Journal of Experimental Stroke & Translational Medicine
JESTM

Clinical risk factors associated with functional outcomes of thrombolytic therapy in stroke and non-stroke units

August 30, 2017 · Volume 10 · Original Research

Meagan Reynolds, Brice Blum, Leanne Brechtel, Jordan Gainey and Thomas I Nathaniel*

University of South Carolina School of Medicine, SC, USA

Article Citation: Meagan Reynolds, Brice Blum, Leanne Brechtel, Jordan Gainey and Thomas I Nathaniel. Clinical risk factors associated with functional outcomes of thrombolytic therapy in stroke and non-stroke units. J Exp Stroke Transl Med. 2017 December. Online access at www.jestm.com

Correspondence should be sent to: Thomas I Nathaniel (Ph.D., FAHA), University of South Carolina, School of Medicine-Greenville, Greenville, SC 29605, USA, Tel: 8644559846, Fax: 8644558404, E-mail: nathanit@greenvillemed.sc.edu

Abstract

Background - The disparities in stroke care between specialized stroke units and non-stroke units have been reported. While most of the existing studies investigated how intrinsic characteristics of specific treatment units have impact on the outcomes, the influence of patients' characteristics on functional outcomes of recombinant tissue plasminogen activator-treated patients in specialized stroke units and non-stroke units is not fully understood.

Method- The demographic and clinical risk factors that significantly impact functional improvement outcomes in recombinant tissue plasminogen activator-treated acute ischemic stroke in the non-stroke unit and the specialized stroke unit were determined. Univariate analysis was used to determine improved functional differences, while adjusted multivariable models were used to determine the association between demographic and clinical variables on the functional outcome.

Results- In stroke patients that received recombinant tissue plasminogen activator in the specialized stroke unit and the non-stroke unit, a history of previous transient ischemic attack (OR_{adj}, 0.347, 95% CI (0.160, 0.752); p=0.007) and patients taking antiplatelet medications (OR_{adj}, 1.954, 95% CI (1.116, 3.421, p=0.019) were significantly associated with improved functional outcome. Patients with a history of carotid artery stenosis (OR_{adj}, 5.265, 95% CI (1.067, 2.977), p=0.041) and a history of transient ischemic attack (OR_{adj}, 0.295, 95% CI (0.100, 0.872), p=0.027) were significantly associated with improved functional outcome following treatment with recombinant tissue plasminogen activator in the specialized stroke unit. In the adjusted model analysis for the non-stroke unit, the major predictors of functional outcome were: the NIH stroke scale (OR_{adj}=1.381, 95% CI (1.086, 1.757), p=0.009), the risk of mortality (OR_{adj} =0.691, 95% CI (0.518, 0.922) p=0.012), female gender (OR_{adj}=0.306, 95% CI (0.120, 0.778), p=0.013), and race/ethnicity (OR_{adj}=0.285, 95% CI (0.084, 0.970), p=0.045).

Conclusion- After the adjusted analysis, the specialized stroke unit and non-stroke unit reveal significantly improved functional outcomes for patients treated with recombinant tissue plasminogen activator in few clinical variables. Values for functional outcomes were not significantly associated with most of the variables for treated patients in both the specialized stroke unit and non-stroke unit even after adjustment in the recombinant tissue plasminogen activator–treated stroke population.

Key Words: Acute ischemic stroke, recombinant tissue-type plasminogen activator, specialized stroke unit, non-stroke unit

Introduction

After many years of being the third leading cause of death in the United States, stroke has dropped to fifth (Mozzafarian et al., 2016). This success may in part be attributed to improved care within the first hours of acute stroke, including the use of thrombolytic therapy (Benjamin, 2017). Although recombinant tissue plasminogen activator (rtPA) continues to be the only Food and Drug Administration (FDA)approved drug treatment for acute ischemic stroke in 1996 (Chapman et al., 2014), the time-dependent nature of rtPA treatment presents a major challenge to improve its use in many healthcare systems. The development of a regional network of healthcare is one of the many attempts to increase the utilization of rtPA (Demaerschalk et al., 2016; Fugate et al., 2014; Tsivgoulis et al., 2015; Tsivgoulis et al., 2015; Zinkstok et al., 2013). Although the exact composition of the regional network system, the principles remain the same: emphasis on timeliness to improve the use of rtPA and stroke care. This is because stroke is considered a medical emergency (Tomio et al., 2017). The consideration of stroke as a medical emergency coupled with the approval of rtPA for stroke treatment prompted the establishment of SSU which have been shown to increase the number of ischemic stroke patients receiving thrombolysis as well as reduce the onset-to-treatment time compared to NSU (Stavem et al., 2011; Kunz et al., 2016).

The differences in components of stroke treatments between SSU and NSU have been reported to account for the observed treatment outcomes (Stavem et al., 2011; Tamm et al., 2014). For example, certain cultural characteristics of different hospital units, such as explicit goals, learning environment, leadership, and partnerships have a significant association with thrombolysis rates (Van Wijngaarden et al., 2009). It has been shown that 40% of physicians were unlikely to use rtPA for ischemic stroke under ideal conditions due to apprehension about risk of hemorrhage, whereas, the majority of neurologists specializing in stroke care believed the benefit of rtPA usually outweighed the risk of adverse effects (Chapman et al., 2014). This suggests that care from specialized physicians may contribute to thrombolysis efficacy and outcome (Eissa et al., 2012; Etgen et al., 2011; Fassbender et al., 2013). While most of the existing studies investigated how intrinsic characteristics of specific treatment units impact functional outcomes, few studies have addressed how clinical risk factors of stroke patients influence functional outcomes of thrombolytic therapy in SSU and NSU. Since the implementation of a stroke unit safely increased the percentage of patients with ischemic stroke receiving rtPA to approximately 90% (Etgen et al., 2011), it is possible that thrombolysis may be less beneficial for patients treated in

NSUs when compared with SSUs. One potential explanation could be that patient demographics and clinical risk factors associated with thrombolysis efficacy are not present in the same proportion in the SSU and NSU.

A prior study has suggested that patients' admission into stroke units or other wards may be based on their clinical risk factors. Moreover, higher risk patients may ignite physician fear toward intensive treatment risks; therefore, they receive more conservative care by remaining in the general wards (Bokhari et al., 2013). Collectively, the existing studies suggest that patient characteristics could have an impact on the perceived benefit of SSU. However, the specific influence of patient characteristics on functional outcomes of rtPA-treated stroke patients in SSU and NSU is not known. The objectives of this study are to analyze the demographic and clinical risk factors that significantly influence functional improvement of rtPA-treated stroke patients, and determine whether these risk factors are different between the NSU and SSU. Understanding the disparities in stroke care between NSU and SSU will contribute to the goal of developing effective stroke systems of care with the ability to deliver acute stroke care, both in the NSU and SSU.

Methods

Data collection

Between January 2010 and June 2016, a total of 1,446 stroke patients were identified. A total of 255 patients presented stroke treated in the SSU, while 136 were treated in the NSU, and comprised those that received rtPA versus those who did not (**Table 1**).
Retrospective data was collected from a registry for consecutive rtPA-treated acute ischemic stroke cases admitted for six years of SSU and NSU operations (January 2010-June 30, 2016). Ethical approval for the study was obtained from Greenville Health System Ethics Committee. The SSU has a universal care model where acute stroke patient are admitted directly from the emergency department to SSU from admission to discharge. The unit is well staffed with multidisciplinary teams coordinated by a stroke neurologist including a permanently assigned nursing practitioner. A stroke neurologist is physically present each day, and the rtPA protocol is well developed and used for stroke treatment. Medical information for admitted stroke patients is recorded in a database. Recorded information includes medical history, risk factors, descriptive variables, demographic details, and neurological evaluations. The SSU allowed 24/7 family access and facilities to support discharge and transition to the post-acute environment. In general, SSUs are well staffed by a multidisciplinary team with a special interest and expertise in stroke care, whereas any less organized form of care for acute stroke patients was considered the NSU, including rtPA treatment in the neurology unit.

Data analysis

Data analysis was performed in a stroke registry on patients that received rtPA in SSU and NSU. The ambulatory status of stroke patients was used as a tool to measure functional outcomes in both SSU and NSU. The inter-and intra-reliability and high validity of ambulation as an assessment tool for functional recovery in the mobility of stroke patients is well reported in the literature (Tsang et al., 2014; Park et al., 2016). All patients that did not have their ambulatory status defined at admission or discharge were excluded from the analysis. To compute functional ambulatory improvement, a new variable was defined from the existing data. If there was improvement from the time of admission to the time of discharge, a value of 1 was given, if there was no improvement, a value of 0 was given. This was used to build a model for improved functional outcomes for stroke patients that received rtPA. An initial set of variable selection was performed, where highly collinear variables and variables with missing values were removed. Thereafter, predictor variables for each logistic regression model were selected by stepwise regression and variables with $p<0.05$ remained in the model. All statistical analyses were performed using SPSS Statistics Software version 24.0 (Chicago, IL) and a $P<0.05$ was used to establish statistical significance in all comparisons between groups.

In the initial analysis, stroke patients that received rtPA were grouped into SSU and NSU groups. Each group was further subdivided by functional outcomes to examine differences in demographic and the clinical characteristics of stroke patients with improved or no improved functional outcomes. Comparisons in demographic and clinical variables for an improvement and no improvement in functional outcomes were performed using a two-tailed, independent samples Student's T-test for discrete variables, while a Pearson's Chi-Squared analysis was performed for categorical variables. Results were presented in **Table 1** as percentages or mean (±SD). A binary logistic regression was performed to examine the clinical factors that were associated with improved functional outcomes in SSU and NSU (**Table 2**). Age, gender and clinical variables were included in the regression models. Demographic and clinical variables associated with improved functional outcomes were analyzed and presented separately for SSU (**Table 3**) and NSU (**Table 4**).

Results

In the SSU, 51.7% were women, while 48.3% were men with improved functional outcomes. In the NSU, 63.2% were men, while 36.8% were women with improved functional outcome. These improvements were not significantly different in both units ($P>0.05$). Stroke patients with improved functional outcome were older in the SSU than the NSU (64.78 ± 15.0 vs 63.18 ± 16.3), but the difference was not significant ($P>0.05$). Several clinical variables including hypertension, coronary artery disease, dyslipidemia, atrial fibrillation, previous stroke and trans ischemic attack (TIA), congestive heart failure, carotid stenosis, peripheral vascular disease, smoking history and diabetes were not significantly different in both the SSU and NSU ($P>0.05$). Moreover, history of medication including antiplatelet, antihypertension, cholesterol reducer, diabetic medication and initial NIH scores prior to treatment with rtPA were not significantly different in both the SSU and NSU ($P>0.05$). The risk of mortality, weakness and BMI were not significantly different between the SSU and NSU ($P>0.05$). In addition, functional outcomes associated with altered level of consciousness and language disorder were not different in the NSU. However, there was a significant difference in improved functional outcomes in the altered level of consciousness for patients treated with rtPA in the SSU ($P<0.05$). An improved functional outcome in language disorder was significantly ($P<0.05$) higher in the SSU.

Following an adjustment to account for the confounding variables (age and gender), the significant effect of both language disorder and altered level of consciousness that were associated with functional outcomes in univariate analysis disappeared. Table 2 reveals two clinical risk factors that were significantly associated with the functional outcome; a history of previous TIA (ORadj, 0.347, 95% CI (0.160, 0.752); p=0.007) and patients taking antiplatelet medications (ORadj, 1.954, 95% CI (1.116, 3.421, p=0.019). Further analysis sorted by their respective treatment locations reveals that history of carotid artery stenosis (ORadj, 5.265, 95% CI (1.067, 2.977), p=0.041) and a history of TIA (ORadj, 0.295, 95% CI (0.100, 0.872), p=0.027) were significantly associated with functional outcomes following treatment with rtPA in the SSU (Table 3). In the adjusted analysis for the NSU (**Table 4**), the major predictors of functional outcomes were: the NIH stroke scale (ORadj =1.381, 95% CI (1.086,1.757), p=0.009), the risk of mortality (ORadj =0.691, 95% CI (0.518, 0.922) p=0.012), female gender (ORadj =0.306, 95% CI (0.120,0.778), p=0.013), and race/ethnicity (ORadj =0.285, 95% CI (0.084, 0.970), p=0.045).

	Specialized Stroke Unit (SSU)			Non-Specialized Stroke Unit (NSU)		
	Not Improved	Improved	p-value	Not Improved	Improved	p-value
Number of Patients	139	116		79	57	
Age Group: No. (%)	20 (14.4)	19 (16.4)		11 (13.9)	10 (17.5)	
<50 years	21 (15.1)	23 (19.8)		19 (24.1)	15 (26.3)	
50-59	40 (28.8)	24 (20.7)	0.172	16 (20.3)	11 (19.3)	0.96
60-69	24 (17.3)	30 (25.9)		13 (16.5)	9 (15.8)	
70-79	34 (24.5)	20 (17.2)		20 (25.3)	12 (21.1)	
>80 years						
Mean ± SD	66.99 ± 13.7	64.78 ± 15.0	0.226	66.03 ± 15.4	63.18 ± 16.3	0.304
Race: No. (%)	111 (79.9)	90 (77.6)		63 (79.7)	50 (87.7)	
Caucasian	27 (19.4)	25 (21.6)	0.198	15 (19.0)	7 (12.3)	0.388
African-American	1 (0.7)	1 (0.9)		1 (1.3)	0 (0.0)	
Other						
Gender: No. (%)	60 (43.2)	60 (51.7)		43 (54.4)	36 (63.2)	
Male	79 (56.8)	56 (48.3)	0.173	36 (45.6)	21 (36.8)	0.309
Female						
Medical History: No. (%)	112 (80.6)	94 (81.0)	0.926	63 (79.7)	43 (75.4)	0.55
Hypertension	42 (30.2)	35(30.2)	0.994	27 (34.2)	12 (21.1)	0.095
Coronary Artery Disease	74 (53.2)	63 (54.3)	0.864	41 (51.9)	26 (45.6)	0.469
Dyslipidemia	25 (18.0)	15 (12.9)	0.269	14 (17.7)	10 (17.5)	0.979
Atrial Fib/Flutter	30 (21.6)	28 (24.1)	0.628	14 (17.7)	11 (19.3)	0.815
Previous Stroke	17 (12.2)	7 (6.0)	0.092	14 (17.7)	7 (12.3)	0.386
Previous TIA	17 (12.2)	7 (6.0)	0.092	8 (10.1)	3 (5.3)	0.305
Congestive Heart Failure	4 (2.9)	8 (6.9)	0.131	2 (2.5)	3 (5.3)	0.404
Carotid Artery Stenosis	7 (5.0)	6 (5.2)	0.961	6 (7.6)	6 (10.5)	0.552
Peripheral Vascular Disease	33 (23.7)	36 (31.0)	0.192	29 (36.7)	24 (42.1)	0.524
History of Smoking	44 (31.7)	33 (28.4)	0.579	25 (31.6)	12 (21.1)	0.171
Diabetes						
Medication History: No. (%)	62 (44.6)	60 (51.7)	0.257	39 (49.4)	31 (54.4)	0.563
Antiplatelet	107 (77.0)	84 (72.4)	0.403	59 (74.7)	37 (64.9)	0.217
Antihypertension	71 (51.1)	59 (50.9)	0.972	34 (43.0)	23 (40.4)	0.754
Cholesterol Reducer	39 (28.1)	24 (20.7)	0.174	20 (25.3)	13 (22.8)	0.736
Diabetes Medication						
Initial NIH Stroke Scale	71 (51.1)	51 (44.0)		53 (67.1)	32 (56.1)	
Group: No. (%)	28 (20.1)	22 (19.0)		10 (12.7)	8 (14.0)	
0-9	19 (13.7)	24 (20.7)	0.453	7 (8.9)	9 (15.8)	0.528
10-14	21 (15.1)	19 (16.4)		9 (11.4)	8 (14.0)	
15-20						
21-25						
Mean ± SD	10.53 ± 7.1	11.92 ± 6.7	0.108	8.66 ± 6.7	10.19 ± 6.7	0.191
Initial Exam Findings: No. (%)	130 (93.5)	111 (95.7)	0.45	68 (86.1)	53 (93.0)	0.205
Weakness/Paresis	40 (28.8)	49 (42.2)	0.025*	26 (32.9)	25 (43.9)	0.193
Altered Level of Consciousness	95 (68.3)	93 (80.2)	0.033*	59 (74.7)	44 (77.2)	0.736
Aphasia/Language Disturbance						
Risk of Mortality GWTG	6.42 ± 6.7	6.73 ± 6.1	0.108	5.54 ± 6.5	5.57 ± 5.1	0.965

Ischemic Stroke:						
Mean ± SD						
Body Mass Index	29.13 ± 7.0	28.80 ± 7.2	0.718	27.71 ± 5.9	28.59 ± 7.0	0.445
Mean ± SD						
Note: Chi-Square test, p<0.05 as significant at 95% CI Student T-test, p<0.05 as significant at 95% CI						

Table 1: Baseline characteristics of demographic and clinical variables (n = 391)

	B Value	**Wald**	**Odds Ratio**	**95% C.I.**	**For OR**	**P Value**
				Lower	**Upper**	
Age	-0.01	0.915	0.99	0.97	1.011	0.339
BMI	0.006	0.107	1.006	0.971	1.042	0.744
NIH Stroke Scale	0.069	2.334	1.072	0.981	1.171	0.127
Presentation of weakness	0.451	0.907	1.57	0.62	3.974	0.341
Altered level of consciousness	0.535	3.079	1.708	0.939	3.105	0.079
Aphasia/Language disturbance	0.308	1.06	1.36	0.757	2.443	0.303
Risk of Mortality GWTG	-0.072	2.127	0.931	0.845	1.025	0.145
Gender	-0.427	3.145	0.653	0.407	1.046	0.076
Race	-0.211	0.587	0.81	0.472	1.39	0.444
Atrial Fibrillation	0.013	0.001	1.013	0.49	2.095	0.973
Coronary Artery Disease	-0.232	0.673	0.793	0.456	1.379	0.412
Carotid Artery Stenosis	1.124	3.224	3.077	0.902	10.496	0.073
Diabetes	0.052	0.01	1.053	0.387	2.868	0.92
Dyslipidemia	-0.027	0.008	0.974	0.546	1.738	0.928
Congestive Heart Failure	-0.813	3.547	0.444	0.19	1.034	0.06
Hypertension	0.55	1.62	1.733	0.743	4.041	0.203
Previous Stroke	-0.27	0.842	0.763	0.429	1.359	0.359
Previous TIA	-1.059	7.199	0.347	0.16	0.752	0.007*
Peripheral Vascular Disease	0.62	1.627	1.859	0.717	4.817	0.202
History of Smoking	0.24	0.737	1.271	0.735	2.2	0.391
Antiplatelet medication	0.67	5.494	1.954	1.116	3.421	0.019*
Antihypertensive medication	-0.606	2.236	0.546	0.247	1.207	0.135
Cholesterol Reducer	-0.149	0.212	0.861	0.457	1.624	0.645
Antidiabetic medication	-0.35	0.431	0.705	0.248	2.002	0.511
Treatment in SSU	0.2	0.665	1.221	0.755	1.976	0.415
Note: Stepwise Regression model was applied Model assumptions were fulfilled Multicollinearity and interactions among independent variables were checked and found. Hosmer-Lemeshow test (P=0.605), Classification table (overall correctly classified percentage = 64.9%) and area under the ROC curve (AUC=0.694) were applied to check the model fitness						

Table 2: Clinical risk factors associated with the functional outcomes in the specialized stroke and non-specialize stroke units (n=391)

	B Value	Wald	Odds Ratio	95% C.I.	For OI	P Value
				Lower	Upper	
Age	-0.007	0.284	0.993	0.967	1.019	0.594
BMI	0.003	0.024	1.003	0.962	1.047	0.877
NIH Stroke Scale	0.04	0.551	1.04	0.937	1.155	0.458
Presentation of weakness	0.288	0.186	1.334	0.36	4.945	0.667
Altered level of consciousness	0.489	1.702	1.631	0.782	3.399	0.192
Aphasia/Language disturbance	0.393	1.106	1.482	0.712	3.083	0.293
Risk of Mortality GWTG	-0.041	0.521	0.96	0.86	1.072	0.471
Gender	-0.166	0.307	0.847	0.47	1.526	0.58
Race	0.096	0.083	1.1	0.573	2.112	0.774
Atrial Fibrillation	-0.276	0.343	0.759	0.301	1.913	0.558
Coronary Artery Disease	0.209	0.33	1.232	0.605	2.509	0.566
Carotid Artery Stenosis	1.661	4.16	5.265	1.067	25.977	0.041*
Diabetes	0.75	1.333	2.116	0.593	7.556	0.248
Dyslipidemia	-0.004	0	0.996	0.472	2.102	0.992
Congestive Heart Failure	-0.886	2.505	0.412	0.137	1.235	0.114
Hypertension	0.328	0.243	1.388	0.377	5.117	0.622
Previous Stroke	-0.313	0.723	0.732	0.356	1.504	0.395
Previous TIA	-1.221	4.868	0.295	0.1	0.872	0.027*
Peripheral Vascular Disease	0.222	0.11	1.248	0.336	4.638	0.741
History of Smoking	0.42	1.353	1.521	0.75	3.085	0.245
Antiplatelet medication	0.474	1.896	1.607	0.818	3.157	0.169
Antihypertension Medication	-0.205	0.106	0.815	0.237	2.798	0.745
Cholesterol Reducer	-0.218	0.286	0.804	0.362	1.787	0.593
Antidiabetic medication	-1.147	2.85	0.318	0.084	1.203	0.091

Note:
Stepwise Regression model was applied
Model assumptions were fulfilled.
Multicollinearity and interactions among independent variables were checked and found.
Hosmer-Lemeshow test (P=0.452), Classification table (overall correctly classified percentage =64.2%) and area under the ROC curve (AUC=0.698) were applied to check the model fitness.

Table 3. Clinical risk factors associated with the functional outcomes in the specialized stroke (n=255)

	B Value	Wald	Odds Ratio	95% C.I.	For OI	P Value
				Lower	Upper	
Age	-0.007	0.102	0.993	0.954	1.034	0.749
BMI	0.045	1.327	1.046	0.969	1.13	0.249
NIH Stroke Scale	0.323	6.924	1.381	1.086	1.757	0.009*
Presentation of weakness	0.998	1.685	2.714	0.601	12.258	0.194

Altered level of consciousness	0.926	2.121	2.525	0.726	8.784	0.145
Aphasia/Language disturbance	-0.311	0.213	0.733	0.196	2.742	0.645
Risk of Mortality GWTG	-0.369	6.322	0.691	0.518	0.922	0.012*
Gender	-1.186	6.18	0.306	0.12	0.778	0.013*
Race	-1.254	4.033	0.285	0.084	0.97	0.045*
Atrial Fibrillation	1.228	2.687	3.414	0.786	14.825	0.101
Coronary Artery Disease	-0.883	2.518	0.414	0.139	1.231	0.113
Carotid Artery Stenosis	0.596	0.285	1.814	0.204	16.148	0.593
Dyslipidemia	0.198	0.119	1.219	0.396	3.746	0.73
Congestive Heart Failure	-1.117	1.503	0.327	0.055	1.952	0.22
Hypertension	0.378	0.257	1.459	0.339	6.289	0.612
Previous Stroke	-0.465	0.568	0.628	0.187	2.107	0.451
Previous TIA	-0.695	0.96	0.499	0.124	2.004	0.327
Peripheral Vascular Disease	1.376	2.872	3.957	0.806	19.42	0.09
History of Smoking	-0.441	0.559	0.644	0.203	2.044	0.455
Antiplatelet medication	1.064	2.985	2.898	0.867	9.687	0.084
Antihypertensive medication	-1.179	2.973	0.308	0.08	1.175	0.085
Cholesterol Reducer	-0.695	1.055	0.499	0.132	1.88	0.304
Note: Stepwise Regression model was applied Model assumptions are fulfilled. Multicollinearity and interactions among independent variables were checked and found. Hosmer-Lemeshow test (P=0.112), Classification table (overall correctly classified percentage=70.7%) and area under the ROC curve (AUC=0.795) were applied to check the model fitness						

Table 4. Clinical risk factors associated with the functional outcomes in the specialized stroke (n=136)

Discussion

The establishment of SSU and specific therapy such as rtPA for the management and treatment of stroke highlights the importance of stroke as a medical emergency (Dawson et al.,2006; Lott et al., 1999). The benefits of SSU in the care of stroke patients have been demonstrated in terms of reduction in mortality and in long institutionalization (Langhorne, 2013). Moreover, a better functional outcome of SSU when compared with NSU has been assessed in terms of efficacy of a reduction in length of stay, complications and acute care costs (Langhorne, 2013; Iwamoto et al., 2015; Langhorne et al., 2013). With these data, the conclusion is that SSUs, not NSUs, are the most effective organizational models for acute stroke treatment and management (Langhorne, 2013; Fuentes et al., 2009; Govan et al.,2007; Langhorne et al., 2012). In general, SSUs make an enormous difference in the care of stroke patients.

Since patients' clinical characteristics could have different impacts on rtPA treatment irrespective of whether stroke patients receive rtPA in the SSU or NSU, this study investigated the effect of demographic and clinical risk factors on rtPA-treated stroke patients and improved functional outcomes in the NSU and the SSU. Functional outcomes after stroke treatment is generally assessed using different variables including mRS or the Barthel Index (BI) (Shih et al., 2009; Kasner, 2006; Lees et al., 2012). The current study used quantified functional ambulation based on the performance or activities of daily living, such as mobility to determine improved functional outcomes in rtPA-treated stroke patients. This approach allowed us to quantify the improvement in the primary functional status associated with specific risk factors in the treatment of stroke patients and compared the resulting improved functional outcomes between SSU and NSU.

In unadjusted analyses, several variables were not significantly associated with improved functional outcomes in rtPA treated patients in SSU and NSU including hypertension, coronary artery disease, dyslipidemia, atrial fibrillation, previous stroke and TIA, congestive heart failure, carotid stenosis, peripheral vascular disease, smoking history, and diabetes. Moreover, there was no significant association between any of the variables in patients that received rtPA in the NSU. Apart from altered level of consciousness and language disorder, all other variables were not significantly associated with improved functional outcomes in the SSU. After adjustment for the confounding effect of comorbidities in stroke population that received rtPA in both SSU and NSU, previous history of TIA and antiplatelet medications were significantly associated with improved functional outcome. This result indicates that risk evaluation in the secondary prevention in patients with a history of TIA (Kernan, 2015) and patients taking antiplatelet agents are more likely to attain a good functional outcome (Sanossian et al., 2006). This finding suggests that the care for complications of this type is one of the main predictors of improved functional outcome after treatment with rtPA.

In the SSU stroke population, patients with a history of previous TIA and carotid artery stenosis were associated with improved functional outcome in the adjusted analysis. Patients with a history of a prior TIA have an increased risk of recurrent stroke, and it is likely that patients undergo secondary prevention measures at the SSU which lower their risk of severe strokes (Kernan, 2015). In this context, the prior evaluation

of TIA etiology in the SSU could assist in determining the causal factor of the current acute ischemic stroke leading to more directed treatment (Al-Khaled et al., 2013) and improved functional outcomes following treatment with rtPA. Patients at risk of carotid artery diseases often undergo screening tests such as Doppler ultrasound and confirmatory tests such as computerized tomography angiography (CTA) or magnetic resonance angiography (MRA). This allows for identification of patients with a high risk of stroke due to carotid artery stenosis (Lanzino et al., 2010). The physicians in SSU are more likely to locate the stroke area and this may help in rtPA decision making. The presence of carotid artery stenosis in stroke patients may be associated with improved functional outcomes in SSU because they are likely to receive more focused care and more interventional treatment from the multidisciplinary healthcare professionals (Lin et al., 2017). Despite the association of functional outcomes with carotid artery stenosis and history of previous TIA in the SSU, the effect of clinical variables on rtPA treatment outcomes could not be linked to the functional situation in most of the variables after the adjusted analysis. Moreover, descriptions of poorer functional outcomes for patients in the SSU have also been reported by other studies (Iwamoto et al., 2015).

In the adjusted analysis for NSU stroke patients treated with rtPA, NIH stroke scale, risk of mortality-GWTG, gender, and race were all significantly associated with improved functional outcomes. In general, NIHSS scores >15 have less than a 20% chance of achieving an excellent outcome, while approximately 90% of patients with a score of 4 to 6 have a good or excellent outcome (Adams et al., 1999). It is possible that most patients with high NIHSS scores are admitted to SSU. Moreover, most patients in NSU likely have low NIHSS scores, and the adjusted analysis removed the effect of confounding variables such that NIH scores reveal less severe strokes and a higher chance of improvement in the NSU. The finding that patients with a low risk of mortality are more likely to have improved functional outcomes in NSU is supported by another study (Smith et al., 2012). The Get-With-The-Guidelines (GWTG) stroke prediction tool's reliability has been validated in a nationwide study of ischemic stroke patients, and it helps to identify patients who may require more intensive resources (Smith et al., 2010). There is a possibility that patients with higher risk of mortality may have a higher chance of being admitted to the SSU rather than NSU; thus, the number of patients with a high risk of mortality remains low in NSU.

An important finding in this study is the significant association of racial disparity with functional outcome in treated patients in the NSU. Such an effect disappeared in the adjustment analysis for the SSU, indicating that the improved care in rtPA for diverse stroke patients significantly improves their functional status following recovery. The impact of gender on stroke outcome is well documented in the literature. The effect of gender, which disappeared in univariate analysis, was significant in the NSU treated patients such that rtPA-treated male stroke patients were significantly associated with functional recovery. In an untreated acute ischemic stroke population, women have a worse outcome than men (Niewada et al., 2005; Eriksson et al., 2008). In contrast, there is no significant difference in treated patients with rtPA, suggesting a better treatment outcome for women. The finding that male stroke patients treated with rtPA were significantly associated with improved functional outcomes in the NSU reveals the beneficial impact of the thrombolytic for men with stroke in the NSU. It is also possible that the incidence of stroke in the male population treated with thrombolysis is not present in the same proportions among women and men population of stroke patients in the NSU. The observed demographic differences in clinical risk factors between SSU and NSU in the current study of rtPA treated acute ischemic stroke patients have not been observed in prior studies.

In the adjusted analysis, the SSU and NSU reveal significantly improved functional outcomes for patients treated with rtPA associated with few different clinical variables. The observed differences in clinical variables associated with functional outcomes could not be attributed to patients' clinical variables of stroke severity at admission alone. This is because values of functional outcomes were not significant for patients in both the SSU and NSU for most of the variables. This finding indicates that the proportions of stroke patients with complicated comorbidities in the NSU and SSU is important in the evaluation of functional outcome at the population level.

Based on the results of this study, it is difficult to determine why patients in the NSU or SSU present significant improved functional outcomes for few specific risk factors, and with no significant difference for many variables. Several factors appear to link stroke care in the SSU to early stroke neurologist care and management of factors that could result in poor outcome from rtPA treatment or complications (Shinohara et al., 2011; Foley et al., 2007) suggesting that increased experience would have contributed to the improved functional care in both units. Moreover, better communication with non-hospital services resulting in earlier care for stroke and proximity to stroke is important for stroke care (Askim et al., 2010). These factors seem to have significant effects on rtPA-treated functional outcome for stroke patients, mainly due to care they receive irrespective of the units of treatment.

Conclusion

Many limitations must be considered before interpreting the findings of this study. This is a single institution study; therefore, there is a tendency for selection bias that could have affected the selection of patients. Moreover, the effect of neurology or stroke consults that may have occurred in the NSU is unknown. Factors contributing to physician decisions to admit patients to certain areas are also unknown. In the data analysis, some patients had to be excluded due to their ambulatory status not being defined at admission or discharge. The strengths of this study stem from the fact that the database used covers six years of patient treatment. A major contribution of this study to literature on specialized stroke units is the characterization of the impact of clinical risk factors on functional outcomes in SSU and NSU in rtPA-treated stroke patients.

References

1. Mozzafarian D, Benjamin E, Go A, Arnett D, Blaha M, et al. (2016) American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2016 update: a report from the American Heart Association. Circulation 133(4): 38–360.
2. Benjamin (2017) Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation 135(10): 146-603.
3. Chapman S, Mehndiratta P, Johansen M, McMurray T, Johnston K, et al. (2014) Current Perspectives on the use of intravenous recombinant tissue plasminogen activator (tPA) for treatment of acute ischemic stroke. Vascular Health and Risk Management 10: 75-87.
4. Demaerschalk BM, Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, et al. (2016) Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 47(2): 581-641.
5. Fugate JE, Rabinstein AA (2014) Update on Intravenous Recombinant Tissue Plasminogen Activator for Acute Ischemic Stroke. Mayo Clinic Proceedings 89(7): 960-972.
6. Tsivgoulis G, Safouris A, Alexandrov AV (2015) Safety of intravenous thrombolysis for acute ischemic stroke in specific conditions. Expert Opinion on Drug Safety 14(6): 845-864.
7. Tsivgoulis G, Zand R, Katsanos AH, Goyal N, Uchino K, et al. (2015) Safety of Intravenous Thrombolysis in Stroke Mimics Prospective 5-Year Study and Comprehensive Meta-Analysis. Stroke 46(5): 1281-1287.
8. Zinkstok SM, Engelter ST, Gensicke H, Lyrer PA, Ringleb PA, et al. (2013) Safety of Thrombolysis in Stroke Mimics Results From a

Multicenter Cohort Study. Stroke 44(4): 1080-+.
9. Tomio J, Nakahara S, Takahashi H, Ichikawa M, Nishida M, et al. (2017) Effectiveness of Prehospital Epinephrine Administration in Improving Long-term Outcomes of Witnessed Out-of-hospital Cardiac Arrest Patients with Initial Non-shockable Rhythms. Prehospital Emergency Care 21(4): 432-441.
10. Stavem K, Ronning OM (2011) Survival over 12 years following acute stroke: initial treatment in a stroke unit vs general medical wards. Acta neurologica Scandinavica 124(6): 429-433.
11. Kunz A, Ebinger M, Geisler F, Rozanski M, Waldschmidt C, et al. (2016) Functional outcomes of pre-hospital thrombolysis in a mobile stroke treatment unit compared with conventional care: an observational registry study. Lancet Neurology 15(10): 1035-1043.
12. Tamm A, Siddiqui M, Shuaib A, Butcher K, Jassal R, et al. (2014) Impact of Stroke Care Unit on Patient Outcomes in a Community Hospital. Stroke 45(1): 211-216.
13. Van Wijngaarden JDH, Dirks M, Huijsman R, Niessen LW, Fabbricotti IN, et al. (2009) Hospital Rates of Thrombolysis for Acute Ischemic Stroke The Influence of Organizational Culture. Stroke 40(10): 3390-3392.
14. Eissa A, Krass I, Bajorek BV (2012) Optimizing the management of acute ischaemic stroke: a review of the utilization of intravenous recombinant tissue plasminogen activator (tPA). Journal of Clinical Pharmacy and Therapeutics 37(6): 620-629.
15. Etgen T, Freudenberger T, Schwahn M, Rieder G, Sander D (2011) Multimodal strategy in the successful implementation of a stroke unit in a community hospital. Acta neurologica Scandinavica 123(6): 390-395.
16. Fassbender K, Balucani C, Walter S, Levine SR, Haass A, et al. (2013) Streamlining of prehospital stroke management: the golden hour. Lancet Neurology 12(6): 585-596.
17. Bokhari F, Wellwood I, Rudd A, Langhorne P, Dennis M, et al. (2013) Selective admission into stroke unit and patient outcomes: a tale of four cities. Health Economics Review 4:1-10.
18. Tsang RCC, Chau RMW, Cheuk THW, Cheung BSP, Fung DMY, et al. (2014) The measurement properties of modified Rivermead mobility index and modified functional ambulation classification as outcome measures for Chinese stroke patients. Physiotherapy Theory and Practice 30(5): 353-359.
19. Park C, Heon S (2016) Reliability and validity of the modified functional ambulation category scale in patients with hemiparalysis. J Phys Ther Sci 28(8): 2264–2267.
20. Dawson J, Walters M, Lees KR (2006) 21st century stroke - A medical emergency. Scottish Medical Journal 51(3): 34-41.
21. Lott C, Hennes HJ, Dick W (1999) Stroke - a medical emergency. Journal of Accident & Emergency Medicine 16(1): 2-7.
22. Langhorne P (2013) Stroke Unit Trialists C. Organised inpatient (stroke unit) care for stroke. Cochrane Database of Systematic Reviews 9: 1-
23. Iwamoto T, Hashimoto H, Horiguchi H, Yasunaga H (2015) Effectiveness of Hospital Functions for Acute Ischemic Stroke Treatment on In-Hospital Mortality: Results From a Nationwide Survey in Japan. Journal of Epidemiology 25(8): 522-528.
24. Langhorne P, Fearon P, Ronning OM, Kaste M, Palomaki H, et al. (2013) Stroke Unit Care Benefits Patients With Intracerebral Hemorrhage Systematic Review and Meta-analysis. Stroke 44(11): 3044-3049.
25. Fuentes B, Diez-Tejedor E (2009) Stroke units: many questions, some answers. International Journal of Stroke 4(1): 28-37.
26. Govan L, Langhorne P, Dennis M, Hankey G, Weir C, et al. (2007) Organised inpatient (stroke unit) care for stroke. Cochrane Database of Systematic Reviews 4: 2-67.
27. Langhorne P, de Villiers L, Pandian JD (2012) Applicability of stroke-unit care to low-income and middle-income countries. Lancet Neurology 11(4): 341-348.
28. Shih MM, Rogers JC, Skidmore ER, Irrgang JJ, Holm MB (2009) Measuring Stroke Survivors' Functional Status Independence: Five Perspectives. American Journal of Occupational Therapy 63(5): 600-608.
29. Kasner SE (2006) Clinical interpretation and use of stroke scales. Lancet Neurology 5(7): 603-612.
30. Lees KR, Bath PMW, Schellinger PD, Kerr DM, Fulton R, et al. (2012) Contemporary Outcome Measures in Acute Stroke Research Choice of Primary Outcome Measure. Stroke 43(4): 1163-U451.
31. Kernan WN (2015) Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association (vol 45, pg 2160, 2014). Stroke 46(2): 1-96.
32. Sanossian N, Saver JL, Rajajee V, Selco SL, Kim D, et al. (2006) Premorbid antiplatelet use and ischemic stroke outcomes. Neurology 66(3): 319-323.
33. Al-Khaled M, Matthis C, Eggers J (2013) The prognostic impact of the stroke unit care versus conventional care in treatment of patients with transient ischemic attack: a prospective population-based German study. J Vasc Interv Neurol 13(5):22-25.
34. Lanzino G, Tallarita T, Rabinstein A (2010) Internal carotid artery stenosis: natural history and management. Semin Neurol 30(5): 518-527.
35. Lin CM, Su JC, Chang YJ, Liu CK, Lu HHS, et al. (2017) Is carotid sonography a useful tool for predicting functional capabilities in ischemic stroke patients following carotid artery stenting? Medicine 96(12): 1-7.
36. Adams HP, Davis PH, Leira EC, Chang KC, Bendixen BH, et al. (1999) Baseline NIH Stroke Scale score strongly predicts outcome after stroke - A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Neurology 53(1): 126-131.
37. Smith EE, Von Kummer R (2012) Door-to-needle times in acute ischemic stroke How low can we go? Neurology 79(4): 296-297.
38. Smith EE, Shobha N, Dai D, Olson DM, Reeves MJ, et al. (2010) Risk Score for In-Hospital Ischemic Stroke Mortality Derived and Validated Within the Get With The Guidelines-Stroke Program. Circulation 122(15): 1496-1504.
39. Niewada M, Kobayashi A, Sandercock PAG, Kaminski B, Czlonkowska A, et al. (2005) Influence of gender on baseline features and clinical outcomes among 17,370 patients with confirmed ischaemic stroke in the International Stroke Trial. Neuroepidemiology 24(3): 123-128.
40. Eriksson M, Norrving B, Terent A, Stegmayr B (2008) Functional outcome 3 months after stroke predicts long-term survival. Cerebrovascular Diseases 25(5): 423-429.
41. Shinohara Y, Yanagihara T, Abe K, Yoshimine T, Fujinaka T, et al. (2011) Stroke in general. Journal of Stroke & Cerebrovascular Diseases 20(4): S7-S30.
42. Foley N, Salter K, Teasell R (2007) Specialized stroke services: A meta-analysis comparing three models of care. Cerebrovascular Diseases 23(2-3): 194-202.
43. Askim T, Morkved S, Engen A, Roos K, Aas T, et al. (2010) Effects of a Community-Based Intensive Motor Training Program Combined With Early Supported Discharge After Treatment in a Comprehensive Stroke Unit A Randomized, Controlled Trial. Stroke 41(8):1697-1703.