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Raised D-dimer is an Independent Predictor of Unfavorable Short-Term Outcome in Aneurysmal Subarachnoid Hemorrhage

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Abstract

Background: *Plasma d-dimer is raised during acute stage of aneurysmal subarachnoid hemorrhage and may be related to outcome.* ***Objective****: The aim of the study was to evaluate the association of d-dimer with short term outcome in aneurysmal subarachnoid hemorrhage.* ***Methods:*** *This prospective cohort study was conducted at the department of Neurology, National Institute of Neurosciences & Hospital, for one and half year of period. A total of 120 admitted aSAH patients were enrolled in this study, among them 60 patients had raised d-dimer and another 60 patients had normal d-dimer. D-dimer was measured quantitatively by nephelometric assay using AGAPPE(MISPA-i2) reagent. A value < 0.5mg/L was labelled as normal and e"0.5mg/L was labelled as raised according to user manual. A detailed history and thorough clinical examination were carried out in each patient during admission and follow ups were done during hospital stay to see the complications. Functional outcome was measured at 90 days using Modified Rankin Scale (mRS). A mRS score 0-2 and 3-6 was considered as favorable and unfavorable outcome respectively.* ***Results:*** *Participants with raised d-dimer on admission had significantly higher age, clinical severity (according to World Federation of Neurosurgical Societies Grade, Hunt & Hess grade), high grade hemorrhage in Modified Fisher grade and neurological complications in comparison to those with normal d-dimer (P<0.05). Patients with unfavorable outcome were more in raised d-dimer group than normal d-dimer group (76.5% vs 23.5%) (P<0.001). Multivariant logistic regression shows d-dimer is an independent predictor for unfavorable outcome (OR 1.79 [95% CI 1.08-2.36], P=0.018) at 90 days.* ***Conclusion:*** *Raised d-dimer level on admission was significantly associated with unfavourable short-term outcome in aneurysmal SAH patients at 90 days and had an additive predictive value. However, further larger study is recommended*

Keywords: *Aneurysmal SAH; D-dimer; Unfavourable outcome*

Introduction:

Subarachnoid hemorrhage is a devastating disease of CNS affecting significant number of population. It accounts for 5% of all strokes and carries an exceptionally high disease-specific burden.[1] Excluding head trauma the most common cause of SAH is rupture cerebral aneurysm.[7] In a systematic review and meta-analysis, the overall crude global incidence of aneurysmal SAH across all study periods was 7.9 per 100,000 person years.[1] This is a disease with high rates of case fatality (~40%) and morbidity.[12] Sudden death occurs in 12-15% of patients even before reaching medical attention.[14] For patient who arrive alive at hospital , the mortality rate is about 45% over next month, of those who survives, more than half are left with major neurologic and cognitive deficit.[7] Multiple factor predicts both short term and long

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term functional outcome in aSAH , like age of the patient, hypertension, hyperglycemia, smoking, high grade hemorrhage in different scaling system & initial clinical presentation measured by GCS (Glasgow Coma Scale), Hunt & Hess Grade or WFNS (World Federation of Neurosurgical Societies) grade, size of the aneurysms etc.[4,6,20] In spite of these clinical factors, it is still necessary for clinicians to find more functional outcome predictors because predicting outcomes solely based on clinical factors are sometimes inaccurate.[5,15,18] Biomarkers have potential role in the pathological process after aSAH, so they might be more reliable in predicting the outcomes of patients with aSAH.[20] There is emerging evidence that raised d-dimer level in aneurysmal subarachnoid hemorrhage have strong predictive prognostic value.[3,6,13,19] Plasma d-dimer levels elevate during acute stages (0-3 days) of aneurysmal subarachnoid hemorrhage.[3] Serum d-dimer levels exhibit high sensitivity of 78.1% (95% confidence interval (CI): 72.9-83.8%) among patients with spontaneous aSAH.[17] During aneurysm rupture blood contacts the extravascular matrix, leading to an activation of both blood coagulation and fibrinolysis and after initial insult the coagulation cascade can be further activated by endothelial dysfunction, rebleed & sepsis results in raise d-dimer in aSAH.[8,10,12,16] However what has remained unclear is whether d-dimer, independently of severity of bleeding as well as with other confounding factor assessed clinically and radiologically, is a risk factor for poor functional outcome. In this study we will try to investigate whether elevated plasma d-dimer levels at admission independently predicts functional outcome after aSAH.

Material & Method

This single center hospital based prospective cohort study was conducted at the department of Neurology, National Institute of Neurosciences & Hospital, Dhaka. All patients of aneurysmal SAH patient who met the inclusion and exclusion criteria were approached for this study. The blood sample was sent for estimation of d-dimer level within first 24 hour of admission. A total of 120 admitted aSAH patients were enrolled in this study, among them 60 patients had raised d-dimer level and another 60 patients had normal d-dimer level. The patient's neurological status was recorded, the severity of neurological deficit was evaluated with the WFNS and Hunt & Hess scale. Severity of SAH was assessed with Modified Fissure scale based on computed tomography (CT) imaging. Aneurysmal bleeding was confirmed by CT angiogram (CTA) or MRA or Digital Subtraction Angiogram (DSA). Patient's functional outcome was measured at 90 days (3 months) of the ictus in follow up visit in OPD and if not possible then over telephone. All data including patient's clinical profile, risk factor for SAH & confounding variables, functional outcome at 90 days (3 months), level of d-dimer along with some routine investigations were recorded in a preformed data collection sheet. After collection of all the required data, data were checked, verified for consistency and tabulated using the SPSS 22 software. Statistical significance was set at 95% confidence level. Continuous data were expressed as mean and standard deviation and categorical data were expressed as frequency and percentage. To compare continuous data among two groups (raised d-dimer & normal d-dimer) we use independent sample t test (students t-test). To compare categorical variables, we used chi-square test. To asses independent predictive value of variables, we did multivariant binary logistic regression. For clinically intercorrelated variables that measure similar construct (e.g., GCS, HHG & WFNS grade), we only selected the variable with highest measure of association (Odds ratio) and smallest P value. Probability (p) value of <0.05 were considered statistically significant for all type of analysis.

Result:

Baseline clinical and radiological Characteristics of 120 patients according to d-dimer level are summarized in Table1. Increasing age (p =0.032), Patient present

with vomiting (p=0.001), and poorer initial neurological state (WFNS grade 4-5 & HHG III-IV) is more likely to present with raise d-dimer (p value<0.001 & 0.031 respectively). Patient present with high grade hemorrhage in CT head according to Modified fisher Grade is significantly associated with raise d-dimer (p <0.001). No significant

association is found among respondent with hypertension, Diabetes Mellitus, Ischemic Heart disease and antiplatelet drug use with d-dimer level. D-dimer is significantly associated with neurological complication during hospital stay. Seizure (p =0.002), delayed cerebral ischemia (p=0.001), hydrocephalus (p=0.002) & rebleed (p-=0.031) were significantly higher in raised d-dimer group, however non-neurological complications like hospital acquired infection, hyponatremia, and cardiac event were not significantly associated with d-dimer level (Table 2). Most of the patient (76.5%) with unfavorable outcome (mRS score 3-6) at 90 days were in the raised d- dimer group which is statistically significant (p<0.001) (Table 3). We did multivariate regression analysis (Table-4) with unfavorable outcome at 90 days (3 months).

It shows d-dimer can independently predict unfavorable outcome at 90 days (P-value=0.018, OR=1.79, 95% CI: 1.08-2.36) .We also find that seizure (p=0.016),rebleed (p=0.002) and size(mm) of the aneurysm(0.018) can also independently predict the outcome at 90 days .

Table-I

Baseline clinical and radiological characteristics of 120 patient associated with d-dimer level (N=120)

Variables	Serum d-dimer level		TotalN=120(%)	P-value
	Raisedn=60(%)	Normaln=60(%)		
Mean Age ±SD	56.13±12.09	51.45±11.47	53.79±11.97	0.032**
Gender (Female)	39 (65)	36 (60)	75 (62.5)	0.572
Headache(Moderate to severe)	59 (98.3)	57 (95)	116 (96.7)	0.309
Vomiting	46 (76.7)	29 (48.3)	75 (62.5)	0.001
Neck stiffness	57 (95)	55 (91.7)	112 (93.3)	0.464
Focal neurological deficit	6 (10)	2 (3.3)	8 (6.7)	0.143
WFNS Grade (4-5)	23 (38.3)	10 (16.7)	33 (27.5)	<0.001
HHG (III-IV)	32(53.3)	17(28.3)	49(40.9)	0.031
Hypertension	31 (51.7)	25(41.7)	56(46.70)	0.272
Diabetes mellitus	7 (11.7)	9 (15)	15 (12.5)	0.591
IHD	8 (13.3)	6 (10)	14 (11.7)	0.570
Anti-platelet	4 (6.7)	5 (8.3)	9 (7.5)	0.729
MFG(III-IV)	36(60)	13(21.6)	49(40.8)	<0.001
Aneurysm size (mm)	7.24 ±2.61	6.93±2.50	7.08±2.55	0.510**

Values are expressed as Mean±SD and within parenthesis percentage (%) over column total.
* Chi-squared Test (c^2) and ** Student t-test were performed to determine the P-value
WFNS =World Federation of Neurosurgical Societies,HHG & Hunt & Hess Grade,IHD=Ischemic Heart Disease MFG=Modified Fisher Grade

Table-II

Association of complications during hospital stay with serum d-dimer level among respondents (N=120)

Complications during hospital stay	Serum d-Dimer level		TotalN=120(%)	P-value
	Raisedn=60(%)	Normaln=60(%)		
Seizure	17 (28.3)	7 (11.7)	24 (20)	0.022
Delayed cerebral ischemia	18 (30)	4 (6.7)	22 (18.3)	0.001
Hydrocephalus	29 (48.3)	13 (21.7)	42 (35)	0.002
Rebleed	15 (25)	6 (10)	21 (17.5)	0.031
Hyponatremia	14 (23.3)	10 (16.7)	24 (20)	0.361
Hospital Acquired Infection	4 (6.7)	3 (5)	7 (5.8)	0.697
Cardiac event	13 (5)	1 (1.7)	4 (3.3)	0.309

Values are expressed as Mean±SD and within parenthesis percentage (%) over column total.
* Chi-squared Test (c^2) were performed to determine the P-value

Table-III

Association of outcome at 90 days with serum d-dimer level among respondents (N=120)

Outcome	Serum d-dimer level		Total	P-value
	Raised n=60 (%)	Normal n=60 (%)	N=120 (%)	
Favorable Outcome(mRS score 0-2)	21 (30.4)	48 (69.6)	69 (100)	<0.001
Unfavorable Outcome(mRS score 3-6)	39 (76.5)	12 (23.5)	51 (100)	

Values are expressed within parenthesis percentage (%) over row total.
* Chi-squared Test (c^2) was performed to determine the P-value

Table-IV

Multivariate binary logistic regression for unfavorable outcome

Variable	OR	CI at 95%	P-value
Age	1.01	0.96-1.07	0.710
WFNS grade	1.24	0.72-2.13	0.436
HTN	1.71	0.53-5.51	0.368
DCI	1.28	0.23-7.13	0.788
Seizure	6.56	1.42-30.28	0.016
Hydrocephalus	2.79	0.794-9.80	0.110
Rebleed	21.21	3.10-145.13	0.002
HAI	0.59	0.02-13.65	0.740
MFG	0.77	0.30-1.59	0.521
Aneurysm size (mm)	1.34	1.05-1.71	0.021
D-dimer	1.79	1.08-2.36	0.018

OR=Odds Ratio, CI=Confidence interval, WFNS =World Federation of Neurosurgical Societies,HTN=Hypertension DM=Diabetes Mellitus, DCI=Delayed Cerebral ischemia, HAI=Hospital Acquired Infection MFG=Modified Fisher Grade

Discussion:

Significant association had been found in the mean age of respondent with raised and normal d-dimer level in this study and the mean values were 56.13±12.09 (SD) year and 51.45±11.47(SD year respectively in raised and normal level of d-dimer among respondents. Previous study shows median age of positive d-dimer level among spontaneous Subarachnoid Hemorrhage patients was 58 (46.0,71.0) years where in negative d-dimer respondents median age was 50.5 (43.5, 64.5) years and both findings are very close to our findings .In case of gender majority of the patients in positive d-dimer group is female (63.8%) which is also very much close(65%) to our finding.[17] In the study of Fukuda et al., 2017 ,they found increase age is statistically significant (P<0.001) for raised d-dimer ,which match to our findings, however they also find female sex statistically significant for raised d-dimer but we didn't, which is may be due to relatively less female participant or sample size of our study. Most of the respondents had moderate to severe headache (96.7%) and neck stiffness (93.3%) in both raised and normal d-dimer level respondents, although, those were not statistically significant. However, vomiting (76.7%) and poor Initial clinical status by WFNS grade (3-4) and Hunt and Hess grade (HHG) (III-IV) was significantly associated with raised serum d-dimer level. In previous study the also found significant association of raised d-dimer with WFNS grade 4-5 (P<0.001).[3] In the study of

Juvela et al., (2006) they found raised d-dimer is significantly associated with increase in WFNS grade (P=0.001). Both findings are consistent with our study. Fang et al., (2022) found increase in d-dimer level is (d-dimer quartile, mg/L) significantly associated with increase HHG (P=0.001) which is similar to our findings.[2] Most of the respondents with raised d-dimer had grade III MFG (43.3%), while among respondents with normal d-dimer level most of them had grade I (60%) which indicate raised d-dimer is associated with severity of bleeding (p<0.001). Previous study find significant association of increase d-dimer quartile(mg/l) with increase in Fisher Grade (P<0.001).[2] In the study of Juvela et al., (2006) they found thick layer hemorrhage in fisher grade at admission is associated with raise d-dimer at discharge. These findings are consistent with our findings. Size of the aneurysm had no significant association with d-dimer level . In a previous study plasma d-dimer D-dimer values did not associate significantly with location of ruptured aneurysm, number of (P=0.72).[3] In the study of Fang et al., (2022) they found an association of raise d-dimer with increase in mean‘ size of aneurysm, this difference may be due to design of the study (they do not include nondefinitive and fusiform aneurysm in their study).Seizure (P=0.022), Delayed cerebral ischemia (DCI) (P=0.001)), hydrocephalus (P=0.002) and rebleed (P=0.031) were significantly associated with raised d-dimer among respondents. Though, hyponatremia, hospital acquired infection, cardiac event was not statistically significant in this study. In the study of Fukuda et al., (2017) among neurological complications, hydrocephalus was significantly (P=0.01) associated with elevated D-dimer level, also with marginally significant associations of DCI (P=0.078) and systemic complications as, nosocomial infection (P=<0.001), Serum sodium disorder (P=0.043),And cardiopulmonary complication (P=<0.001). [3] In the study of Juvela et al., (2006) they found significant association (P<0.01) of rebleeding with raised d-dimer at discharge [12] .In our study we find most of respondents (76.5 %) with unfavorable outcome was in the raise d-dimer group, whereas most of the respondents (69.6%) with favorable outcome was in the normal d-dimer group, which is statistically significant (P<0.001). In the study of Juvela et al., (2006), they found raise d-dimer is associated with poor outcome at 3 months (P<0.001).[12] Multivariate logistic regression analysis showed d-dimer can independently (P=0.018) predict the unfavorable outcome at 90 days. Fukuda et al., (2017), and Juvela et al, (2006) also find similar findings where d-dimer can also independently predict (P=0.003 & 0.006 respectively) the outcome after 3 months. [3,12]

Conclusion: Death and disabilities rate were significantly higher raised d-dimer group. Hence, it can be concluded, d-dimer level is an independent marker for short term unfavorable outcome and has a additive prognostic value beside conventional risk factors. Further multicenter studies with larger sample size are recommended. Patients with elevated D-dimer levels should receive extra attention since they have more chance of developing complications and death

Ethical Clearance: Ethical clearance was taken from Institutional Review Board

Conflict of Interest: There was no conflict of intertest

Reference:

1. Etminan N, Chang HS, Hackenberg K, De Rooij NK, Vergouwen MD, Rinkel GJ, Algra A. Worldwide incidence of aneurysmal subarachnoid hemorrhage according to region, time period, blood pressure, and smoking prevalence in the population: a systematic review and meta-analysis. JAMA neurology. 2019 May 1;76(5):588-97.
2. Fang F, Wang P, Yao W, Wang X, Zhang Y, Chong W, Hai Y, You C, Jiang Y. Association between D-dimer levels and long-term mortality in patients with aneurysmal subarachnoid hemorrhage. Neurosurgical Focus. 2022 Mar 1;52(3):E8.
3. Fukuda H, Lo B, Yamamoto Y, Handa A, Yamamoto Y, Kurosaki Y, Yamagata S. Plasma D-dimer may predict poor functional

outcomes through systemic complications after aneurysmal subarachnoid hemorrhage. Journal of Neurosurgery. 2017 Aug 1;127(2):284-90.

4. Galea JP, Dulhanty L, Patel HC. Predictors of outcome in aneurysmal subarachnoid hemorrhage patients: observations from a multicenter data set. Stroke. 2017 Nov;48(11):2958-63.
5. Greenberg JK, Guniganti R, Arias EJ, Desai K, Washington CW, Yan Y, Weng H, Xiong C, Fondahn E, Cross DT, Moran CJ. Predictors of 30-day readmission after aneurysmal subarachnoid hemorrhage: a case-control study. Journal of neurosurgery. 2016 Aug 1;126(6):1847-54.
6. Hokari M, Uchida K, Shimbo D, Asaoka K, Itamoto K. D-dimer Predict Poor Outcome and Early Brain Injury after Aneurysmal Subarachnoid Hemorrhage. Neurosurgery. 2020 Dec;67(Supplement_1):nyaa447_302.
7. Hauser S, Josephson SA. Harrison's neurology in clinical medicine. 4th ed. Columbus, OH: McGraw-Hill Education; 2017.
8. Haapaniemi E, Tatlisumak T. Is D dimer helpful in evaluating stroke patients? A systematic review. Acta Neurologica Scandinavica. 2009 Mar;119(3):141-50.
9. Hong CM, Tosun C, Kurland DB, Gerzanich V, Schreibman D, Simard JM. Biomarkers as outcome predictors in subarachnoid hemorrhage–a systematic review. Biomarkers. 2014 Mar 1;19(2):95-108.
10. Ilveskero S, Juvela S, Siironen J, Lassila R. D-dimer predicts outcome after aneurysmal subarachnoid hemorrhage: no effect of thromboprophylaxis on coagulation activity. Neurosurgery. 2005 Jul 1;57(1):16-24.
11. Juvela S, Siironen J, Kuhmonen J. Hyperglycemia, excess weight, and history of hypertension as risk factors for poor outcome and cerebral infarction after aneurysmal subarachnoid hemorrhage. Journal of neurosurgery. 2005 Jun 1;102(6):998-1003.
12. Juvela S, Siironen J. D-dimer as an independent predictor for poor outcome after aneurysmal subarachnoid hemorrhage. Stroke. 2006 Jun 1;37(6):1451-6.
13. Liu JH, Li XK, Chen ZB, Cai Q, Wang L, Ye YH, Chen QX. D-dimer may predict poor outcomes in patients with aneurysmal subarachnoid hemorrhage: a retrospective study. Neural Regeneration Research. 2017 Dec;12(12):2014.
14. Lee VH, Ouyang B, John S, Conners JJ, Garg R, Bleck TP, Temes RE, Cutting S, Prabhakaran S. Risk stratification for the in-hospital mortality in subarachnoid hemorrhage: the HAIR score. Neurocritical care. 2014 Aug;21(1):14-9.]
15. Le Roux PD, Elliott JP, Newell DW, Grady MS, Winn HR. Predicting outcome in poor-grade patients with subarachnoid hemorrhage: a retrospective review of 159 aggressively managed cases. Journal of neurosurgery. 1996 Jul 1;85(1):39-49.
16. Parra A. Are D-dimer levels after aneurysmal subarachnoid hemorrhage predictive of outcome?. Nature Clinical Practice Neurology. 2006 Nov;2(11):592-3.
17. Solomon T, Kotter H, Mower W. Sen-sitivity of serum D-dimer for sponta-neous subarachnoid hemorrhage. Emerg Med Open J. 2016;3(1):6-10.
18. Turner CL, Budohoski K, Smith C, Hutchinson PJ, Kirkpatrick PJ. Elevated Baseline C-Reactive Protein as a Predictor of Outcome After Aneurysmal Subarachnoid Hemorrhage. Neurosurgery. 2015 Nov 1;77(5):786-93.
19. Zheng J, Cheng C, Zhou C, Chen H, Guo Z, Sun X. The clinical value of d-dimer level in patients with nonaneurysmal subarachnoid hemorrhage. World Neurosurgery. 2018 Jun 1;114:e1161-7.
20. Hong CM, Tosun C, Kurland DB, Gerzanich V, Schreibman D, Simard JM. Biomarkers as outcome predictors in subarachnoid hemorrhage–a systematic review. Biomarkers. 2014 Mar 1;19(2):95-108.