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RESEARCH ARTICLE

ADMISSION PLASMA D DIMER AS A PREDICTOR OF OUTCOME IN PATIENTS WITH PRIMARY INTRACEREBRAL HEMORRHAGE.

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Abstract

Introduction Spontaneous intracerebral hemorrhage (sICH) accounts for about 15% of strokes and is associated with high mortality, severe disability, and unfavorable functional outcome**.** Information regarding factors contributing to early neurologic deterioration after stroke can guide the early management strategies and lead to more favorable outcomes**.** The aim of our study was to evaluate the predictive value of admission serum D dimer level in patients with primary ICH regarding their outcome **Patient and methods:** In our present study, we included 116 patients diagnosed with spontaneous ICH, their mean age 62.54±11.45 years and ranged from 22-90 years with median of age 63 years. Males were 57.8% and 42.2% were females. Most of our patients were right handed 96.6%. All patients were subjected to Full history taking, General and neurological examination with assessment of neurological function on admission using National institutes of Health Stroke Scale (N.I.H.S.S.). Serum D dimer level and Computerized Tomography on admission. All the included patients were followed up, both clinically using the NIHSS score and mRS, radiologically with CT brain after 1 week and 4 weeks of the onset to assess the growth, complications or resolution. **Results:** showed that the 30 day mortality was about one third of the patients. Elevated serum D dimer level on admission positively correlates with the 30 days mortality and poor outcome measured by mRS **Conclusion:** Admission serum level of D dimer, has a significant predictive value of the 30 day mortality and disability in cases of SICH.

Introduction:-

Spontaneous intracerebral hemorrhage (sICH) is a devastating illness with limited treatments. It remains a major challenge for public health. According to a large meta-analysis from 36 studies conducted worldwide between 1980 and 2008, the overall incidence of ICH is 24.6 per 100,000 person-years, with a median 30-day mortality of 40.4%, and only 12%–39% of patients are able to remain independent after ICH. Despite the decrease in annual incidence of ICH from 2000 to 2010, the short- and long-term mortality following ICH did not change **(Hung et al., 2017).** Coagulation disorders and impaired hemostasis are established risk factors associated with ICH **(Masotti et al. 2016).** D-dimer represents the final product of plasmin-mediated degradation of fibrin-rich thrombi. Over the last

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two decades numerous studies have explored whether D dimer measurements would help stroke clinicians **(Haapaniemi and Tatlisumak 2009).** Elevation of plasma D-dimer has been reported in ischemic stroke, subarachnoid hemorrhage, traumatic intracranial hemorrhage, and sICH. Moreover, elevated plasma D-dimer has been related to unfavorable outcomes and has been suggested as a prognostic factor for these conditions **(Hu et al., 2014).** In this context, the primary purpose of the present study was to evaluate the predictive value of admission serum level of D dimer in patients with sICH regarding their outcome.

Patients and Methods:-

According to the power of study 80% & 95% confidence interval and the markers of severity &outcomes; the sample size estimated to be 116 patients included in our study, 67 of them were males and 49 were females with their mean age 62.54 ± 11.45 years. The study included patients older than 18 years with recent primary ICH , admitted to Neuro-Critical Care Unit and Stroke Unit of Neurology Department of ZUH. We excluded the patients with age under 18 years, head trauma, recent surgical hematoma evacuation, recent ischemic stroke, hemorrhagic transformation, patients with recent subarachanoid hemorrhage, chronic liver or kidney disease, malignancy, recent diagnosis of deep venous thrombosis, and patients with delayed admission after 72 hours).

The study was approved by the local ethical committee (IRB), All patients were subjected to: Informed written consent from patient's first degree relatives. Full history taking, stressing on vascular risk factors including hypertension, diabetes mellitus, dyslipidemia, smoking, use of anticoagulants and previous stroke. General and neurological examination with assessment of neurological function on admission using Glasgow Coma Score (GCS), NIHSS and Intra-Cerebral Hemorrhage score (ICHS). Laboratory assessment on admission including: Complete blood count with special interest on the total leukocytic count, urine analysis and HB level. The D-dimer test (INNOVANCE D-Dimer; Siemens AG, Munich, Germany) is a particle enhanced, immunoturbidimetric assay for the quantitative determination of cross-linked fibrin degradation products in human plasma. In our laboratory, the reference range for healthy controls is <500 µg/dl fibrinogen equivalent units (FEU). We did for all patients CT brain on admission and follow up after 1st week and also after 4 weeks of onset with stress on All the included patients were followed up, both clinically using the NIHSS score (neurological deterioration is defined as an increase of the score ≥ 4 points than the baseline score) (8), radiologically with CT brain after 1 week and 4 weeks of the onset to assess the growth, complications or resolution. Correlation between patient's NIHSS and hematoma parameters in follow up CT brain. Patients' outcome is assessed using modified Rankin scale (mRs) at discharge from hospital.

Statistical Analysis:-

All data were analyzed using SPSS 18.0 for windows (SPSS Inc., Chicago, IL, USA) & MedCalc 13 for windows (MedCalc Software bvba, Ostend, Belgium). To determine predictors for overall mortality, any variables with p-value ≤ 0.05 in univariate analysis were subjected to multivariate logistic regression analysis with forward method for entering of covariates. All tests were two sided. $p < 0.05$ was considered statistically significant (S), $p < 0.01$ was considered highly statistically significant (HS), and $p \geq 0.05$ was considered non statistically significant (NS).

Results:-

The study included 116 patients, 67 of them were males and 49 were females with their mean age 62.54 ± 11.45 years. Their age ranged from 22-90 years. The number of deaths among our patient was 33 patients (27.5%) in total, 16 patients were died in the first week of onset (13.3%) and 17 patients were died after the first week (14.16%). We found that 39% of overall mortality was among those patients who had higher levels of serum D-dimer on admission. The higher levels of D-dimer were strongly correlates with higher rates of disabilities scored by mRS, and when using the forward method to evaluate the different factors that can predict the outcome, it was found that initial D-dimer can independently predict the poor short term outcome.

Table 1:- correlation of D-dimer level with patient's motality.

Variable	D-dimer				Test	p-value (Sig.)
	≤500 µg/dl		>500 µg/dl			
	No.	%	No.	%		
Overall mortality	(n=39)		(n=77)			
Survive	36	92.3%	47	61%	12.435•	<0.001 (HS)
Died	3	7.7%	30	39%		

Mortality in 1st week	(n=39)		(n=77)			
Survive	38	97.4%	62	80.5%	6.230•	0.013 (S)
Died	1	2.6%	15	19.5%		
Mortality after 1st week	(n=38)		(n=62)			
Survive	36	94.7%	47	75.8%	5.984•	0.014 (S)
Died	2	5.3%	15	24.2%		
mRS	(n=39)		(n=77)			
Mean ± SD	2.82 ± 1.29		4.18 ± 1.59		-4.350*	<0.001 (HS)
Median	3		4			
Range	1 – 6		1 – 6			

* Mann Whitney U test. • Chi-square test. p< 0.05 is significant. Sig.: significance.

Table 2:- Predictors for overall mortality in the studied cross section (N=116) by univariate analysis.

	β	SE	OR (95% CI)		p-value
Age (years)	0.000	0.018	1.000	(0.965 – 1.036)	0.999 (NS)
Smoking	-0.467	0.440	0.627	(0.265 – 1.483)	0.288 (NS)
Hypertension	-0.156	0.584	0.856	(0.273 – 2.685)	0.789 (NS)
Diabetes	+1.405	0.531	4.076	(1.440 – 11.537)	0.008 (HS)
GCS	-0.862	0.175	0.422	(0.300 – 0.596)	<0.001 (HS)
WBCs (/mm^3)	+0.201	0.056	1.223	(1.095 – 1.366)	<0.001 (HS)
RBS (mg/dl)	+0.011	0.003	1.011	(1.005 – 1.017)	<0.001 (HS)
ESR (mm)	+0.049	0.013	1.050	(1.024 – 1.077)	<0.001 (HS)
CRP (mg/L)	+0.037	0.011	1.038	(1.016 – 1.060)	0.001 (HS)
D-dimmer	+0.001	0.000	1.001	(1.001 – 1.001)	<0.001 (HS)
Initial hematoma volume	+0.047	0.011	1.049	(1.027 – 1.071)	<0.001 (HS)
Midline shift	+0.443	0.103	1.557	(1.273 – 1.903)	<0.001 (HS)
IVH	+0.197	0.505	7.172	(2.668 – 19.280)	<0.001 (HS)

Proportional by chance accuracy criteria=80.7% . The model predict overall accuracy rate=84%.
Null model -2 Log Likelihood=107.855; Full model -2 Log Likelihood=66.203. Overall model chi square=41.652, d.f=13, p<0.001 (HS). Hosmer and Lemeshow goodness of fit test p=0.624 (NS) β: regression coefficient; SE: standard error; OR: Odds ratio; 95%CI: 95% confidence interval. p< 0.05 is significant.

Table 3:- Correlation between Glassgow Coma Score, Intracerebral Hemorrhage score, National institute of health stroke score, modified Rankin Score and selected study parameters

Variables	**GCS**		**ICH score**		**NIHSS**		**mRS**	
	r	p-value (Sig.)	r	p-value (Sig.)	r	p-value (Sig.)	r	p-value (Sig.)
WBCs (x103/mm3)	-0.259	0.005 (HS)	+0.309	0.001 (HS)	+0.282	0.002 (HS)	+0.333	<0.001 (HS)
Random Blood Glucose (mg/dl)	-0.389	<0.001 (HS)	+0.391	<0.001 (HS)	+0.364	<0.001 (HS)	+0.382	<0.001 (HS)
D dimer	-0.456	<0.001 (HS)	+0.376	<0.001 (HS)	+0.315	0.001 (HS)	+0.510	<0.001 (HS)
Volume of hematoma (Cm3)	-0.455	<0.001 (HS)	+0.599	<0.001 (HS)	+0.456	<0.001 (HS)	+0.483	<0.001 (HS)
Midline shift (Cm)	-0.463	<0.001 (HS)	+0.468	<0.001 (HS)	+0.386	<0.001 (HS)	+0.481	<0.001 (HS)

Table 4:- Predictors for overall mortality in the studied cross section (N=116) by multivariate analysis (Forward method).

	β	SE	OR (95% CI)		p-value
D-dimmer	+0.001	0.001	1.001	(1.000 – 1.002)	0.044 (S)

Initial volume	+0.107	0.054	1.113	(1.002 – 1.237)	0.046 (S)
NIHSS	+1.210	0.512	3.354	(1.231 – 9.140)	0.018 (S)
Constant	-18.427				

Proportional by chance accuracy criteria=89.7% .The model predict overall accuracy rate=99%.Null model -2 Log Likelihood=91.177; Full model -2 Log Likelihood=12.247. Overall model chi square=78.930, d.f=4, p<0.001 (HS) Hosmer and Lemeshow goodness of fit test p=1.000 (NS) β: regression coefficient; SE: standard error; OR: Odds ratio; 95%CI: 95% confidence interval. p< 0.05 is significant.

Discussion:-

Elevated plasma D-dimer has been related to unfavorable outcomes and has been suggested as a prognostic factor for ICH **(Hu et al. 2014).** Our results revealed elevated D-dimer level above 500 µg/dl in 77 patients, 39% of them died in the first month and this was significantly related to the patient mortality (P= 0.001).This in agreement with the results that obtained by **Delgado and colleagues (2006),** as they concluded that patient's mortality was significantly related to plasma D-dimer level among 98 patients with ICH. Nearly the same findings by **Chiu et al. (2012),** who investigated the association between serum D-dimer concentration and clinical outcomes in 170 patients diagnosed with sICH and found that there is statistically significant relation between mortality and D-dimer level (P= 0.014). **Hu et al. (2014),** recently also found a high significant relation of the D- dimer level with the patient's early mortality in a study done on 259 patients with sICH.

High plasma D-Dimer levels proved a risk factor for 30-day mortality with a sensitivity of 70% and a specificity of 60% **(Senn et al., 2014).** The range of the recorded mRS was 1-6 points with no patients scored 0/6 or 5/6. Patients scored 1-2 were 18.9%, those with score 3-4 were 52.6% and patients with 6/6 score were equal to mortality (28.4%). The outcome of our patients as regards the mortality and disability was quietly in same line with the previous studies like that of **EL Tallawy et al. (2005),** who reported that 32.3% of patients were died within the first month. Similarly **Zis et al. (2014),** found that 30-day case fatality rate in their ICH patients was 31.9%, as 61 patients died within 30 days after the ICH out of 191 patients included in their study. Again **Stein et al. (2011),** who observed that 30-day mortality was 28.6%, but in contrast to our results regarding disability, they found only 17.4% of the patients showed a favorable functional outcome (mRS ≤ 3) versus 56.8% in our patients. In **(2013), Hu et al.,** reported that overall hospital mortality was 24.4% and mean time from admission to death was (10.5±18.5) days, of them 36 patients died in the first 72 h due to neurological complications. Of their total sample, 21.8% recovered fully (with no lasting sequelae), while 50.4% improved after therapy but with lasting sequelae but the discrepancy of their results with ours may be due to the larger sample size (266 vs 116) and not all patients were of primary type of ICH. In our results the absence of patients that had independent life activity after one month of ICH may be due to the short time of follow up, small sample size as compared to multicenter studies or epidemiological ones and also the defect in complementary treatment strategies as nutritional, rehabilitation and psychological.

In the present study, the results of laboratory tests, radiological variables and different clinical scores that we used in patients' assessment, showed that admission leukocytosis, hyperglycemia, elevated ESR, CRP, serum D-dimer, large hematoma volume and presence of midline shift were all highly correlated with ICH score, NIHSS, and mRS (positive correlation) and with GCS (negative correlation). In our enrolled patients we found that high levels of D dimer on admission predicts a poor outcome and considered as potent risk and predictor for overall mortality by the end of first month after the onset (OR 1.001, 95% CI:1.000-1.002, P=0.004) and this also matches with the results of Chiu et al, (2012), who found nearly same results (OR: 2.72; 95% CI: 1.08–6.9, $p = 0.002$).

In view of our results in the present study we can conclude that assessment of admission serum level of patient's D dimer correlates with mRS after one months and the higher the admission D dimer levels, the poorer the outcome and the higher the mortality in those presented with sICH.

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