CORRELATION BETWEEN PLASMA D-DIMER LEVEL AND LESION VOLUME IN ACUTE ISCHEMIC STROKE

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ABSTRACT:

INTRODUCTION: In the recent times, acute stroke has been ranked as the third leading cause of mortality all over the world particularly in industrialized countries. The fact was highlighted in 1970s and 1980s' through various studies of the epidemiology of stroke. The percentage of ischemic stroke was 73% to 83% whereas that of the hemorrhagic stroke was only 8% to 18%. Efforts are underway all over the world to make a timely diagnosis of stroke and prevent its harmful impacts. Neurological examination is a cost-friendly tool for starting a diagnostic assessment and it often helps localizing a lesion site. Out of the two initial assessments of acute stroke i.e., CT scan and MRI, the former might appear normal in early hours of ischemic stroke while the later, even being more sensitive, is economically incompatible.

AIMS & OBJECTIVE: To assess the increase in plasma levels of D-dimers with the volume of lesion in patients having acute ischemic stroke.

MATERIAL & METHODS: This was a cross-sectional study which establishes a correlation between D-dimer levels and infarcts volume and was conducted at the Department of General Medicine Combined Military Hospital Abbottabad for about six months from March to August 2020. Patients of both genders, aged between thirty five to sixty five years suffering from acute ischemic stroke were included in this study.

RESULTS: Patient's mean age was 47.46±10.373 ranging from 35 to 65 years, mean infarct volume on CT was 53.69±29.211 ranging from 20 to 120/ml, mean plasma D-dimer level was 0.7445±0.69046 ranging from 0.12 to 1.95/µg/ml and mean BMI was 29.042±4.7666 ranging from 19.4 to 48.7 kg/m². With regard to the gender of patients, out of total 80 patients 44(55.0%) were male and 36(45.0%) were female. With regard to the infarct volume of patients, out of total 80 patients 46(57.5%) had below 50ml infarct volume and 34(42.5%) had above 50ml infarct volume. Referring to the levels of D-dimer in blood plasma of patients, out of total 80 patients 52(65.0%) were having below 1.0 µg/ml and 28(35.0%) found above 1.1 µg/ml of plasma D-dimer level.

CONCLUSION:	This study has demonstrated that plasma amounts of D-dimer raised with the rise in severity of stroke and volume of infarct. These collaborations were exclusive of other conceivable variables. Furthermore, cardio-embolic etiologies of stroke can be differentiated from various other stroke etiologies by calculating levels of D-dimer in blood plasma very timely (within 48hrs from the outset of signs and symptoms of stroke)
KEY WORDS:	Correlation, D-dimer levels of plasma, Lesion volume, Acute ischemic stroke.

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Author's Contribution: IK: Study design and concept. HMSJ: Questionnaire design. HSK: Data collection and interpretation. AN: Data analysis and interpretation. ABB: Data collection. MSA: Data collection.

INTRODUCTION:

In the recent times, acute stroke has been ranked as the third leading cause of mortality all over the world particularly in industrialized countries.[1] The fact was highlighted in 1970s and 1980s' through various studies of the epidemiology of stroke. The percentage of ischemic stroke was 73% to 83% whereas that of the hemorrhagic stroke was only 8% to 18%.[2] Efforts are underway all over the world to make a timely diagnosis of stroke and prevent its harmful impacts.

Neurological examination is a cost-friendly tool for starting a diagnostic assessment and it often helps localizing a lesion site. Out of the two initial assessments of acute stroke i.e., CT scan and MRI, the former might appear normal in early hours of ischemic stroke while the later, even being more sensitive, is economically incompatible. There are many biological tracers such as CRP, D-dimer, and MMP-9 that are raised particularly in acute phase[3], which not only aid in progressing towards other diagnostic tests, but also assessing further progression and prognosis of stroke.[4]

Fibrin mesh, after factor XII stabilization, breaks down to form a product known as D-dimer. It is one of the baseline laboratory tracers of plasminogen-plasmin system's activity. D-dimer has been shown to correlate with severity of ischemic stroke[5] and their levels rise within 6 hrs after the outset of stroke, that is higher in patients suffering from the occlusion of larger vessels.[3] A thorough review of literature established positive relation between the levels of D-dimer in plasma and the volume of lesion in acute stroke on Computerized Tomography scan. In a recent study, D-dimer level at admission was $566.2\,\mu g/L$ in those having 1-19 cc infarction volume, $668.8\,\mu g$ per Liter in 20-49 cc infarction volume, $702.5\,\mu g$ per Liter in 50-199 cc infarction volume, and $844.0\,\mu g$ per Liter in those having greater than 200 cc infarction volume (p=0.044). On the seventh day of therapy, the levels of D-dimer in plasma had decreased to $201.0\,\mu g$ per Liter, $293.2\,\mu g$ per Liter, $272.0\,\mu g$ per Liter, $232.8\mu g$ per Liter, $336.6\mu g$ per Liter and $180.0\,\mu g$ per Liter respectively (p=0.530).[6] However, according to some of the reports, D-dimer test is not sensitive enough to rule out disease severity particularly when its suspicion is little and should not be weighed as a criterion for performing brain imaging studies.[7,8,9]

Another study conducted in Japan in 2013 in which 124 patients suffering from acute ischemic stroke was admitted within 24 hours in which infarct volume and D-dimers were evaluated at the time of admission and their relationship was analysed. Volume of infarction was significantly associated with D-dimer levels (r = 0.309, p < 0.001).[10]

Elevation in D-dimer levels with increase in volume of lesion in patients who present with acute ischemic stroke and these D-dimer levels can be used for screening purposes in future for prevention and early diagnosis of stroke in high risk population.

OBJECTIVE:

To approximate the increase in plasma levels of D-dimers with the volume of lesion in patients having acute ischemic stroke.

OPERATIONAL DEFINITIONS:

Acute Ischemic Stroke: It will be described as "neurological loss (of either focal or global nature) of cerebrovascular etiology that lasts for more than 24 hrs, confirmed through CT scan of brain manifesting itself as hypo dense area with brain parenchyma".

Levels of D-Dimer: The D-dimer test is employed for the measurement of plasma levels of the product formed by the breakdown of fibrin meshwork. The D-dimer levels will be measured in terms of μg/L, in laboratory by expert pathologist. Volume of infarct or lesion: To determine the infarction volume on CT scan, the succeeding formula shall be applied: $A \times B \times C/2$. In the given formula, A stands for the greatest diameter, B stands for the vertical diameter of the ischemic lesion, whereas C stands for the summation of the wideness of the strips where the lesion was evident.

MATERIAL AND METHODS:

This was a cross-sectional study which establishes a correlation between D-dimer levels and infarcts volume and was conducted at the Department of General Medicine Combined Military Hospital Abbottabad for about six months from March to August 2020. Sample size was calculated by presumed association between the levels of D-dimer in blood plasma and lesion volume rs 0.307 9
Significance Level = 5% (0.05)
Statistical Power = 0.8

Consecutive Non-probability sampling method was implied. Patients of both genders having their ages between thirty five to sixty five years suffering from acute ischemic stroke were included. Patients on anticoagulants therapy or suffering from any kind of other bleeding abnormalities, History of any recurrent stroke, Doubt of any illness like pulmonary embolism, DVT, sepsis, or other coincident illnesses that might alter D-dimer levels in plasma, were ruled out of our study. The aforesaid stated conditions act as distractions and if involved would found a bias in the outcomes of our study.

DATA COLLECTION PROCEDURE

Our study was organized and directed after compliance from the ethical and research committee of the hospital and only patients that were falling in the criteria of inclusion were involved in it. Ischemic stroke was diagnosed has described earlier. After explaining the pros and cons along with the intention of the study, a written expressed consent was obtained from all the patients.

A detailed history was obtained and all of the patients were examined thoroughly. Infarct volume was measured on CT brain by using the formula as cited above. 5cc of blood was obtained from every patient under uncompromising sterile technique and was sent to hospital labortary on the very same day. Plasma levels of D-dimer were evaluated under the supervision of an expert pathologist with more than ten years of experience who was a fellow of College of Physicians and Surgeons Pakistan (CPSP).

All the aforesaid mentioned information including name of patients, and their age, gender and address was noted in the study proforma.

DATA ANALYSIS PROCEDURE:

Data gathered was enrolled in SPSS 16. Mean $\pm$ S.D. was computed for continuous variables e.g., age, infract volume on Computerized Tomography scan and Plasma levels of D dimer. Categorical variables e.g., gender, BMI were listed in the form of frequency and percentage. The coefficient correlation (Pearson's 'r') between plasma levels of D dimer with the volume of infarct lesion was calculated and stratification of Pearson's correlation was done by age, gender and BMI.

RESULTS

The study was conducted to find out the rise in plasma amount of D-dimer with lesion volume in those patients who are suffering from acute ischemic stroke in Combined Military Hospital (CMH) Abbottabad.

Average age of the patient was 47.46 ± 10.373 between thirty five to sixty five years, mean infarct volume on CT was 53.69 ± 29.211 ranging from 20 to 120/ml, mean plasma D-dimer level

Table 1: Frequency of variables.

		Frequency	Percentage
Gender	Male	44	55.0
	Female	36	45.0
Weight	Normal weight	16	20.0
	Overweight	20	25.0
	Obese	44	55.0
Infract volume	Below 50ml	46	57.5
	Above 50ml	34	42.5
Plasma level of D-dimer	below 1.0 µg/ml	52	65.0
	Above 1.1 µg/ml	28	35.0
Stratification of age	35 to 50 years	49	61.2
	51 to 65 years	31	38.8

Table-2: Association of startified variables with plasma D-dimer levels.

	BMI	Below 1.0 µg/ml	Above 1.1 µg/ml	Total	Correlation (r)
Plasma level of D-dimer	Normal weight	11 (13.8%)	5 (6.2%)	16 (20.0%)	-.026
	Overweight	11 (13.8%)	9 (11.2%)	20 (25.0%)	
	Obese	30 (37.5%)	14 (17.5%)	44 (55.0%)	
	BMI	**Below 50ml**	**Above 50ml**	**Total**	**Correlation (r)**
Infarct Volume	Normal weight	9 (11.2%)	7 (8.8%)	16 (20.0%)	-.029
	Overweight	11(13.8%)	9 (11.2%)	20 (25.0%)	
	Obese	26 (32.5%)	18 (22.5%)	44 (55.0%)	
	Age	**Below 1.0 µg/ml**	**Above 1.1 µg/ml**	**Total**	**Correlation (r)**
Plasma level of D-dimer	35 to 50 years	31 (38.8%)	18 (22.5%)	49 (61.2%)	-.046
	51 to 65 years	21 (26.2%)	10 (12.5%)	31 (38.8%)	
	Age	**Below 50ml**	**Above 50ml**	**Total**	**Correlation (r)**
Infarct Volume	35 to 50 years	29 (36.2%)	20 (25.0%)	49 (61.2%)	0.043
	51 to 65 years	17 (21.2%)	14 (17.5%)	31 (38.8%)	
	Gender	**Below 1.0 µg/ml**	**Above 1.1 µg/ml**	**Total**	**Correlation (r)**
Plasma level of D-dimer	Male	29 (36.2%)	15 (18.8%)	44 (55.0%)	0.021
	Female	23 (28.8%)	13 (16.2%)	36 (45.0s%)	
	Gender	**Below 50ml**	**Above 50ml**	**Total**	**Correlation (r)**
Infarct Volume	Male	25 (31.2%)	19 (23.8%)	44 (55.0%)	-.015
	Female	21 (26.2%)	15 (18.8%)	36 (45.0%)	

was 0.7445±0.69046 ranging from 0.12 to 1.95/µg/ml and mean BMI was 29.042±4.7666 ranging from 19.4 to 48.7 kg/m² out of total 80 patients as listed in table 1.With regard to the gender of patients, out of total 80 patients 44(55.0%) were male and 36(45.0%) were female as listed in table 1. With regard to the BMI of patients, out of total 80 patients 16(20.0%) had normal weight 20(25%) were overweight and 44(55.0%) were obese as listed in table 1. With regard to the infarct volume of patients, out of total 80 patients 46(57.5%) had below 50ml infarct volume and 34(42.5%) had above 50ml infarct volume, as listed in table 1.

Table 3: Correlation of infarct volume with respect to plasma D-dimer level:				
Infarct volume	Plasma D-dimer level		Total	Correlation (r)
	below 1.0 µg/ml	Above 1.1 µg/ml		
Below 50 ml	34	12	46	0.217
	42.5%	15.0%	57.5%	
Above 50 ml	18	16	34	
	22.5%	20.0%	42.5%	
Total	52	28	80	
	65.0%	35.0%	100.0%	

Referring to the amount of D-Dimer in blood plasma of patients, out of total 80 patients 52(65.0%) found below 1.0 µg/ml and 28(35.0%) found above 1.1 µg per ml of plasma D-dimer level, as listed in table 1. With regard to the stratification of age of patients, out of total 80 patients 49(61.2%) found 35 to 50 years of age and 51(38.8%) found 51 to 65 years of age group, as listed in table 1.

In stratification of BMI with respect to plasma D-dimer level, 11(13.8%) had below 1.0 µg/ml and 5(6.2%) had above 1.1 µg/ml with normal weight, 11(13.8%) had below 1.0 µg/ml and 9(11.2%) had above 1.1 µg/ml with overweight while 30(37.5%) had below 1.0 µg/ml and 14(17.5%) had above 1.1 µg/ml were obese with correlation r=-.026, out of total 80 patients as listed in table 2.

In stratification of BMI with respect to infarct volume, 9(11.2%) had below 50ml and 7(8.8%) had above 50ml with normal weight, 11(13.8%) had below 50ml and 9(11.2%) had above 50ml with overweight while 26(32.5%) had below 50ml and 18(22.5%) had above 50ml were obese with correlation r=-.029, out of total 80 patients as listed in table 2.

In stratification of age with respect to plasma D-dimer level, 31(38.8%) had below 1.0 µg/ml and 18(22.5%) had above 1.1 µg/ml were in age group of 35 to 50 years, 21(26.2%) had below 1.0 µg/ml and 10(12.5%) had above 1.1 µg/ml were having their ages between of fifty one to sixty five years with correlation r=-.046, out of total 80 patients as listed in table 2.

In stratification of age with respect to infarct volume, 29(36.2%) had below 50ml and 20(25.0%) had above 50ml were in age group of 35 to 50 years and 17(21.2%) had below 50ml and 14(17.5%) had above 50ml were having age between 51 to 65 years with correlation r=0.043, out of total 80 patients as listed in table 2.

In stratification of gender with respect to plasma D-dimer level, 29(36.2%) had below 1.0 µg/ml and 15(18.8%) had above 1.1 µg/ml were male patients, 23(28.8%) had below 1.0 µg/ml and 13(16.2%) had above 1.1 µg/ml were female patients with correlation r=0.021, out of total 80 patients as listed in table 2.

In stratification of gender with respect to infarct volume, 25(31.2%) had below 50ml and 19(23.8%) had above 50ml were male patients and 21(26.2%) had below 50ml and 15(18.8%) had above 50ml were female patients with correlation r=-.015, out of total 80 patients as listed in table 2.

In stratification of infarct volume with respect to plasma D-dimer level, 34(42.5%) had below 1.0 µg/ml and 12(15.0%) had above 1.1 µg/ml have had below 50ml and 18(22.5%) had below 1.0 µg/ml and 16(20.0%) had above 1.1 µg/ml have had above 50ml infarct volume with correlation r=0.217, out of total 80 patients as listed in table 3.

DISCUSSION:
Stroke is labelled as the main cause

of neurological impairment worldwide. According to various studies conducted around the globe, it is ranked as the 3rd commonest reason of death.[9] This study focused on grouping of various attributing factors among patients suffering from ischemic stroke.

We conducted this study to estimate the rise in plasma amount of D-dimer with lesion volume in those patients who are suffering from acute ischemic stroke. Average age of the patient was 47.46 ± 10.373 with ages, mean infarct volume on CT was 53.69 ± 29.211 ranging from 20 to 120/ml, mean plasma D-dimer level was 0.7445 ± 0.69046 ranging from 0.12 to 1.95/µg/ml and mean BMI was 29.042 ± 4.7666 ranging from 19.4 to 48.7 kg/m². Our study demonstrated that raised concentrations of D-dimer in the twenty four hours after acute attack of ischemic stroke were correlated with brain's volume of infarct irrespective of other factors. These results were consistent with the results obtained from other studies illustrating that the plasma concentrations of D-Dimer and brain infarct were interrelated[10,11], and also that the plasma concentrations of D-Dimer were statistically correlated with infarct volume.[9,12]

This study shows the stratification of infarct volume with respect to plasma D-dimer level, 34(42.5%) had below 1.0 µg/ml and 12(15.0%) had above 1.1 µg/ml have had below 50ml and 18(22.5%) had below 1.0 µg/ml and 16(20.0%) had above 1.1 µg/ml have had above 50ml infarct volume with correlation r=0.217. Comparable results have been seen in literature.[11]

Proportion of male patients was slightly higher in relation to females with regard to the gender of patients. Similar gender distribution has been reported in a study at UK.[12] With regard to the BMI of patients our study shows that out of 80 patients 16(20.0%) had normal weight 20(25%) were overweight and 44(55.0%) were obese. Infarct volume of patients, out of total 80 patients 46(57.5%) had below 50ml infarct volume and 34(42.5%) had above 50ml infarct volume. In this study the stratification of BMI with respect to

infarct volume, 9(11.2%) had below 50ml and 7(8.8%) had above 50ml with normal weight, 11(13.8%) had below 50ml and 9(11.2%) had above 50ml with overweight while 26(32.5%) had below 50ml and 18(22.5%) had above 50ml were obese with correlation r=-.029. However, infarct volume was un related to obesity (P>0.05). This stratified variable was also not correlated with plasma D-dimers in our study. This is in accordance to available literature.[10,11]

This study shows the stratification of age of patients, out of total 80 patients 49(61.2%) found to have 35 to 50 years of age and 51(38.8%) had 51 to 65 years of age group. This age distribution is similar to a literature report of European population signifying occurrence of stroke in similar age group.[12]

In our study the stratification of age with respect to infarct volume, 29(36.2%) had below 50ml and 20(25.0%) had above 50ml were in age group of 35 to 50 years and 17(21.2%) had below 50ml and 14(17.5%) had above 50ml were having age between of 51 to 65 years with correlation r=0.043. This shows a higher volume of the lesion is likely to be related with age. This was reported by Park et al and matsumoto et al.[11,12] Another Relation of gender was studied with respect to lesion volume, Our study reported to be strong association between the two variables. This was accentuated by another study of Europe.[12]

In this study, we documented that blood plasma concentration of D -dimer were notably raised in instances of first acute ischemic stroke. The main outcomes of this study were that the D-dimer concentrations in plasma and infarct volume were interrelated. Additionally, we came to know that the plasma concentrations of D-dimer raised with extending severity of stroke and infarct volume. Even after correction of probable confounding factors, positive trends were still seen.

CONCLUSION:

This study has demonstrated that plasma amounts of D-dimer raised with the rise in severity of stroke and volume of infarct. These collaborations were exclusive of

other conceivable variables. Furthermore, cardio-embolic etiologies of stroke can be differentiated from various other stroke etiologies by calculating levels of D-dimer in blood plasma very timely (within 48hrs from the outset of signs and symptoms of stroke).

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