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FACTORS INFLUENCING SEVERITY IN ACUTE ISCHEMIC STROKES

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ABSTRACT:

Background: Stroke severity is one of the factors that determines stroke related disability. We explored possible associations between stroke severity and commonly evaluated clinical parameters of stroke patients.

Objective: To determine the relationships between clinical features including routine in- hospital investigations done in first 24 hours of admission and variations in the stroke severity.

Patients and Methods: This was a retrospective, analytical study performed in the Department of Neurology at Shifa International Hospital, Shifa Tameer-e-Millat University, Islamabad, Pakistan. Adult patients admitted with ischemic stroke, over a period of 39 months, with Middle Cerebral Artery infarctions, were included. National Institute of Heath Stroke Scale (NIHSS) score was taken as a measure of stroke severity. The pertinent information was filled in a predesigned data sheet, and analyzed using SPSS version 20.0.

Results: A total of 207 patients were included in the study. The highest stroke severity was found in old age ([>64 years]), and patients with cardio embolic and unclassified (> one etiology) strokes, while the lowest severity was found in small artery occlusion strokes. Higher fasting serum triglyceride levels were associated with lower stroke severity and vice versa ([P=.002]). Among supra aortic large artery atherosclerosis the pre-stroke anti-platelet ([52 %]) and beta blocker use ([53.6 %]) was significantly associated with lower stroke severity. In cardio embolic strokes active smoking was associated with increased severity ([90%]).

Conclusion: Stroke severity is not only related to stroke etiology, but also, age, fasting serum triglyceride levels, active smoking and pre-stroke medications may also play significant roles. Nevertheless, further studies are required with prospective design, to confirm our findings.

Key words: infarction; middle cerebral artery; lacunar; hypertriglyceridemia; stroke severity; NIHSS score; atherosclerosis.

INTRODUCTION: Acute ischemic stroke is considered as one of the most common fatal diseases, in our times.[1] Those who survive strokes, suffer from their undesirable outcomes that include the subsequent long-term or sometimes life-long disability [1] which constitutes a significant burden on patients' personal well-being and on the care givers as well. Stroke severity is one of the factors associated with disability [2.] Stroke severity can be assessed and measured by clinical examination. There are many scoring systems that quantify or measure stroke severity. One of these is National Institute of Health Stroke Scale (NIHSS), which is a validated and a widely used scoring system for this purpose.[3] Currently, acute thrombolysis, revascularization, prophylaxis (preventing first or further strokes) and rehabilitation are the main domains of stroke therapy. We believe that identifying reversible factors that may play a role in reducing stroke severity may give us clues to look for novel neuroprotection and possibly disease modifying strategies. We designed our research work as an exploratory study, aiming to observe relationships between the clinical, laboratory and radiological features, and stroke severity among ischemic stroke patients. We identified clinical characteristics that are usually evaluated for nearly all hospitalized patients suffering ischemic stroke, and analyzed them for any significant relationship with stroke severity as measured by NIHSS. Given possibility of confounding factors and limitations of NIHSS we restricted our study only for ischemic strokes in middle cerebral artery ([MCA]) distribution.

METHODS:

This study was designed as an exploratory retrospective cross sectional survey. It was carried out in the department of Neurology, at Shifa International Hospital, Islamabad, Pakistan which is one of the largest tertiary care hospitals in the capital city. The research protocol was approved by the Institutional Review Board of the same hospital. Only adult patients ([18 years and above]) admitted in the neurology service, with the diagnosis of acute Middle Cerebral Artery (MCA) ischemic stroke (territorial or lacunar infarcts in MCA distribution), within three days of onset of ischemic symptoms over a period of 39 months ([September 2009 to November 2012]) were considered. During the study period Intravenous tissue plasminogen activator, acute endovascular intervention, were not available in our hospital, therefore none of the patients received acute thrombolytic therapy. Patients with posterior circulation ischemia, having history of previous stroke, and those suffering from any disabling neurological disease other than stroke were excluded as the patients with previous strokes, and having a baseline neurological deficit may have a more severe deficit, because of the recurrent stroke, which may not be related to the more acute laboratory findings that we measured. The file records of selected patients were extracted and relevant clinical information pertaining to first 24 hours of hospital admissions was obtained. The laboratory values were taken from Hospital Information System (HIS), and radiological data was reviewed from Picture Archiving and Communication System ([PACS]) of the hospital. For etiological classification of stroke the online Causative Classification of Ischemic Stroke ([CSS]) System was used [4]. The information thus obtained was entered in a predesigned data sheet. At the completion of the data collection all the data was entered in SPSS 20. All the case histories, laboratory data in first 24 hours of admission, and radiological information was reviewed and analyzed by a consultant neurologist and statisticians.

Operational definitions:

1. Acute MCA ischemic stroke: An acute event that was diagnosed by the attending neurologist as ischemic stroke ([with or without hemorrhagic conversion]) and corresponds to areas supplied by middle cerebral artery and/ or its smaller perforator branches which was further radiologically confirmed by MRI ([DWI/ ADC sequences]) or CT scans.

2. Co- morbid hypertension: The file records showed that the patient was known to be hypertensive and he was on regular anti-hypertensive therapy, or was found to have a blood pressure of 160 mmHg / 90 mmHg or more on admission, that was not considered by the attending physician as transient rise due to cerebral compensating mechanisms.

3. Co- morbid diabetes: The file records showed that the patient was known to be diabetic and he/ she was taking regular anti diabetic medications, or his HbA1c was 6.5 % or more.

4. Co – morbid Ischemic heart disease and chronic renal failure: The patient was labelled to have above mentioned co-morbid conditions in the file records, diagnosed on the basis of clinical, electrocardiographic, biochemical, echocardiographic and ultra-sonographic investigations.

Categories by stroke etiology / stroke type:

We utilized the online software, CCS ([which is derived from TOAST classification]) to determine the stroke type by its etiology. [4] However we made some modifications in this classification system, so that statistical analyses were possible as some of the categories had very low number of patients. In the original CCS classification there are 5 major categories and 4 subcategories. But, in our study we merged some of the subcategories and thus made in total 6 categories ([without any subcategories]) at the time of analyses of the data ([table 1]). The subtype “unknown – cryptogenic embolism” and “unknown- other cryptogenic” in CCS were also combined together into cryptogenic type. The category “Unclassified” was used when more than one etiologies are identifiable in the same patient ([same as in original CCS classification]).

Categories by stroke severity:

Determined by NIHSS score. They were as follows[5] ;
Mild: < 5, Moderate: 5- 14, Severe: ≥ 15

Statistical analysis:

Data analysis was done by using SPSS version-20.0 ([IBM Product-USA]). The categorical response variables included patient's demographic features, etiology of stroke, co- morbid conditions, family history, clinical features and severity of stroke. The numeric response variables like fasting triglyceride and other lipid levels, HbA1c, random blood sugar ([RBS]), Systolic Blood Pressure, and fasting lipid profile were presented as mean (standard deviation). Analysis of variance ([ANOVA]) was performed to compare these numeric response variables. Later, these numeric variables were stratified in order to control the confounding effect and effect modifiers. Stroke severity was also stratified into three categories i.e., mild, moderate and severe. Bivariate analysis by using Chi-square test was done to see relationship of aforementioned variables with the severity of stroke measured by NIHSS and divided into categories. Pearson's correlation coefficient was calculated to see the relationship of triglyceride level with the NIHSS. P-value $\leq$.05 was considered statistically significant result.

RESULTS:

Baseline characteristics of patients:

Total 207 patients were selected after applying the inclusion and exclusion criteria. The mean ([SD]) age of patients was 63.5 ([13.7]) yrs. ([range 26 yrs. – 95 yrs.]). There were 117 ([56.5 %]) males and 90 ([43.5 %]) females. Among males mean ([SD]) age was 64.1 ([13.6]) yrs., and that of females was 62.8 ([13.8]) yrs.The age distribution was not uniform among different stroke etiologies. The mean age in unclassified stroke type ([more than one etiologies]) was 70 yrs. that was highest than the rest of stroke types, while the mean age in uncommon causes of stroke was 34 years that was significantly lower than the other stroke types. According to stroke etiology most of the patients were in supra aortic large artery atherosclerosis that totaled 98 ([47.3%]) patients, followed by, Cardio embolism in 40 ([19.3%]) patients, small artery occlusion in 22 ([10.6 %]) patients, cryptogenic type in 21 ([10.1 %]), unclassified in 20 ([9.7 %]), and uncommon causes in [5] ([2.4 %]), of patients. One patient had incomplete evaluation.

Stroke severity analysis:

When stroke severity was taken as mean NIHSS or as NIHSS categories ([mild, moderate or severe]), the results appeared similar (see Table 1 and figure 1). Higher number of patients were in moderate to severe category in cardio embolic strokes ([mean NIHSS 10.4]) and unclassified ([mean NIHSS 9.3]) stroke types. Small vessel occlusion type strokes had the lowest severity. When stroke severity ([mean NIHSS and/or NIHSS categories]) was compared with all variables other than stroke etiology, significant associations were found only with age and fasting triglyceride levels. Stroke severity was found to be higher with advancing age. NIHSS scores were significantly lower with higher triglyceride levels and vice versa. ([see table 2 and figure 2]). When radiological features were compared to stroke severity ([Table 3]) it was found that higher stroke severity was associated with whole MCA territory / malignant MCA infarctions, while partial MCA infarctions were less severe. MRI DWI (Diffusion Weighted Imaging) assessment showed that large sized infarctions with more than 15 mm size ([territorial, lobar or deep subcortical]) and those with hemorrhagic conversion, were more likely to be moderate or severe.

Sub category analysis ([stroke severity analysis by stroke etiology]):

We analyzed the relationship of different variables with stroke severity categories, in each stroke type / etiology. In this analysis we found that only the Supra Aortic Large artery atherosclerosis and cryptogenic types ([Table 4]) had the inverse relationship between stroke severity and triglyceride levels ([P = .04]). Apparently triglyceride levels did not produce similar effect on stroke severity in cardio aortic embolism and small vessel occlusion. In this sub category analysis, we also found that the pre-stroke anti platelet ([aspirin, clopidogrel or both]) and beta blocker use ([Table 5]) was significantly associated with lower stroke severity only in Supra Aortic Large artery atherosclerosis ([P=.02]). In cardio aortic embolic strokes 10 patients were actively smoking out of which 6 patients suffered from severe stroke, 3 patients with moderate stroke and only one had mild stroke ([P=.03]).

DISCUSSION:

In this exploratory study we compared many different characteristics of patients with acute ischemic stroke and analyzed them for their relationship with stroke severity. The stroke etiology / type, as is already known, was one of the main factors related to stroke severity ([table 1]). The cardio aortic embolism and unclassified type (more than one etiology) were associated with more severe strokes, while supra aortic large artery atherosclerosis mostly with moderate severity and cryptogenic strokes, small artery occlusion, and uncommon causes were associated with predominantly lower stroke severity. Similar results have been shown in other studies[6,7]. Furthermore the triglyceride levels were found to be inversely related to stroke severity, as the higher triglyceride levels were significantly associated with lower stroke severity and vice versa ([table 2 and figure 2]). In fact, the role of higher serum triglycerides in reducing the stroke severity is a relatively novel concept, as hypertriglyceridemia is considered a risk factor for stroke. The association of triglyceride levels in blood, with stroke severity and outcome has emerged in a few other recently published studies[8]. Dziedzic et al., correlated the Scandinavian stroke scale ([which is another measure of stroke severity]) to triglyceride levels, and concluded that lower triglyceride levels were associated with increased stroke severity[9]. A prospective study by Ryu etal, reported that higher fasting triglycerides on admission predict less disability, reduced disability progression, and all-cause mortality in patients with acute ischemic stroke[10]. Another study by Choi etal also confirmed that low serum triglyceride level is an independent predictor of mortality after ischemic stroke, but noted that this association did not hold true in the subgroup with cardioembolic stroke[11]. History of dyslipidemia was found to have a favorable effect on out come in ischemic stroke patients in Kyoto stroke registry[12]. In one study higher cholesterol levels were also reported to be associated more frequently with minor strokes[13]. Our study elaborates this unusual phenomenon, as we further analyzed the distribution of triglycerides levels among different stroke severity categories in each stroke etiology/ type. What appeared in this later analysis is that the effect of serum triglyceride levels (as mentioned above) was significant only in supra aortic large artery atherosclerosis and cryptogenic types (table 4). The other types including cardioaortic embolic and small artery occlusion stroke types were not affected by triglyceride levels. The loss of this triglyceride effect in cardio aortic embolic strokes was also seen by Choi etal ([see above])[11]. Current stroke pathophysiology models do not explain this phenomenon, as hypertriglyceridemia is actually considered a risk factor for stroke because of its long term effects on vascular endothelium. There can be many explanations for this associations. (1) Some authors consider serum triglycerides as an acute phase reactant that is decreased in severe strokes as a result of cerebral ischemia and perhaps may not actually have a direct protective effect against cerebral neuronal damage[8]. (2) Another likely possibility, though debatable, is the fact that high lipid containing plaque / clot is very likely to be friable, and thus embolise easily into more distal cerebral vasculature thus it may cause more incident stroke but that of lesser severity.(3) There is also a possibility that high lipids especially triglycerides, may have a more positive role in acute ischemic strokes. It is a well-known fact that fats in general have a favorable effect on brain metabolism. For example; fatty diets like ketogenic diet is well known to have a therapeutic effect in refractory epilepsy in children, [14] although similar diet has not been thoroughly evaluated in adults with stroke or epilepsy. Thus more research is needed to elucidate the role of lipids/ triglycerides in during the acute phases of ischemic stroke. In supra aortic large artery atherosclerotic strokes pre stroke antiplatelet (aspirin, clopidogrel or both) and beta blocker use was significantly associated with lower stroke severity ([table 5]). Aspirin use before stroke has been shown to have a beneficial effect in some other studies as similar findings were reported by Park etal [15] in atherothrombotic stroke. Same effect could not be seen in cardio aortic embolism and other stroke types [16,17]. The effect of beta blockers (propranolol and carvedilol) on brain ischemia has been shown in experimental models of stroke that suggest a neuroprotective effect on cerebral neurons[18-20]. Dziedzic T et al, found lower rates of early mortality after ischemic stroke in patients taking beta blockers, however, they did not report any effect on stroke severity[22]. They did not take stroke etiology into account, in their patients. Active current smoking was also found to be related to increased stroke severity in cardioembolic stroke but not in other types. Similar findings were reported by Edjoc etal.[22] Among the radiological features, it was the size and not the site of the infarction that was mainly associated with stroke severity ([table 3]). In plain CT brain and MRI scans the whole MCA territory and malignant MCA infarctions had significantly higher stroke severity, while among the different MRI DWI patterns we found only the large ([> 15 mm in size]) pattern irrespective of the location (lobar or deep subcortical) had significant association with severe strokes.

Weaknesses:

The study was a retrospective analysis with an exploratory design. We preferred such a study design because; (1) we were not testing any hypothesis, rather we aimed to look into possible novel strategies for neuroprotection that might generate newer studies.(2)The authors found it more feasible because of the limited resources at their disposal. Furthermore, a multivariate analysis could not be performed for specification of potential confounding effect and predictors of stroke severity due to design of study.

Rather, we used restriction and stratification strategies in data selection and analysis to control for possible confounders.
We also did not have the pre stroke or baseline triglyceride levels of our subjects, which was practically not possible either, therefore the theory of acute phase reaction to explain the inverse triglyceride relationship with stroke severity could not be evaluated.

Strengths:

In spite of all the weaknesses we think that this study provides valuable information. Furthermore we analyzed our variables in different subsets and found that the relationship between stroke severity and triglyceride levels, pre-stroke anti platelet as well as beta blocker use and smoking, seemingly depends upon the etiological category of the stroke, a fact not particularly looked into as yet.

CONCLUSION:

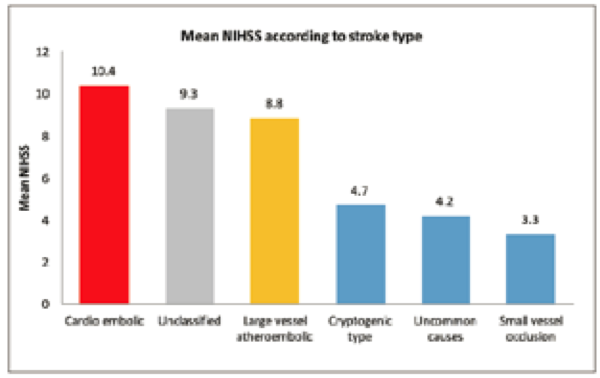
Stroke severity is related to age and its etiology. There is also a possible inverse correlation between stroke severity and fasting triglyceride levels, which is seen predominantly in supra aortic large artery atherosclerotic and cryptogenic stroke etiologies. People who suffer ischemic strokes due to supra aortic large artery atherosclerosis, with pre-stroke use of anti-platelets and beta blockers, also seem to have a reduced stroke severity. Furthermore, patients who actively smoke may have more severe strokes, if they have a cardio embolic etiology. We would recommend future studies to verify if factors we found have a consistent causal association, in the context of different stroke etiologies.

Table 1: stroke severity by categories vs stroke etiology.

Stroke etiology	NIHSS at admission categorized			Total
	Mild (<5)	Moderate (5-14)	Severe (≥ 15)	
Supra aortic Large artery atherosclerosis	33 (33.7%)*	44 (44.9%)*	21 (21.4%)	98
Cardio aortic embolism	8 (20.0%)	21(52.5%)*	11 (27.5%)*	40
Small artery occlusion	17 (77.3%)*	5 (22.7%)	0 (0.0%)	22
Cryptogenic type	13 (61.9%)*	8 (38.1%)	0 (0.0%)	21
unclassified	4 (20.0%)	10 (50.0%)*	6 (30.0%)*	20
Uncommon causes	3 (60.0%)	2 (40.0%)	0 (0.0%)	5
Total	78 (37.9%)	90 (43.7%)	38 (18.4%)	206

*Shows statistically significant proportion of severity of stroke with stroke types (P<.001)

Figure 1 : Mean NIHSS score Difference according to stroke etiology



Bar graph showing significant mean NIHSS score associated with stroke sub-types ([F= 6.317, P=.001]). Cardio aortic embolic strokes and unclassified strokes had the highest severity.

Table 2 : stroke severity as compared to different variables:

Demographics		Mild	Moderate	Severe	P – value
Mean age		60.6	65.7	64.5	.04
Sex	Female	31 (34.4%)	45 (50 %)	14 (15%)	.25
	Male	48 (41%)	45 (38.4 %)	24 (20.5%)	
Occupational status	Employed	16 (53.3 %)	8 (26.7%)	6 (20%)	.07
	Unemployed	52 (32.7%)	75(47.1%)	32(20.1%)	
Marital status	Single	0 (0%)	3 (75 %)	1 (25 %)	.35
	Married	67 (40 %)	70 (41.6%)	31 (18.5 %)	
	Widow	6 (25 %)	13 (54.2 %)	5 (20.8 %)	
Co- morbid conditions					
Diabetes mellitus		41 (40 %)	42 (41.1 %)	19 (18.6 %)	.40
Hypertension		57 (40.4%)	58 (41%)	26 (18.4%)	.60
Ischemic heart disease		14 (29.2%)	20 (41.7%)	14 (29.2%)	.07
Smoking (current)		20 (37.7 %)	19 (35.8%)	14 (26.4 %)	.18
Chronic renal failure		4 (57.1 %)	2 (28.6 %)	1 (14.3%)	.57
Other baseline values (means)					
Systolic BP (mean value during first 6hrs of presentation)		142.2	142.95	144	.91
RBS		177.25	155.77	170.86	.31
HbA1c		7.8	7.51	8.64	.14
Triglycerides		196	145.5	137.7	.002
Total cholesterol		172.5	180.5	186.5	.279
HDL cholesterol		35.5	39.1	38	.120
LDL cholesterol		109.5	117.5	127.7	.065

Figure 2 : Scatter plot showing inverse relationship between NIHSS at admission and triglyceride levels

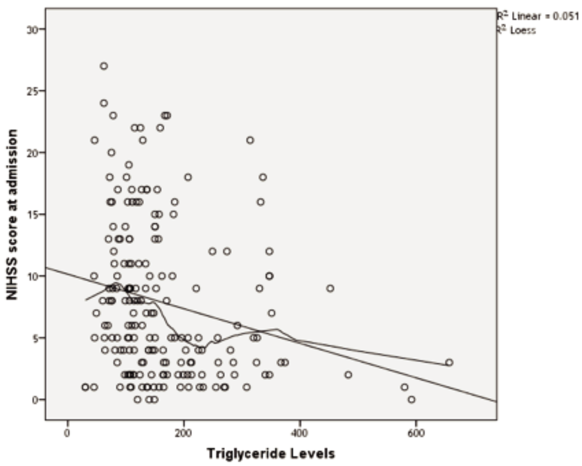


Table 3 : Radiological features vs stroke severity

Vascular territory (CT and MRI brain)	Mild (n = 78)	Moderate (n = 90)	Severe (n = 38)	P- value
Lacunar infarct (MCA perforator)	17 (21.8)*	7 (7.8)	0 (0)	.011
Partial MCA	54 (69.0)*	56 (62.2)	15 (39.5)	.018
Whole MCA	0 (0)	8 (8.9)	8 (21.0)*	.028
DWI patterns				
Large (> 15 mm)	6 (7.7)	38 (42.2)*	14 (36.8)*	.001
Small superficial	17 (21.8)*	2 (2.2)	0 (0.0)	.001
Cortical mixed patterns	16(20.5)	21 (23.3)	7 (18.4)	.736
Small deep	7 (9.0)	3 (3.3)	0 (0)	.083
Water shed infarcts	7 (9.0)*	2 (2.2)	1 (2.6)	.046
Hemorrhagic conversion	1 (1.3)	4 (4.4)	4 (10.5)*	.007

*significant values.

Table 4 : Mean Triglyceride levels in different stroke categories

Stroke types	Mild	Moderate	Severe	P- value
Supra aortic large artery atherosclerosis	212.18	149.00	156.42	.04
Cardio aortic embolism	142.71	133.72	116.45	.74
Small artery occlusion	174.75	184.60	--	.85
Cryptogenic	216.08	141.86	--	.04
Unclassified	152.00	111.78	107.25	.49

Table 5: impact of pre-stroke medicines and stroke severity

Antiplatelet use :				
	Mild	Moderate	Severe	P-value
Supra aortic Large artery atherosclerosis	14 (52 %)	6 (22.2 %)	7 (25.9 %)	.02[a]
Cardio aortic embolism	1 (10 %)	6 (60%)	3 (30%)	.12[a]
Small artery occlusion	3 (60%)	2(40%)	0	.29[a]
Cryptogenic	3 (100%)	0	0	.14[a]
Unclassified	1 (14.3%)	5 (71.4%)	1 (14.3%)	.36[a]
Uncommon causes	1 (50%)	1(50%)	0	.70[a]
Beta- blocker use:				
	Mild	Moderate	Severe	P-value
Supra aortic Large artery atherosclerosis	15 (53.6 %)	10 (35.7%)	3 (10.7 %)	.02[a]
Cardio aortic embolism	4 (40 %)	3 (30 %)	3 (30%)	.66[a]
Small artery occlusion	2(50%)	2(50%)	0	.21[b]
Cryptogenic	3 (100%)	0	0	.21[b]
Unclassified	1 (14.3%)	5 (71.4%)	1 (14.3%)	.36[a]
Uncommon causes	0	1 (100%)	0	.59[a]

a Statistical significance using Pearson's chi-square test b Fischer's exact test.

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Inam E Khuda; data collection, data analysis, manuscript writing, manuscript review
Intisar Siddiqi; data analysis,manuscript writing, manuscript review
Saad Munzar; data analysis, manuscript writing, manuscript review
Rashid Nazir; data analysis, manuscript writing, manuscript review
Arsalan Ahmed; concept, data analysis,manuscript review