Article

Clinical risk factors that predict functional recovery in ischemic stroke patients with pre-stroke depression

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Abstract: *Background.* Specific clinical risk factors that may be associated with ambulatory outcome following thrombolysis therapy in ischemic stroke patients with pre-stroke depression is not fully understood. This was investigated. *Methods.* Multivariate analyses were performed to identify predictors of functional ambulatory outcomes. Patient demographics and clinical risk factors served as predictive variables, while improvement or no improvement in ambulatory outcome was considered as the primary outcome. *Results.* A total of 595 of these patients received rtPA of which 310 patients presented with pre-stroke depression, 217 had no improvement in functional outcome, while 93 patients presented with an improvement in functional outcome. Carotid artery stenosis (OR= 11.577, 95% CI, 1.281 – 104.636, P=0.029) and peripheral vascular disease (OR= 18.040, 95% CI, 2.956-110.086, P=0.002) were more likely to be associated with an improvement in ambulation. Antihypertensive medications (OR= 7.810, 95% CI, 1.401 –43.529, P=0.019), previous TIA (OR= 0.444, 95% CI, 0.517 –0.971, P=0.012), and congestive heart failure (OR= 0.217, 95% CI, 0.318 –0.402, P=0.030) were associated with a no improvement in ambulation. *Conclusion.* After adjustment for covariates, more clinical risk factors were associated with no improvement when compared with improvement in functional outcome following thrombolysis therapy in an acute ischemic stroke population with pre-stroke depression.

Keywords. Ambulation; Ischemic stroke; pre-stroke depression; recombinant tissue plasminogen activator (rtPA)

1. Introduction

Clinical outcomes following ischemic stroke in patients with depression manifest in various forms, including ambulation, which is relevant in the assessment of treatment outcomes [1]. Ambulatory behavior is known to be modulated by emotions and has long been recognized as an integral sign of depression [2], and can predict the course of the disease [3, 4]. Alterations in the ambulatory status are well-known as clinically observable phenomena of depressed patients [5]. These alterations may be linked to abnormalities in the motor pathways that may also lead to alterations of ambulatory patterns in depressed patients [6]. Several studies [7-10] provide evidence that an improvement or lack of improvement in the ambulatory status of patients with depression is relevant for evaluation of course and treatment response [3, 4, 11]. After stroke, more than 60% of survivors present with a reduced ambulatory status [12, 13]. It is known that in ischemic stroke patients, pre-stroke clinical risk factors may predict ambulatory recovery following thrombolysis therapy [14, 15].

While post-stroke depression is a common occurrence and linked with poor outcome [16-19], the effect of pre-stroke depression on treatment outcome in ischemic stroke patients is not well understood. Pre-stroke depression may be associated with abnormal modification of risk factors in ischemic stroke [20, 21], and may affect functional ambulatory outcome following rtPA. However, clinical risk factors that may predict ambulatory outcome of ischemic stroke patients with pre-stroke depression are yet to be fully understood. We developed a logistic regression model to predict the

recovery of ambulatory functions 14 days after stroke recovery. We tested the hypothesis that specific clinical risk factors may be predictive of ambulatory outcome in ischemic stroke patients with pre-stroke depression treated with thrombolysis therapy. There is a likelihood that the population of ischemic stroke patients with pre-stroke depression with improvement in functional ambulation after treatment with thrombolysis therapy maybe different from those with no improvement. In this context, there is a possibility that different clinical risk factors would be associated with improvement, when compared with no improvement in ambulatory function after rtPA in ischemic stroke patient with pre-stroke depression. The aim of this study is to identify clinical risk factors associated with ambulatory recovery in ischemic stroke patients with pre-stroke depression treated with thrombolysis therapy 14 days after recovery. Thrombolysis therapy is an FDA-approved treatment for acute ischemic stroke, and there is no clinical reason to withhold the use of rtPA based on pre-stroke depression alone. Therefore, understanding clinical risk factors that may affect ambulatory recovery in ischemic stroke patients with pre-stroke depression may help in the development of management strategies to improve the use of rtPA in ischemic stroke patients with pre-stroke depression.

2. Materials and Methods

2.1. Research Design

This study contains retrospective data obtained from a large stroke registry and was approved by the institutional Ethics Committee (approval number Pro00046787). Data within the Greenville Health System (GHS) stroke registry has been standardized according to the "Get with The Guidelines" (GWTG) stroke registry formed by the American Heart Association (AHA). Details in the ascertainment and data collection have previously been described [22-24]. Briefly, data was collected from 1466 ischemic stroke patients admitted to the stroke Unit of GHS between January 2014 and June 2016 with a diagnosis of acute ischemic stroke. Eligibility for rtPA was based on the AHA inclusion guidelines for early management of patients with acute ischemic stroke [25]. All cases of prospective clinical identification of acute ischemic stroke were confirmed by computed tomography (CT). Our data analysis utilized retrospective data of confirmed cases of acute ischemic stroke from the standardized registry. In this study, patients were included if they were, 1) discharged from the stroke unit of GHS between January 2014 and June 2016 with acute ischemic as their primary cause for hospitalization, 2) entered into the GWTG-Stroke registry and, 3) with documented history pre-stroke depression on admission.

We excluded patients if there was no documentation of medical history on admission, as well as patients with mild or improving stroke symptoms. Data on symptomatic hemorrhage was not included in our data collection.   Our inclusion criteria allowed us to focus our analysis on ischemic stroke patients with a history of pre-stroke depression. We collected data on patient demographics, including age, sex, race (African–American/black, white or other) and Hispanic ethnicity. Information about medical history was obtained from electronic medical records, and we collected and analyzed data on clinical risk factors for stroke in patients with pre-stroke depression. Clinical risk factors include atrial fibrillation, coronary artery disease or prior myocardial infarction, carotid stenosis, drug abuse, diabetes mellitus, dyslipidemia, congestive heart failure, obesity, hypertension, peripheral vascular disease, previous stroke, transient ischemic attack (TIA), renal insufficiency, or smoking. While data from history of pre-stroke depression was abstracted from the medical record, data collected for antidepressant medication was not directly linked to pre-stroke depression for each patient. Data for use of antihypertensive medication, cholesterol reducing agents, and antihypertensive agents also collected. Medical records on hospital course, initial NIHSS score and examination findings including weakness, aphasia, systolic and diastolic blood pressures, and status at discharge were collected. Clinical parameters relating to the hospital course included data of stroke patients in the use of rtPA for the 4.5 hours of the protocol. We included data on laboratory analyses of samples including serum lipid panel, LDL, total cholesterol and creatinine levels. Ambulatory status was characterized using a three-level tiered system at both admission and at discharge,

assigning each patient to one of the following: 1) unable to ambulate, 2) able to ambulate with assistance, 3) able to ambulate independently. This allowed us to analyze changes in ambulation status from admission to discharge in patients who received rtPA, as well as identify risk factors associated with improvement or no improvement in ambulatory status.

3. Statistical analysis

We analyzed our data using the SPSS Statistics Software version 15.0 (Chicago, IL). We utilized descriptive statistics to characterize the demographic and clinical risk factors in ischemic stroke patients with pre-stroke depression treated with rtPA and characterize them based on improvement or no improvement in ambulatory status. We tested the normality of our data using the Kolmogorov-Smirnov test. All continuous variables were analyzed using a Student-t-test, while discrete variables were analyzed using Pearson's Chi-Squared analyses. The mean, standard deviation, and range were determined for all continuous variables and significant differences at $P<0.05$ were determined. The number of patients and percentage of patients in each category were analyzed for all discrete variables.

We used logistic regression analysis to identify predictive clinical risk factors in a population of ischemic stroke patients with pre-stroke depression who were treated with rtPA. This sample population was then divided into two groups: improvement ambulatory status after treatment and no improvement in ambulatory status after treatment. In our logistic regression analysis, we retained parameters that the p-value were less than 0.05, and parameters with p-values > 0.05 were excluded and eliminated stepwise. We then re-considered and added parameters that were initially eliminated in the model if they met the criteria of $p < 0.05$. We adjusted for clinical covariates that were significant in the unadjusted univariate analysis using the backward elimination method with conventional P value <0.05.

The primary outcome of our logistic model was the identification of baseline clinical risk factors that were significantly associated with improvement or no improvement in ambulation following thrombolysis therapy in ischemic stroke patients with pre-stroke depression. This approach allowed us to identify specific clinical risk factors associated with an improvement or no improvement in ambulation recovery in the multivariate analysis. We used the variance inflation factor to determine independence of variables included in the regression model to address the issue of collinearity or interactions between independent variables. We tested the validity of our model using a Hosmer-Lemeshow test, and the overall correct classification percentage and the area under the Receiver Operating Curve (ROC) for score prediction was determined. This allowed us to test the sensitivity, specificity and accuracy of our logistic model. Odds ratios (ORs) were determined from the logistic regression and significance was set at the probability level of 0.05. We then use the odds ratio values to predict the odds of attaining a specific ambulation outcome in ischemic stroke patients with pre-stroke depression treated with thrombolysis therapy.

4. Results

A total of 4,665 ischemic stroke patients were identified. Of this population, 1,446 patients were eligible for rtPA and 595 of these patients received rtPA. Of the 595 patients treated with thrombolysis therapy, 310 patients presented with a documented history of pre-stroke depression. Of the acute ischemic stroke patients with pre-stroke depression who received rtPA, 217 patients presented with no improvement, and there was an improvement in ambulation for 93 patients (Table 1).Compared to the no improvement group, the improvement rtPA population was younger (64.18 ± 15.2 vs. 67.17 ± 14.5), included more males (66.7% vs 61.3%), and fewer females (33.3% vs 38.7%).Those with an improvement in ambulation were more likely to present with lower rates of atrial fibrillation or atrial flutter (15.1% vs 19.8%), less likely to have dyslipidemia (60.2% vs. 64.1%), family history of stroke (9.7% vs 13.4%), congestive heart failure (9.7% vs. 17.5%), hypertension(82.8% vs 85.3%), prior TIA (9.7% vs 14.7%),chronic renal disease (9.7% vs 15.7%), diabetes (40.9% vs 44.2%), and are less likely to receive treatment in a telestroke setting (8.6% vs 10.1%).

Table 1. Demographic and clinical characteristics of ischemic stroke patients with pre-stroke depression. Results for continuous variables are presented as Mean ± S.D, while discrete data are presented percentage frequency. Pearson's Chi-Squared is used compare differences between improvement and no improvement in ambulatory outcome in rtPA treated groups.

	Not Improved (217)	Improved (93)	Significance
Age Group			0.432
<50 years	26 (12.0)	18 (19.4)	
50-59	39 (18.0)	16 (17.2)	
60-69	49 (22.6)	23 (24.7)	
70-79	54 (24.9)	18 (19.4)	
>80 years	49 (22.6)	18 (19.4)	
Mean ± SD	67.17±14.5	64.18±15.2	0.110
Race			0.200
Caucasion	186 (85.7)	79 (85.5)	
African-American	25 (11.5)	14 (15.1)	
Other	6 (2.8)	0 (0.0)	
Gender			0.369
Male	133 (61.3)	62 (66.7)	
Female	84 (38.7)	31 (33.3)	
Medical History			
Atrial Fibrillation	43 (19.8)	14 (15.1)	0.321
CAD	90 (41.5)	30 (32.3)	0.127
Carotid Stenosis	15 (6.9)	7 (7.5)	0.847
Diabetes	96 (44.2)	38 (40.9)	0.582
Drug Abuse	16 (7.4)	11 (11.8)	0.202
Dyslipidemia	139 (64.1)	56 (60.2)	0.521
Family stroke history	29 (13.4)	9 (9.7)	0.364
Congestive heart failure	38 (17.5)	9 (9.7)	0.078
Hypertension	185 (85.3)	77 (82.8)	0.584
Obesity	153 (70.5)	68 (73.1)	0.641
Prior Stroke	74 (34.1)	33 (35.5)	0.815
Prior TIA	32 (14.7)	9 (9.7)	0.227
Peripheral vascular disease	20 (9.2)	11 (11.8)	0.482
Chronic renal disease	34 (15.7)	9 (9.7)	0.162
Smoking History	53 (24.4)	29 (31.2)	0.216
GHS Telestroke	22 (10.1)	8 (8.6)	0.675
Medications			
Antihypertensives	170 (78.3)	70 (75.3)	0.553
Cholesterol reducing agents	125 (57.6)	51 (54.8)	0.652
Antidiabetic agents	80 (36.9)	29 (31.2)	0.337
Antidepressants	170 (78.3)	80 (86.0)	0.117
tPA	97 (44.7)	56 (60.2)	0.012*
NIH Stroke Scale			0.005*
0-9	138 (67.0)	40 (44.4)	
10-14	22 (10.7)	20 (22.2)	
15-20	19 (9.2)	15 (16.7)	
21-25	15 (7.3)	9 (10.0)	
26-42	12 (5.8)	6 (6.7)	
Mean ± SD	8.84±8.0	12.29±7.6	0.001*
BMI			
Mean ± SD	29.56±7.1	29.96±8.1	0.691
Total Cholesterol			
Mean ± SD	168.34±47.9	170.27±51.8	0.769
LDL			
Mean ± SD	100.77±38.6	98.26±40.2	0.751
Serum Creatinine			
Mean ± SD	1.47±2.3	1.24±0.96	0.387
Systolic Blood Pressure	146.2±27	150.2±19	0.315
Diastolic Blood pressure	80.3±23	84.1±17	0.293

In addition, the improvement in ambulation group demonstrated higher rates of carotid artery stenosis (7.5% vs 6.9%), prior stroke(35.5% vs 34.1 %), history of drug abuse (11.8% vs 7.4%), obesity (73.1% vs 70.5%), peripheral vascular disease (11.8% vs 9.2%), and smoking history (31.2% vs 24.4%). Patients with improvement in ambulation were less likely to take antihypertensive medication (75.3% vs 78.3%), and cholesterol reducing agents (54.8% vs 57.6%). Compared with the no improvement group, those with an improvement in ambulation were more likely to take antidepressants(86.0% vs 78.3%), present with higher NIHSS scores (12.29±7.6 vs 8.84±8.0), high serum cholesteroal (170.27±51.8 mg/dl vs 168.34±47.9 mg/dl), and BMI (29.96±8.1 vs 29.56±7.1), lower low density lipoprotein (LDL) (98.26±8.1 vs 100.77±38.6 mg/dl), serum creatine(1.24±0.96 vs 1.47±2.3mg/dl), high systolic blood pressure (150.2±19.0 vs 146.2±27.0mm Hg) and diastolic blood

pressure values (84.1 ±17.0 vs 80.3±23 mm Hg). Apart from use of rtPA, and NIH scale scores, all other clinical variables including age, race, gender, atrial fibrillation or atrial flutter, carotid artery disease, dyslipidemia, congestive heart, hypertension, prior stroke, prior, and chronic renal disease were not significantly different between the   improvement and the no improvement   in ambulation group.

Following adjustment for the cofounding effects of non-significant variables in the total population (Table 2), only NIHSS score (OR= 1.275, 95% CI, 1.006 - 1.616, P=0.045) was associated with an improvement in ambulatory outcome. The area under the curve (AUROC= 0.707, 95% CI, 0.639-0.776, P<0.001) of accurate classification, indicates a good fit for the regression model. For the improvement in ambulation group (Table 3), carotid artery stenosis (OR= 11.577, 95% CI, 1.281 – 104.636, P=0.029) and peripheral vascular disease (OR= 18.040, 95% CI, 2.956-110.086, P=0.002) were more likely to be associated with an improved ambulatory outcome, while antihypertensive medication (OR= 0.192, 95% CI, 0.035 – 1.067, P=0.051) was predicted to be associated with no improvement in ambulation following thrombolysis therapy. The discriminatory capability of the model was strong with area under the curve (AUROC= 0.827, 95% CI, 0759-0.895, P<0.001).

For the no improvement group, NIH scale score (OR= 0.887, 95% CI, 0.830 - 0.948, P<0.001), antihypertensive medications (OR= 7.810, 95% CI, 1.401 –43.529, P=0.019), previous TIA (OR= 0.444, 95% CI, 0.517 –0.971, P=0.012), and congestive heart failure (OR= 0.217, 95% CI, 0.318 –0.402, P=0.030) were significantly associated with no improvement in ambulation (Table 4). The discriminating ability of the model was strong as shown by the ROC curve, with area under the curve (AUROC= 0.842, 95% CI, 0778-0.906, P<0.001).

Table 2. Results for the logistic regression model that predicts clinical risk factors associated with improvement or no improvement in ambulatory recovery for an ischemic stroke population with pre-stroke depression.

	B	Wald	Sig.	Odds Ratio	95% C.I.for Odds Ratio Lower	Upper
Age	-0.015	1.458	0.227	0.985	0.961	1.009
Gender	-0.056	0.029	0.864	0.945	0.495	1.803
Afib	-0.048	0.011	0.915	0.954	0.400	2.275
CAD	-0.360	1.194	0.275	0.697	0.365	1.331
Carotid Stenosis	0.587	0.970	0.325	1.798	0.559	5.780
Diabetes	0.886	3.042	0.081	2.425	0.896	6.564
Drug Abuse	0.597	0.995	0.319	1.817	0.562	5.880
DysLip	-0.193	0.248	0.619	0.825	0.386	1.761
Family history of stroke	-0.707	2.132	0.144	0.493	0.191	1.274
Heart Failure	-0.739	2.299	0.129	0.478	0.184	1.241
Hypertension	0.451	0.727	0.394	1.570	0.557	4.429
Obesity	0.074	0.028	0.867	1.077	0.453	2.558
Previous Stroke	0.172	0.254	0.614	1.187	0.609	2.316
Previous TIA	-0.811	3.007	0.083	0.444	0.178	1.112
Peripheral vascular disease	0.756	2.422	0.120	2.131	0.822	5.523
Chronic renal disease	-0.499	0.929	0.335	0.607	0.220	1.674
History of Smoking	0.081	0.048	0.827	1.084	0.524	2.242
Race	-0.352	0.694	0.405	0.704	0.308	1.609
NIHSS	0.243	4.024	0.045*	1.275	1.006	1.616
Treatment with rTPA	0.570	3.268	0.071	1.768	0.953	3.278
Antihypertensive Medication	-0.472	0.994	0.319	0.624	0.247	1.577
Chlosterol Reducing Agent	0.203	0.265	0.607	1.225	0.565	2.657
Antidiabetic Agent	-0.849	2.333	0.127	0.428	0.144	1.272
Antidepressant Agent	0.457	1.165	0.280	1.579	0.689	3.616
Totalcholesterol	0.000	0.001	0.974	1.000	0.982	1.018
LDL	0.001	0.015	0.902	1.001	0.979	1.024
Serum creatinine	-0.109	0.329	0.566	0.897	0.618	1.301
Systolic Blood Pressure	0.002	0.056	0.813	1.002	0.988	1.015
Diastolic Blood Pressure	0.005	0.309	0.578	1.005	0.988	1.022
BMI	0.012	0.177	0.674	1.013	0.956	1.073

Adjusted OR<1 indicates clinical and demographic factors associated with no improvement in ambulation while Adjusted OR>1 reveal factor associated an improvement in ambulation following thrombolysis therapy. Hosmer-Lemeshow test, Cox & Snell (R^2=0.0.707), and the overall classified percentage of 70.7% was applied to check the model fitness. * Indicates statistical significance (P<0.05) with 95% a confidence interval.

Table 3. Predictive clinical and demographic variables associated with an improvement in ambulation for ischemic stroke population with pre-stroke depression, treated with rtPA.

	B	Wald	Sig.	Odds Ratio	95% C.I.for Odds Ratio Lower	Upper
Age	-0.007	0.117	0.732	0.993	0.957	1.032
Gender	-0.015	0.001	0.980	0.985	0.310	3.130
Afib	-1.071	1.153	0.283	0.343	0.048	2.421
CAD	-0.855	2.419	0.120	0.425	0.145	1.249
Carotid Stenosis	2.449	4.754	0.029*	11.577	1.281	104.636
Diabetes	0.878	0.793	0.373	2.407	0.348	16.636
Drug Abuse	1.806	3.914	0.048	6.086	1.017	36.424
DysLip	-0.869	1.923	0.166	0.420	0.123	1.432
Family history of stroke	-1.371	2.721	0.099	0.254	0.050	1.294
Heart Failure	-1.832	4.650	0.031	0.160	0.030	0.846
Hypertension	1.425	2.046	0.153	4.157	0.590	29.295
Obesity	0.900	1.711	0.191	2.460	0.639	9.474
Previous Stroke	0.158	0.070	0.792	1.172	0.361	3.798
Previous TIA	-1.734	4.914	0.027	0.177	0.038	0.818
Peripheral vascular disease	2.893	9.825	0.002*	18.040	2.956	110.086
Chronic renal disease	-1.394	1.650	0.199	0.248	0.030	2.081
History of Smoking	0.389	0.432	0.511	1.476	0.462	4.716
Race	-0.009	0.000	0.987	0.991	0.314	3.125
NIHSS	0.438	3.976	0.046	1.549	1.008	2.383
Antihypertensive Medication	-1.648	3.557	0.051*	0.192	0.035	1.067
Chlosterol Reducing Agent	0.269	0.197	0.657	1.308	0.400	4.282
Antidiabetic Agent	-0.127	0.015	0.902	0.881	0.117	6.632
Antidepressant Agent	0.478	0.407	0.524	1.613	0.371	7.011
Totalcholesterol	0.008	0.293	0.588	1.008	0.980	1.035
LDL	-0.009	0.291	0.590	0.991	0.958	1.025
Serum creatinine	-0.070	0.058	0.810	0.933	0.529	1.644
Systolic Blood Pressure	-0.003	0.111	0.739	0.997	0.976	1.017
Diastolic Blood Pressure	-0.004	0.093	0.760	0.996	0.967	1.025
BMI	-0.011	0.061	0.805	0.989	0.904	1.082

Adjusted OR<1 denote factors that are associated with no improvement in ambulation while adjusted OR>1 denote factors that are associated with an improvement in ambulation. Hosmer-Lemeshow test, Cox & Snell (R^2=0.827). The overall classified percentage of 82.7% was applied to check for the fitness of the logistic regression model. * Indicates statistical significance (P<0.05) with 95% a confidence interval.

Table 4. Clinical factors that were associated with no improvement in ambulation for ischemic stroke population with pre-stroke depression treated with rtPA.

	B	Wald	Sig.	Odds Ratio	95% C.I.for Odds Ratio	
					Lower	Upper
Age	0.006	0.095	0.757	1.006	0.970	1.043
Gender	0.159	0.089	0.766	1.173	0.411	3.350
Afib	0.970	1.336	0.248	2.637	0.509	13.646
CAD	0.529	1.080	0.299	1.697	0.626	4.598
Carotid Stenosis	-2.549	5.874	0.015	0.078	0.010	0.614
Diabetes	-0.334	0.138	0.710	0.716	0.123	4.169
Drug Abuse	-1.066	1.597	0.206	0.344	0.066	1.799
DysLip	0.675	1.272	0.259	1.963	0.608	6.342
Family history of stroke	1.118	2.100	0.147	3.059	0.674	13.874
Heart Failure	2.503	0.709	0.030*	0.217	0.318	0.402
Hypertension	-1.663	2.789	0.095	0.190	0.027	1.335
Obesity	-0.530	0.746	0.388	0.589	0.177	1.958
Previous Stroke	-0.065	0.012	0.912	0.937	0.296	2.971
Previous TIA	1.863	0.374	0.012*	0.444	0.517	0.971
Peripheral vascular disease	-2.052	6.683	0.081	0.128	0.027	0.609
Chronic renal disease	1.128	1.276	0.259	3.090	0.437	21.866
History of Smoking	0.184	0.108	0.743	1.203	0.400	3.620
Race	-0.104	0.037	0.848	0.901	0.309	2.625
NIHSS	-0.120	12.429	<0.001*	0.887	0.830	0.948
Antihypertensive Medication	2.055	5.4990	0.019*	0.810	0.401	0.529
Chlosterol Reducing Agent	-0.206	0.131	0.717	0.814	0.267	2.481
Antidiabetic Agent	-0.379	0.161	0.688	0.685	0.108	4.357
Antidepressant Agent	-0.815	1.333	0.248	0.443	0.111	1.766
Totalcholesterol	-0.010	0.576	0.448	0.991	0.966	1.015
LDL	0.013	0.658	0.417	1.013	0.982	1.044
Serum creatinine	0.100	0.128	0.720	1.105	0.639	1.911
Systolic Blood Pressure	0.007	0.556	0.456	1.007	0.989	1.026
Diastolic Blood Pressure	-0.006	0.235	0.628	0.994	0.968	1.020
BMI	0.012	0.080	0.778	1.012	0.930	1.102

Adjusted OR<1 indicates factors associated with no improvement while adjusted OR>1 indicates factors associated with an improvement. Hosmer-Lemeshow test, Cox & Snell (R^2=0.842), and the overall classified percentage of 84.2% was applied to check for the fitness of the logistic regression model. * Indicates statistical significance (P<0.05) with 95% a confidence interval.

5. Discussion

The goal of this study was to investigate clinical risk factors that may be associated with an improvement or no improvement in the recovery of ambulatory functions following thrombolysis therapy in acute ischemic stroke patients with pre-stroke depression. In the univariate analysis, we found that the proportion of ischemic stroke patients with pre-stroke depression who presented with no improvement in ambulation after treatment with rtPA was higher than those with an improvement in ambulation. This may be linked to differences in the proportion of clinical factors between patients that presented with an improvement and those with no improvement in their ambulation status. We expected that the use of antidepressants would be identified as a variable associated with ambulatory status.   However, the univariate analysis as well as the adjusted analysis did not reveal a significant association of antidepressants with ambulatory outcome in ischemic stroke patients with pre-stroke depression treated with thrombolysis therapy. It is possible that the variation in the effects or use of antidepressants may be associated with stroke severity, rather than with the ambulation status.

In the univariate analysis, NIHSS (indicator of stroke severity) was associated with a significant improvement in ambulation among ischemic stroke patients with pre-stroke depression. This effect

was sustained in the adjusted analysis for the total population of ischemic stroke patients with pre-stroke depression and was associated with no improvement in the group with no improvement in ambulation following rtPA. In general, the initial NIHSS score is a strong predictor of stroke severity and may predict functional outcome as well. In the univariate analysis, stroke severity, demonstrated by NIHSS, was between 0 and 14 for many of the patients with no improvement following treatment with rtPA. The adjusted analysis associated initial NIHSS with both an improvement and no improvement in ambulation following rtPA. This finding indicates that the severity of stroke is not enough to predict functional ambulatory outcomes, and that clinical risk factors may as well play a significant role [26, 27].

In the population that presented with an improvement in ambulation, we observed that in the adjusted analysis, patients that presented with carotid artery stenosis and peripheral vascular disease were more likely to be associated with an improvement in ambulation. However, patients that took antihypertensive medications were more likely to be associated with no improvement following thrombolysis therapy. Because clinical risk factors associated with an improvement in functional ambulatory recovery maybe be different between the population with an improvement and those with no improvement, we performed additional analyses to evaluate if these factors may significantly differ. Our findings indicate that in the no improvement group, the effect of carotid artery disease and peripheral vascular disease, which were significant in the improvement group, were attenuated in the no improvement group. Moreover, our adjusted analysis revealed that previous TIA, congestive heart disease, and use of antihypertensive medications were more likely to be significantly associated with no improvement in functional ambulatory recovery in ischemic stroke patients with pre-stroke depression.

Previous TIA is not a formal contraindication for rtPA, especially if the TIA was at least three months before the onset of stroke [28] [22, 29]. However, it has been shown that the onset of TIA within 24 hours of stroke may lead to a poor outcome following rtPA [30, 31]. It is possible that some ischemic stroke patients with pre-stroke depression may present an invisible TIA in the CT scans making it difficult to detect and this may affect treatment outcome with rtPA. This might be the case in ischemic stroke patients with pre-stroke depression that received rtPA resulting in no improvement outcome in functional ambulatory recovery. The association between antihypertensive medication and depression is well documented in the literature [32, 33]. It is known that if depression occurs prior to stroke, medication use plays a role in the treatment outcome of the stroke [21, 34]. It is also known that clinical risk factors contribute to, or worsen, the underlying disease such as depression and stroke [28]. However, the relationship between certain clinical risk factors, such as congestive heart failure, with treatment response to rtPA and functional ambulatory outcome in ischemic stroke patients with pre-stroke depression is not known.

Depression is an independent risk factor for the onset of congestive heart failure [35, 36], and subclinical depressive symptoms are also correlated with an increased risk of stroke [37]. The biological variables that trigger this relationship are due to multiple alterations in neuroimmunoendocrine proteins in depressed patients, especially in the acute phase [38]. It is not clear how these factors interact with rtPA to affect functional ambulatory recovery in ischemic stroke patients with pre-stroke depression, and this is beyond the scope of the current study. However, ample evidence indicates that congestive heart failure may have a causal relationship with depression in stroke patients [39-42]. This is especially important since certain areas in the brain, including the medial temporal region, an area associated with the pathophysiology of depression, are particularly vulnerable to perfusion deficits which arise in the context of congestive heart failure [43, 44]. Clinically, our results indicate that congestive heart failure, antihypertensive medications, and previous TIA are important clinical risk factors that may affect the treatment outcomes of thrombolysis therapy and affect functional ambulatory recovery in ischemic stroke patients with pre-stroke depression. Our findings have practical implications and suggest the need for the development of an effective strategy to manage the combined effect of congestive heart failure, antihypertensive medications, and TIA in ischemic stroke patients with pre-stroke depression.

Our study has limitations. The retrospective nature of our data may indicate the possibility of selection bias. In addition, the absence of pre-stroke functional status data including pre-stroke mRS and post treatment NIHSS scores did not allow for the comparison of ambulatory recovery and NIHSS scores or mRS to be evaluated. Depression is a common post-stroke complication and pre-stroke depression is known to contribute to treatment outcome following thrombolysis therapy. An important contribution of the current study to existing literature is identification of specific clinical risk factors that are significantly associated with functional ambulatory outcome in ischemic stroke patient with incidence of pre-stroke depression who received thrombolysis therapy.

6. Conclusion

In this study, we have shown that few acute ischemic stroke patients with pre-stroke depression received rtPA, and more clinical risk factors were associated with   no improvement in functional outcome when compared with those that were associated an improvement in ambulation among ischemic stroke patients with a history of pre-stroke depression. Our findings reveal that congestive heart failure, antihypertensive medications, and previous TIA are significant clinical risk factors that may affect the treatment outcomes of thrombolysis therapy in ischemic stroke patients with a history of pre-stroke depression. Future studies should focus on effective strategies to manage these clinical risk factors to improve treatment outcomes of thrombolytic therapy in ischemic stroke patients with pre-stroke depression.

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