 0.15	<0.001*[b]
Vital Signs: Mean ± SD			
Heart Rate	82.07 ± 18.94	81.81 ± 17.18	0.644
Blood Pressure Systolic	151.99 ± 30.04	151.31 ± 26.92	0.439
Blood Pressure Diastolic	82.29 ± 19.38	82.92 ± 18.3	0.277
Ambulation Status Prior to Event: No. (%)			
Ambulate Independently	3628 (87.6)	1259 (94.9)	<0.001*[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)	<0.001*[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)	<0.001*[a]
Ambulate with Assistance	1466 (35.4)	354 (26.7)	

Unable to Ambulate	847 (20.4)	222 (16.7)	
Not Documented	19 (0.5)	4 (0.3)	
First Care Received: No. (%)			
Emergency Department	3285 (80.1)	1012 (76.6)	0.006*[a]
Direct Admission	815 (19.9)	309 (23.4)	
Improved Ambulation: No. (%)	1141 (29.7)	684 (55.3)	<0.001*[a]
NIHSS > 7: No. (%)	1177 (33.5)	690 (52.4)	<0.001*[a]

Notes:

[a]Pearson's Chi-Squared test

[b]Student's T test

* *P*-value < 0.05

Table 2. Demographic and clinical characteristics of ischemic stroke patients treated with rtPA in combination with a cholesterol reducer, or no cholesterol reducer and with worsening neurologic functions (NIHSS score ≥7) and neurologic improvements(NIHSS score ≤7).Results for continuous variables are presented as Mean ± SD, while discrete data are presented as percentage frequency. Pearson's Chi-Square is used to compare differences between demographic and clinical characteristics in groups with a NIHSS score ≥ 7 and ≤7 who received rtPA and either took or did not take a cholesterol reducer.

	rtPA with Cholesterol Reducer			rtPA without Cholesterol Reducer		
Characteristic	NIHSS ≤ 7	NIHSS > 7		NIHSS ≤ 7	NIHSS > 7	
Number of patients	321	309	P-value	306	381	P-Value
Age Group: No. (%)						
<50 years	32 (10.0)	20 (6.5)	<0.001*[a]	79 (25.8)	60 (15.7)	<0.001*[a]
50-59	59 (18.4)	44 (14.2)		75 (24.5)	80 (21.0)	
60-69	103 (32.1)	73 (23.6)		71 (23.2)	67 (17.6)	
70-79	81 (25.2)	76 (24.6)		49 (16.0)	80 (21.0)	
>=80	46 (14.3)	96 (31.1)		32 (10.5)	94 (24.7)	
Age Mean ± SD	65.95 ± 12.09	70.83 ± 13.26	<0.001*[b]	59.67 ± 15.47	66.31 ± 15.82	<0.001*[b]
Race: No (%)						
White	277 (86.3)	244 (79.0)	0.050*[a]	243 (79.4)	287 (75.3)	0.446
Black	37 (11.5)	56 (18.1)		54 (17.6)	80 (21.0)	
Other	7 (2.2)	9 (2.9)		9 (2.9)	14 (3.7)	
Gender: No. (%)						
Female	130 (40.5)	159 (51.5)	0.006*[a]	159 (52.0)	205 (53.8)	0.630
Male	191 (59.5)	150 (48.5)		147 (48.0)	176 (46.2)	
Hispanic Ethnicity: No. (%)	7 (2.2)	8 (2.6)	0.737	5 (1.6)	10 (2.6)	0.377
BMI: Mean ± SD	29.72 ± 6.67	28.94 ± 7.72	0.180	29.07 ± 6.72	27.83 ± 6.24	0.014*[b]
Medical History: No. (%)						
Atrial Fib	37 (11.5)	74 (23.9)	<0.001*[a]	35 (11.4)	62 (16.3)	0.070

Coronary Artery Disease	135 (42.1)	135 (43.7)	0.679	50 (16.3)	74 (19.4)	0.296
Carotid Artery Stenosis	24 (7.5)	17 (5.5)	0.315	4 (1.3)	11 (2.9)	0.159
Depression	58 (18.1)	60 (19.4)	0.664	39 (12.7)	48 (12.6)	0.954
Diabetes	135 (42.1)	124 (40.1)	0.623	66 (21.6)	86 (22.6)	0.753
Drugs or Alcohol	14 (4.4)	19 (6.1)	0.314	15 (4.9)	28 (7.3)	0.188
Dyslipidemia	273 (85.0)	265 (85.8)	0.800	75 (24.5)	81 (21.3)	0.312
Stroke Family History	45 (14.0)	22 (7.1)	0.005*[a]	39 (12.7)	24 (6.3)	0.004*[a]
Heart Failure	31 (9.7)	47 (15.2)	0.034*[a]	16 (5.2)	41 (10.8)	0.009*[a]
Hormonal Replacement Therapy	10 (3.1)	7 (2.3)	0.510	8 (2.6)	6 (1.6)	0.338
Hypertension	291 (90.7)	289 (93.5)	0.182	182 (59.5)	273 (71.7)	0.001*[a]
Migraine	11 (3.4)	7 (2.3)	0.382	19 (6.2)	8 (2.1)	0.006*[a]
Obesity	187 (58.3)	146 (47.2)	0.006*[a]	172 (56.2)	173 (45.4)	0.005*[a]
Previous Stroke	90 (28.0)	90 (29.1)	0.762	46 (15.0)	62 (16.3)	0.657
Previous TIA (>24 hours)	45 (14.0)	41 (13.3)	0.784	25 (8.2)	30 (7.9)	0.887
Prosthetic Heart Valve	2 (0.6)	4 (1.3)	0.386	1 (0.3)	3 (0.8)	0.430
Peripheral Vascular Disease	25 (7.8)	25 (8.1)	0.888	12 (3.9)	16 (4.2)	0.855
Chronic Renal Disease	23 (7.2)	24 (7.8)	0.774	11 (3.6)	21 (5.5)	0.236
Sleep Apnea	16 (5.0)	15 (4.9)	0.940	9 (2.9)	5 (1.3)	0.133
Smoker	88 (27.4)	69 (22.3)	0.140	117 (38.2)	111 (29.1)	0.012*[a]
Medication History: No (%)						
HTN medication	286 (89.1)	283 (91.6)	0.291	150 (49.0)	216 (56.7)	0.045*[a]
Diabetes medication	117 (36.4)	106 (34.3)	0.574	45 (14.7)	60 (15.7)	0.706
Antidepressant	63 (19.6)	64 (20.7)	0.734	44 (14.4)	51 (13.4)	0.708

Lab values: Mean ± SD						
Total cholesterol	155.76 ± 41.36	153.88 ± 46.06	0.598	184.85 ± 46.97	178.75 ± 43.84	0.087
Triglycerides	149.43 ± 115.24	133.22 ± 100.57	0.067	153.54 ± 119.4	128.33 ± 95.18	0.003*[b]
HDL	39.51 ± 11.76	40.65 ± 12.61	0.250	42.49 ± 15.41	44.19 ± 14.03	0.140
LDL	91.22 ± 34.93	88.74 ± 37.96	0.404	116.22 ± 38.58	112.65 ± 37.26	0.230
Lipids	6.37 ± 1.61	6.33 ± 1.45	0.727	6.17 ± 1.69	6.17 ± 1.65	0.973
Blood Glucose	136.22 ± 63.35	147.04 ± 73.66	0.049*[b]	138.19 ± 81.28	143.76 ± 79.88	0.372
Serum Creatinine	1.15 ± 0.54	1.21 ± 0.79	0.233	1.04 ± 0.4	1.16 ± 1.04	0.036*[b]
Initial Platelet Count	159087.99 ± 131106.09	170621.77 ± 120785.15	0.519	196175.97 ± 133607.09	175315.17 ± 128742.52	0.245
INR	1.04 ± 0.12	1.07 ± 0.12	0.005*[b]	1.04 ± 0.15	1.07 ± 0.18	0.016*[b]
Vital Signs: Mean ± SD						
Heart Rate	79.62 ± 15.03	81.31 ± 17.38	0.191	80.71 ± 16.21	84.98 ± 18.94	0.002*[b]
Blood Pressure Systolic	150.34 ± 25.3	150.94 ± 26.19	0.768	151.62 ± 28.49	152.87 ± 27.51	0.561
Blood Pressure Diastolic	81.42 ± 16.2	80.44 ± 17.35	0.465	84.92 ± 19.27	84.82 ± 19.41	0.941
Ambulation Status Prior to Event: No. (%)						
Ambulate Independently	315 (98.1)	276 (89.3)	<0.001*[a]	297 (97.1)	361 (94.8)	0.038*[a]
Ambulate with Assistance	2 (0.6)	9 (2.9)		7 (2.3)	5 (1.3)	
Unable to Ambulate	2 (0.6)	10 (3.2)		1 (0.3)	7 (1.8)	
Not Documented	2 (0.6)	14 (4.5)		1 (0.3)	8 (2.1)	
Ambulation						

Status on Admission: No. (%)						
Ambulate Independently	93 (29.0)	17 (5.5)	<0.001*[a]	95 (31.0)	24 (6.3)	<0.001*[a]
Ambulate with Assistance	98 (30.5)	50 (16.2)		104 (34.0)	52 (13.6)	
Unable to Ambulate	18 (5.6)	198 (64.1)		21 (6.9)	238 (62.5)	
Not Documented	112 (34.9)	44 (14.2)		86 (28.1)	67 (17.6)	
Ambulation Status on Discharge: No. (%)						
Ambulate Independently	224 (69.8)	86 (27.8)	<0.001*[a]	217 (70.9)	128 (33.6)	<0.001*[a]
Ambulate with Assistance	76 (23.7)	98 (31.7)		78 (25.5)	100 (26.2)	
Unable to Ambulate	12 (3.7)	88 (28.5)		9 (2.9)	111 (29.1)	
Not Documented	1 (0.3)	1 (0.3)		0 (0.0)	2 (0.5)	
First Care Received: No. (%)						
Emergency Department	216 (67.3)	261 (84.5)	<0.001*[a]	221 (72.7)	310 (82.2)	0.003*[a]
Direct Admission	105 (32.7)	48 (15.5)		83 (27.3)	67 (17.8)	
Improved Ambulation: No (%)	177 (56.5)	151 (55.3)	0.763	162 (53.3)	193 (56.5)	0.399

Notes:

[a]Pearson's Chi-Squared test

[b]Student's T test

* P-value < 0.05

Figures

Demographic and clinical risk factors | Odds Ratio (95% CI) | Figure 1

- Increasing Age* 1.03(1.019 to 1.041), P<0.001*
- Female* 1.369(1.048to 1.787), P=0.021
- History of Drug of Alcohol Abuse^ 1.775(0.993 3.173),P=0.053*
- Dyslipidemia* 0.709(0.541to 0.927), P=0.012*
- Migraine 0.543(0.257to 1.146), P=0.109*
- Obesity* 0.745(0.572 to 0.971), P=0.029 *
- INR*^ 2.636(0.858 to 8.101), P=0.091
- Heart Rate 1.008(1.0 to 1.016), P=0.052*
- Direct Admission* 0.466(0.324 to 0.67), P<0.001*
- Caucasian* 0.589(0.42 to 0.828), P=0.002*

0   0.5   1   1.5   2
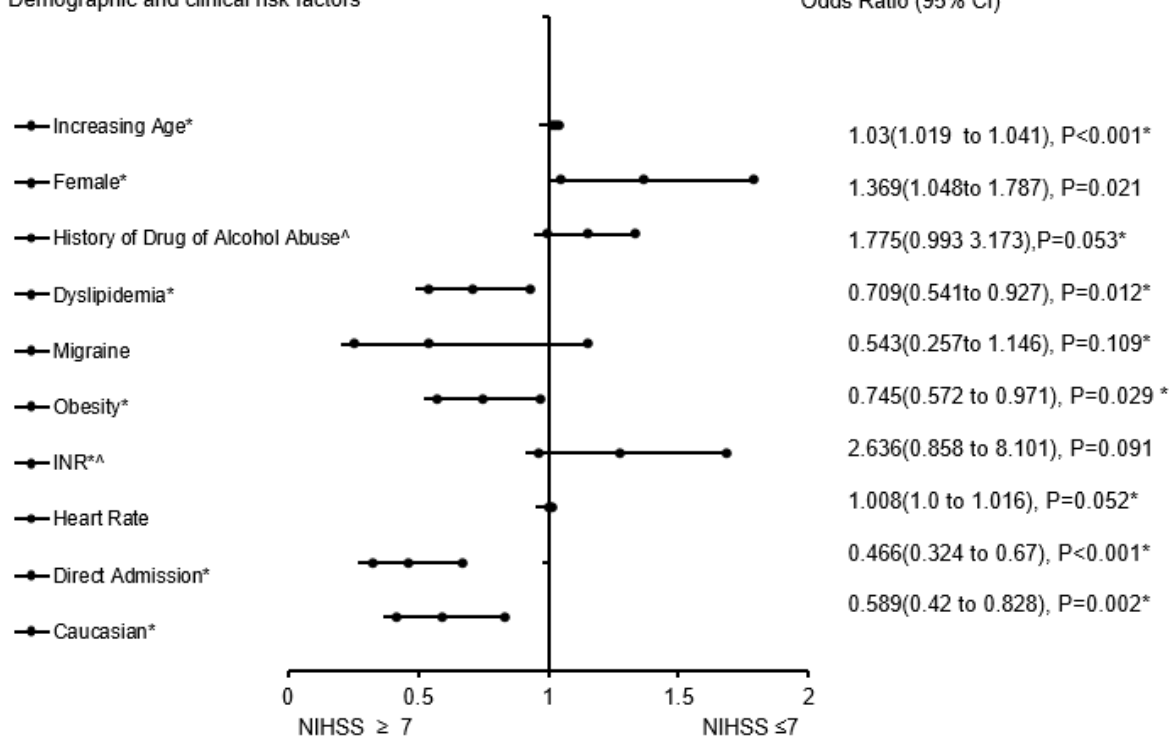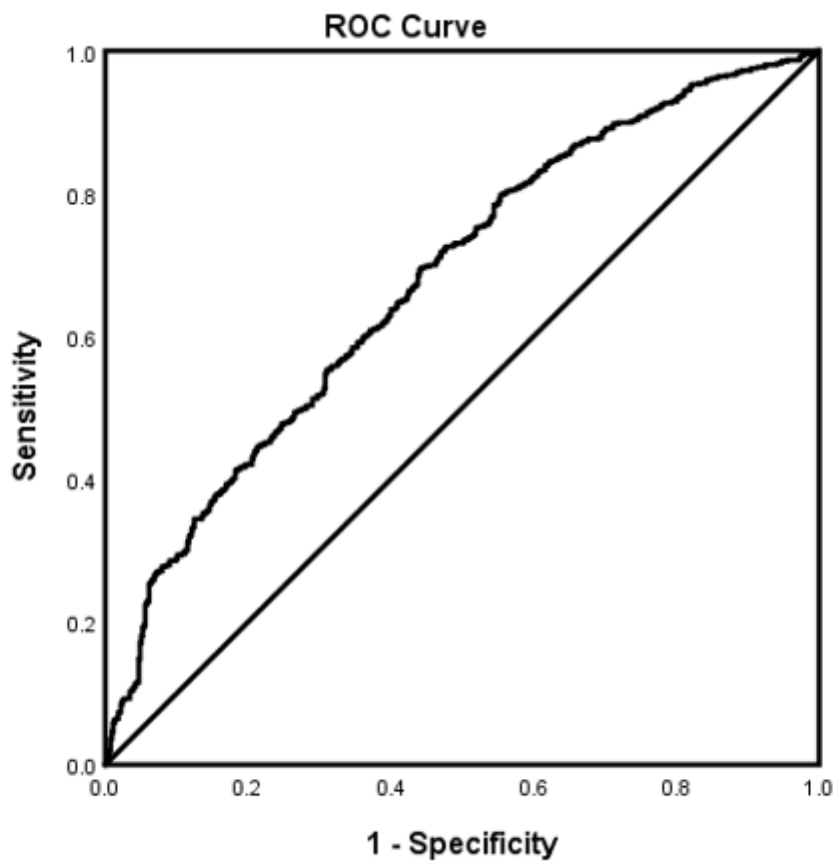NIHSS ≥ 7   NIHSS ≤7

Figure 1

Forest Plot representation of clinical factors that were associated with the severity of stroke for the total ischemic stroke population with rtPA, independent of whether they received cholesterol reducer or not. Adjusted OR<1 denote factors that are associated with neurologic improvements (NIHSS score ≤7) while OR>1 denote factors that are associated with worsening neurologic functions (NIHSS score ≥7). Hosmer-Lemeshow test (P=0.203), Cox & Snell (R2=0.100). The overall classified percentage of 61.8% was applied to check for fitness of the logistic regression model. *Indicates statistical significance (P<0.05) with a 95% confidence interval.

Figure 2

ROC Curve

Diagonal segments are produced by ties.

Figure 2

The ROC curve for the predictive power of the regression model for acute ischemic stroke population with rtPA. Higher area under the curve (AUC) values in ROC analysis indicate better discrimination of the score for the measured outcome. Classification table (overall correctly classified percentage = 61.8%) and area under the ROC curve (AUC = 0.677, 0.646-0.707) were applied to check model fitness.

| Demographic and clinical risk factors | Odds Ratio (95% CI) | Figure 3 |

Increasing Age*   1.027(1.014 to 1.041), P<0.001*
Dyslipidemia*   0.665(0.428 to 1.035), P=0.07
Family History of Stroke* 0.511(0.264 to 0.99),P=0.047*
Migraine*   0.35(0.13 to 0.943), P=0.038*
Obesity*   0.685(0.473to 0.992), P=0.045*
History of Previous Stroke 1.545(0.932 to 2.561), P=0.092
INR^   4.853(0.957 to 24.615), P=0.057
Heart Rate*   1.016(1.005 to 1.027), P=0.005*
Improvement in Ambulation* 1.571(1.078 to 2.289), P=0.019*
Direct Admission   0.512(0.303 to 0.866), P=0.013*
Caucasian*   0.604(0.381 to 0.957), P=0.032*

0   0.5   1   1.5   2   2.5   3
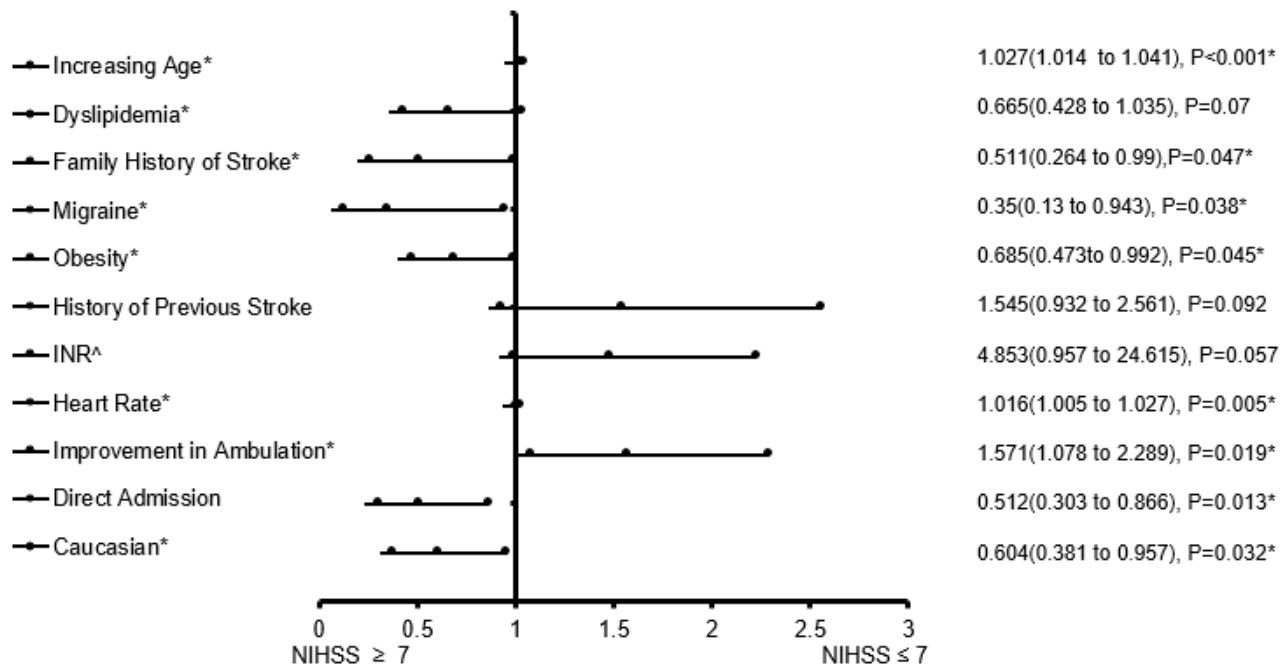NIHSS ≥ 7   NIHSS ≤ 7

Figure 3

Forest Plot representation for clinical factors that were associated with stroke severities in ischemic stroke population with rtPA only. Adjusted OR<1 denote factors that are associated with neurologic improvements (NIHSS score≤7) while OR>1 denote factors that are with worsening neurologic functions (NIHSS score≥7). Hosmer-Lemeshow test (P=0.907), Cox & Snell (R2=0.123). The overall classified percentage of 65.7% was applied to check for fitness of the logistic regression model. *Indicates statistical significance (P<0.05) with a 95% confidence interval.
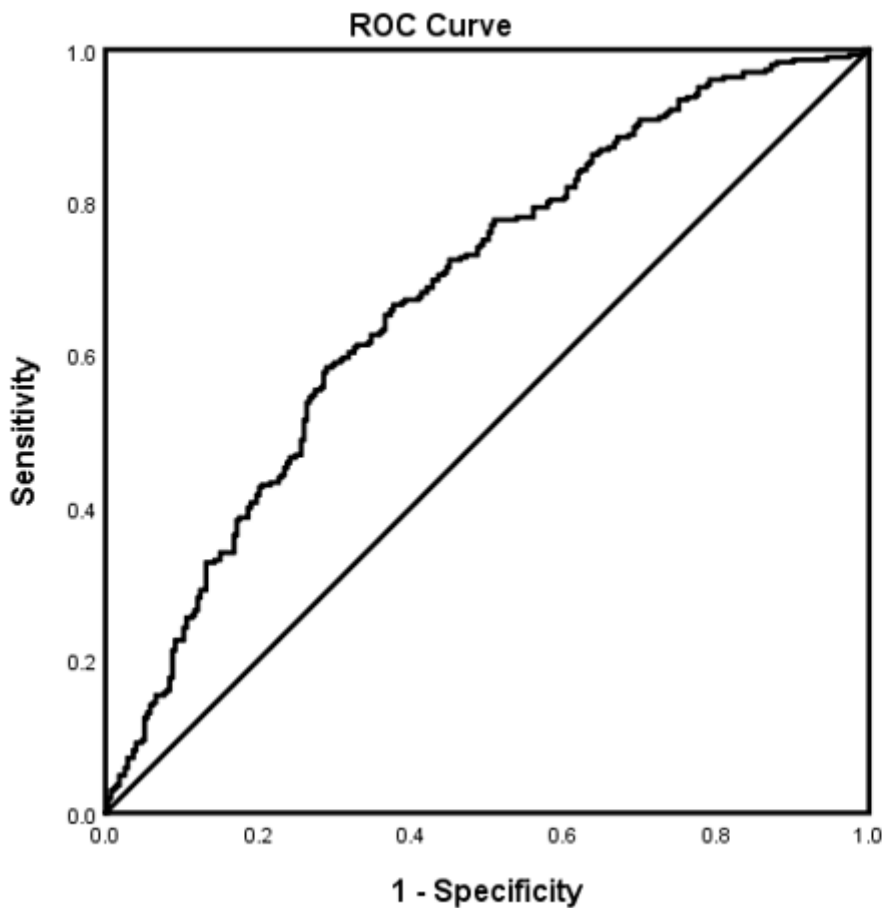
Figure 4

ROC Curve

Figure 4

The ROC curve for the predictive power of the regression model for acute ischemic stroke population who received rtPA and were not taking a cholesterol reducer. Higher area under the curve (AUC) values in ROC analysis indicate better discrimination of the score for the measured outcome. Classification table (overall correctly classified percentage = 65.7%) and area under the ROC curve (AUC = 0.681, 0.637-0.724) were applied to check model fitness.

Demographic and clinical risk factors — Odds Ratio (95% CI) — Figure 5

- Increasing Age* — 1.032(1.015 to 1.048), P<0.001*
- Atrial Fibrillation* — 1.859(1.098to3.149, P=0.021*
- Direct Admission* — 0.411(0.246 to 0.686),P=0.001*
- Caucasian* — 0.496(0.297to 0.827), P=0.007*
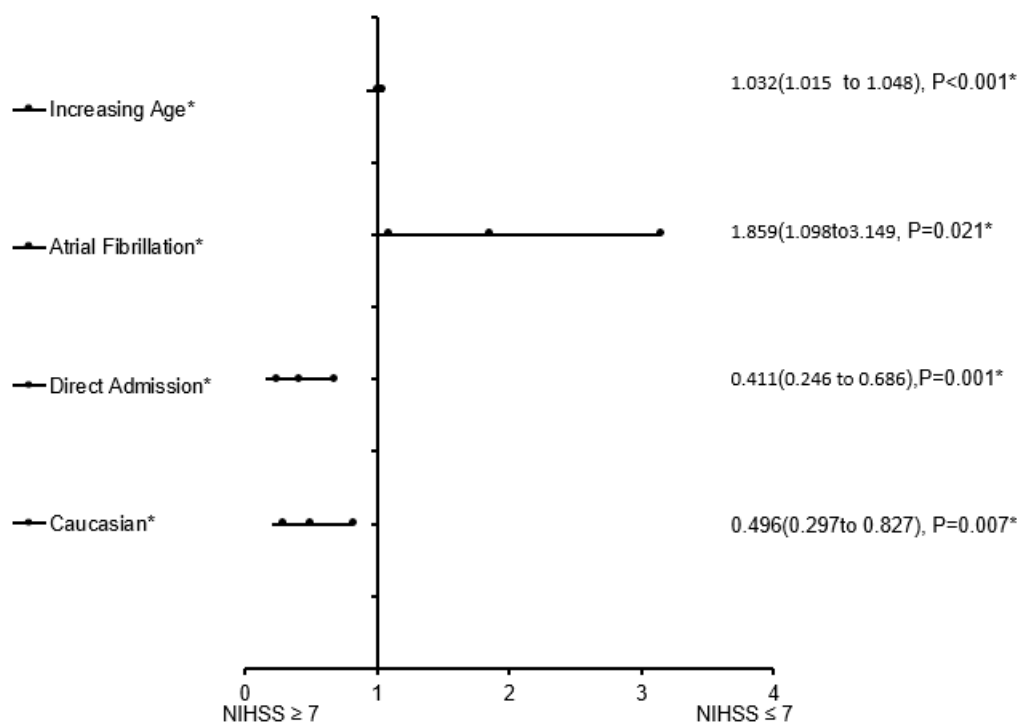
0 1 2 3 4
NIHSS ≥ 7   NIHSS ≤ 7

Figure 5

Forest Plot representation of clinical factors that were associated with stroke severities for ischemic stroke population with rtPA and taking a cholesterol reducer. Adjusted OR<1 denote factors that are associated with neurologic improvements (NIHSS score≤7) while OR>1 denote factors that are with worsening neurologic functions (NIHSS score≥7). Hosmer-Lemeshow test (P=0.415), Cox & Snell (R2=0.097). The overall classified percentage of 64.9% was applied to check for fitness of the logistic regression model. *Indicates statistical significance (P<0.05) with a 95% confidence interval. *Indicates statistical significance (P<0.05) with a 95% confidence interval.
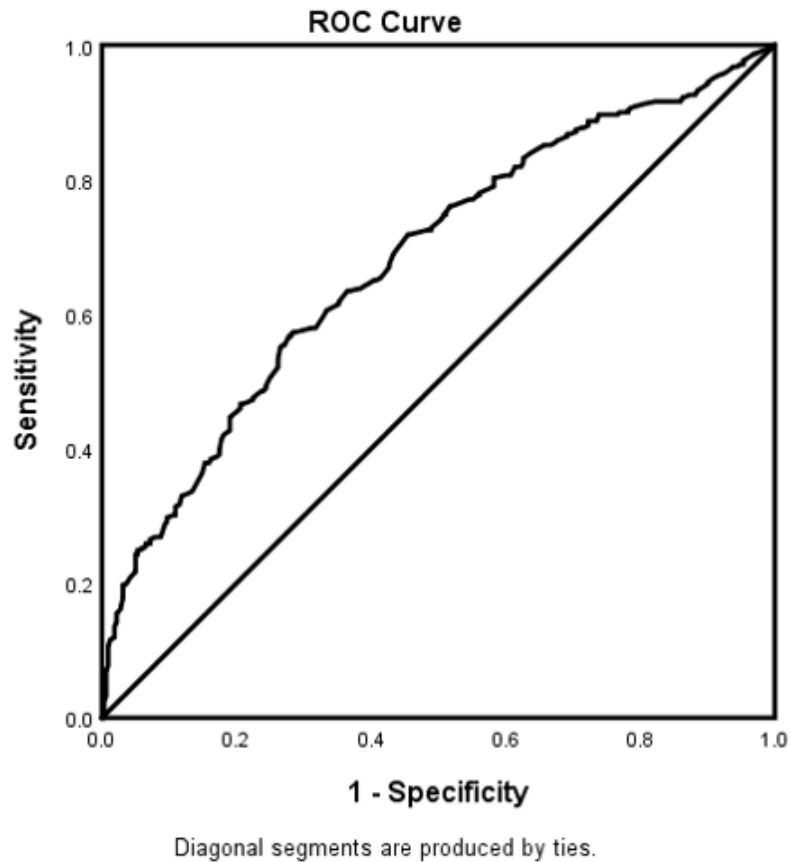
Figure 6

Figure 6

The ROC curve for the predictive power of the regression model for acute ischemic stroke population who received rtPA and were taking a cholesterol reducer. Higher area under the curve (AUC) values in ROC analysis indicate better discrimination of the score for the measured outcome. Classification table (overall correctly classified percentage = 64.9%) and area under the ROC curve (AUC = 0.680, 0.639-0.722) were applied to check model fitness.