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Clinical Profile, Risk Factors and Outcome Assessment of Aneurysmal Subarachnoid Hemorrhage (SAH) Patients: A Multicenter Study in Bangladesh

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Abstract: The vast majority of the literature on aneurysmal Subarachnoid Hemorrhage (aSAH) is flawed by the homogeneity of Caucasian population in western based studies. There is dearth of such studies in the Indian Subcontinent which has different demographics, cultural differences and health problems, which we aim to explore with this study. This cross-sectional observational study on aSAH patients was conducted in 3 different hospitals in Bangladesh from 2016 to 2017. A total of 45 adult patients who fulfilled the selection criteria were enrolled in this study. Patients with confirmed SAH from ruptured cerebral aneurysm by various cerebral angiographic studies were evaluated for clinical profile, risk factors and outcome assessment. Headache (100%) was the most common presenting symptom. We found female predominance (62%), the age group with maximum number of patients was 41-60 years (60%). The most common clinical risk factor was hypertension (55%). Half of the patients have size of the ruptured cerebral aneurysm dome <7 mm. The most common location of the aneurysm was anterior communicating artery (51%). Statistically significant association was found between the Glasgow Outcome Scale at the time of discharge from the hospital with the Fischer Grading of SAH (p value of 0.03). Our study comprising Bangladeshi patients with aSAH had certain similarities and dissimilarities with predominantly white based western studies. Half of the patients in our study had small sized aneurysm which are known to rarely rupture, should provoke new thoughts about their management among neurosurgeons.

Keywords: Subarachnoid Hemorrhage, Cerebral Aneurysm, Risk Factors

1. Introduction

Intracranial saccular aneurysm, an abnormal permanent focal outpouching of cerebral artery, can cause substantial rates of morbidity (30% of survivors have moderate to severe disability) and mortality (about 45% during 1st bleed) [1, 2] when ruptured. The most common presentation of cerebral aneurysm is spontaneous rupture which produces SAH, also known as aneurysmal SAH (aSAH). Estimated annual rate of aSAH in most western population is 6-8 per 100,000 population [3]. Subarachnoid hemorrhage is more common in women than in men (2:1 ratio) with the peak incidence occurring in persons 50 to 60 year's old [4].

The most common histological finding is a decrease in the tunica media, the middle muscular layer of the artery, causing structural defects. These defects, combined with hemodynamic factors, lead to aneurysmal outpunching at arterial branch points in the subarachnoid space at the base of the brain [2].

Reducing the risk of rupture of an unruptured intracranial aneurysm (UIA) is an important method for reducing the incidence of aneurysmal SAH which has remained relatively

stable over the past decades [5]. The demographic risk factors known to cause rupture of cerebral aneurysm are female sex [6] and increased risk with advancing age [1, 7-8]. Similarly, the clinical risk factors for the same include smoking, hypertension, alcohol abuse, cocaine and sympathomimetic drug abuse, oral contraceptive pill use (OCP), pregnancy and parturition, mass effect due to UIA [1, 7-11].

The 3 seminal papers on the natural history of unruptured cerebral aneurysm: ISUIA Investigators [8], UCAS Japanese [7] and Finnish [1] studies concluded that size of the aneurysm (larger the size, more the risk of aneurysm rupture), location (posterior circulation including PCOM aneurysm tend to bleed more compared to anterior circulation aneurysm of equal size), abnormal configuration like daughter sac/aneurysmal bleb are in totality the radiological risk factors for the rupture of intracranial aneurysm. Most studies concur that the risk of aneurysm rupture especially in the anterior circulation have almost 0% percent risk of rupture for the size of the dome <7mm in diameter [1, 8].

Intracranial aneurysms are considered to be sporadically acquired lesions, although a rare familial form has been described [2]. Associated conditions like connective tissue diseases (e.g., autosomal dominant polycystic kidney disease (ADPKD), fibromuscular dysplasia (FMD), Marfan's syndrome, Ehlers–Danlos syndrome (EDS) type IV), and arteriovenous malformations (AVM) of the brain predispose to cerebral aneurysm formation and rupture [12, 13].

Rationale of this study lies in the fact that studies on aneurysmal SAH is miniscule in the Indian subcontinent as compared to sea of literature on it in Western based studies which are flawed by homogeneity of their study population, which is mostly Caucasian [1, 6, 8]. Replication of such studies in the Indian Subcontinent is prudent due to different ethnicity, socio-cultural norms, life style habits and health related problems compared to western population.

Peculiar to Bangladesh is that, alcohol consumption is rare, most likely due to religious norms, the use of illicit drugs is on the rise (there are 1 million drug-addicted people in Bangladesh and most of them are young, between the ages of 18 and 30) [14], OCP are being more frequently used in recent decades [15], cigarette smoking is quite prevalent in Bangladesh; however female smokers are small compared to male smokers in contrast to the western trend [16], the birth rate in Bangladesh is high (21.61/1000 population) [17], hypertension is one of the most prevalent health problem in Bangladesh. It is a known fact that HTN is more common in Asian population and Blacks compared to Caucasians.

Hence, current study may get a different picture on the prevalence of the risk factors for aneurysmal SAH in our study of Bangladeshi population compared to western based studies. It is prudent to mention this study is a cross-sectional observational study comprising hospital based patients with aneurysmal SAH. This is in contrast with community based western studies who prospectively followed patients with UIA till their end point- rupture with SAH, supported by review articles and meta-analysis on aneurysmal SAH [1, 2, 6, 8, 18]. The exception being a large prospective cohort study on unruptured cerebral aneurysm performed in Japan [7].

In the setting of current study, it is rare to find patients with UIA as almost every patient present to the hospital after its rupture due to symptoms from SAH. Incidentally discovered UIA in the Indian subcontinent is rare as is commonly seen in developed western world during screening of the brain for unrelated neurological problems.

The aim of the study is to provide comprehensive information regarding clinical profile, risk factors presence and frequency, radiological assessment of cerebral aneurysms and patient's clinical outcome assessment.

2. Materials and Methods

This study was a cross-sectional observational study on hospitalized aneurysmal SAH patients. The study was conducted in 3 different hospital's department of neurosurgery in Dhaka, Bangladesh (Bangabandhu Sheikh Mujib Medical University, Dhaka Medical College and Hospital, National Institute of Neuroscience and Hospital) from February 2016 to July 2017 after obtaining ethical clearance from each institute. Forty five consecutive adult patients who met the eligibility criteria to be included in the study were evaluated. All the patients were confirmed to have SAH from CT scan of the head and saccular aneurysm as the cause of SAH confirmed by various cerebral angiographic studies Computed Tomography Angiogram (CTA)/ Magnetic Resonance Angiogram (MRA)/ Digital Subtraction Angiogram (DSA). Biplaner DSA was performed through femoral artery catheterization with non-ionic water soluble iodinated contrast administration and real time imaging of cerebral vasculature using fluoroscopy technique, which was electronically saved by subtracting bone and the brain for further review of images in 3 dimensions.

Inclusion criteria: Patients can have SAH along with intracerebral hemorrhage (ICH) and/or intraventricular hemorrhage (IVH) from spontaneous rupture of saccular cerebral aneurysm, the size of the dome of aneurysm should be ≥3mm, study population can be previously untreated cerebral aneurysm which presented with SAH from re-rupture, multiple aneurysms, previous history of ruptured cerebral aneurysm at another location in case of multiple aneurysm which was treated was also included in the study.

Exclusion criteria: Patient <20 years of age, no upper age limit, patients with SAH but no radiographically visible cerebral aneurysm, aneurysms <3mm, fusiform/mycotic and traumatic aneurysms, SAH from arterial dissection, unwilling to sign written informed consent or voluntary withdrawal from the study, incompletely filled pre-set questionnaire (see below).

On admission, detailed history was taken and thorough physical examination, especially neurological examination was warried out. Hunt and Hess Grading [19, 20] to assess the patient's neurological and clinical status was recorded on admission. Glasgow Outcome Scale (GOS) [21] at the time of discharge of all patients were recorded irrespective of their

treatment status.

A pre-set structured questionnaire was prepared which enlists all the risk factors for aneurysmal SAH. To slightly elaborate, demographic risk factors (age and gender), clinical risk factors (HTN, smoking, alcohol abuse, cocaine abuse, OCP use etc.) and radiological risk factors (size, location, configuration and multiplicity of the cerebral aneurysm) was all enlisted.

Electronically saved CT scan of the head was used to determine the Fischer Grading of SAH [22]. A radiographic study which revealed cerebral aneurysm (CTA/MRA/DSA) was electronically saved for further analysis of size, shape, configuration, location and multiplicity of aneurysm. The size of the dome/fundus of the aneurysm was taken as the maximal dimension either in antero-posterior, cranio-caudal or transverse diameter. Size of the ruptured cerebral aneurysm dome/fundus was calculated by the provided measuring scale in CTA/MRA or imprinted measurement on the aneurysm dome itself by the neuro-radiologist. DSA has an inbuilt software that allows the use of measuring tool to determine the size of the aneurysm in various dimensions. Data was analyzed using statistical package for social software (SPSS) version 23. One Way ANNOVA (analysis of variance) was used as a test of significance to determine the strength of association between Hunt and Hess Grade on admission and Fischer Grading of SAH on CT scan of the head individually with GOS at the time of discharge from the hospital.

3. Results

Among 45 patients in the study, 28 patients (62.2%) were female, while 17 (37.8%) were male, with female: male ratio of 1.6:1. The mean (± SD) age of the patients in this study was 45.73 ± 11.78 years with the range (minimum-maximum age) of 24-80 years. The age group with maximum number of patients was 40-60 years (27 patients, 60%), followed by the age group 20-40 years (16 patients, 35.6%) and finally the age group 60-80 years (2 patients, 4.4%).

Table 1. *Distribution of patients by presenting features (n=45).*

Presenting features	Frequency (n)	Percentage (%)
Headache	45	100.0
Vomiting	33	73.3
Focal neurological deficit[1]	22	48.8
Altered mental status[2]	20	44.4

Table 1: Focal Neurological deficit[1] refer to hemiparesis, hemiplegia, dysphasia/aphasia etc.

Altered mental status[2] refer to disturbance in alert and/or awake state. It includes drowsiness, confusion, stupor and coma.

Table 2. *Distribution of patients according to clinical risk factors (n=45).*

Clinical risk factors	Frequency (n)	Percentage (%)
Hypertension	25	55.6
OCP use	13	28.8
Smoking	12	26.7
Alcohol Consumption	2	4.4
Sympathomimetic drug abuse	2	4.4
AVM associated with cerebral aneurysm	1	2.2
Previous history of SAH from the untreated offending aneurysm which re-presented with rupture.	2	4.4

Table 2: There were no patients with aneurysmal SAH who had pregnancy or parturition, family history of cerebral aneurysm, cocaine abuse, family history of cerebral aneurysm, confirmed case of congenital or connective tissue disease known to be associated with cerebral aneurysm, aneurysm rupture during catheter cerebral angiogram or lumbar puncture (LP), history of previous SAH from a separate aneurysm (other than offending aneurysm in case of multiple aneurysms).

Table 3. *Stratification of the size of the offending cerebral aneurysm (n=45).*

Dimension of the aneurysm (in mm)	Frequency (n)	Percentage (%)
<7	23	51.1
7 – 12	17	37.8
13 – 24	3	6.7
≥25	2	4.4
Total	45	100.0
Mean ± SD	8.03 ± 5.16	
Range (min-max)	3 - 35	

Table 3: About 50% of the cerebral aneurysm has the size of the dome of cerebral aneurysm in maximal dimension <7mm.

Table 4. *Distribution of patients according to location of the aneurysm (n=45).*

Location of the aneurysm	Frequency (n)	Percentage (%)
ACOM aneurysm	23	51.1
ACA aneurysm	1	2.2
MCA bifurcation aneurysm	8	17.8
MCA aneurysm (other than MCA bifurcation aneurysm)	5	11.1
ICA aneurysm	2	4.4
PCOM aneurysm	3	6.7
Basilar artery aneurysm	2	4.4
Vertebral artery aneurysm	1	2.2

Table 4: Three most common locations of ruptured cerebral aneurysm in the descending order are Anterior Communicating Artery (ACOM) aneurysm (51.1%), Middle Cerebral Artery (MCA) aneurysm (including MCA bifurcation aneurysm) (28.9%), and Posterior Communicating Artery (PCOM) aneurysm (6.7%).

Table 5. *Distribution of patients according to Hunt and Hess grading on admission (n=45).*

Hunt and Hess grading	Grading	Frequency (n)	Percentage (%)
Asymptomatic or minimal headache and slight nuchal rigidity	Grade I	1	2.2
Moderate to severe headache , nuchal rigidity, but no neurological deficit, other than cranial nerve palsy	Grade II	20	44.4
Drowsiness, confusion or mild focal neurological deficit	Grade III	7	15.6
Stupor, mild or sever hemiparesis, possible early decerebrate rigidity, vegetative disturbance	Grade IV	13	28.9
Deep coma, decerebrate rigidity, moribund appearance	Grade V	4	8.9

Table 5: About 47%, close to half of the patients had Hunt and Hess Grade I and II collectively.

Table 6. *Distribution of patients according to Fischer grading on CT scan of the head (n=45).*

Fischer grading	Grading	Frequency (n)	Percentage (%)
Diffuse thin layer of subarachnoid hemorrhage blood	Grade II	7	15.6
Localized clot or thick layer of subarachnoid blood	Grade III	9	20.0
Intracerebral or intraventricular blood with diffuse or no subarachnoid blood	Grade IV	29	64.4

Table 6: About 65% had the highest Fischer grade of IV. Fisher Grade I (no SAH detected) was not mentioned as all the patients in this study presented with SAH from ruptured aneurysm.

Table 7. *Distribution of patients according to Glasgow outcome scale (n=45). Determination of association between Hunt and Hess Grading of SAH on admission and Fischer Grading of SAH with Glasgow Outcome Scale at the time of discharge using one way ANNOVA[#].*

Glasgow outcome scale	Score	Frequency (n)	Percentage (%)
Death	1	4	8.9
Persistent vegetative state	2	6	13.3
Severe disability	3	8	17.8
Moderate disability	4	6	13.3
Good recovery	5	21	46.7
Glasgow Outcome Scale	Hunt & Hess Grading of SAH	p value = 0.07[#]	
Glasgow Outcome Scale	Fischer Grading of SAH	p value = 0.03[#]	

Annexure:

1) Among 45 patients, 60% of the patients had abnormal configuration of the fundus of ruptured cerebral aneurysm (40% had daughter sac (s)/Multi-lobulated and 20% had Murphy's tit/aneurysmal bleb). 40% ruptured cerebral aneurysm had smooth border with no out-pouching.
2) Six patients (13.3%) had multiple aneurysm. They had 1 additional unruptured aneurysm apart from the offending ruptured aneurysm. ACA, ICA and PCOM were the location of unruptured cerebral aneurysm in 2 patients each, amounting to total 6 patients with multiple cerebral aneurysm.
3) Thirty five (77.8%) subjects had interventions to secure aneurysm (clipping or coiling) while 10 (22.2%) opted for no intervention despite best medical advice.

4. Discussion

SAH from ruptured cerebral aneurysm is a catastrophic event with high morbidity and mortality. Considerable information has been gathered regarding cerebral aneurysm formation and rupture, still a lot is left to be explored regarding its pathophysiology, better management of its complications and reduce the overall morbidity and mortality. The incidence of aneurysmal SAH has remained stable over last few decades despite advancement in its pathophysiology, diagnosis, effective treatment modalities and better management of its complications [5].

The aim of current study has been clearly stated under the introduction section of this article and readers are kindly requested to review the introduction section.

In this study of 45 aneurysmal SAH patients, we found female predominance (62%) with female: male ratio to be 1.6:1, with female predominance matching with western study [23] where it is 2:1. The authors of this article suspected there may be male predominance in our study considering male seek medical attention more frequently than females considering social and financial constraints. It is worthwhile to mention that study conducted in 3 institutes have more male beds compared to female in the neurosurgery department.

The age group with maximum number of patients with aneurysmal SAH is 41-60 years (60%, 27 patients), with mean age of 45 years. This falls within the proximity of the Western studies comprising primarily Caucasians in that they quote 55-60 years as peak age for aneurysmal SAH [2]. Despite the late adulthood presentation of most of the patients in our study, the elderly population (60-80 years) did not exceed them. Hence, it may not be prudent to say literally that increasing age is inversely related to the rate of rupture of cerebral aneurysm as proposed by Juvela and colleagues [1].

The most common clinical presentation of patients with aneurysmal SAH was headache (100%), followed by vomiting (73%), focal neurological deficit (48%) and altered mental status (44%) (Table 1).

The most common clinical risk factors identified in our aneurysmal SAH study in descending order are HTN (55.6%), OCP (28.8%) and smoking (26.7%), with alcohol

consumption came a distant 4th position (4.4%) (Table 2). In the some large prospective cohort studies with homogeneity of white population [1, 8, 18, 24], the most common clinical risk factor was smoking (40% to 60%), followed by HTN (25% to 45%) and alcohol abuse (20% to 35%) respectively. It has been quoted in literature that Asians are more prone to hypertension compared to Caucasians, which is corroborated by the study performed by Japanese UCAS study [7] where HTN was the most prevalent clinical risk factor.

OCP ranked 2nd as the most common clinical characteristic in patients with aneurysmal SAH in this study (28.8%) which is a major deviance from the western studies where it is less frequent in patients with ruptured cerebral aneurysm. The authors assume with increased health awareness and need for family planning among women contributed to OCP use being more frequently present in the current study.

In this study, smoking came as the 3rd most common clinical characteristic associated with aneurysmal SAH. All the 12 (26.7%) patients with smoking history were male, elucidating the fact that female in the Indian subcontinent do not prefer smoking. Smoking has been proven to be the most important and lethal modifiable risk factor for SAH in Western studies. In a study by Juvela and colleagues [1], smoking had the hazard ratio of 2.4 in causing rupture of unruptured intracranial aneurysm, with 40% all SAH can be attributed to smoking.

We had only 2 patients (4.4%) with alcohol abuse, which is miniscule compared to westerners where alcohol abuse is higher (20-35%) [1, 8, 18, 24]. The religious and cultural norms in Bangladesh might be the reason for low prevalence of alcohol use in our study.

We had 1 patient who had AVM associated with ruptured cerebral aneurysm. We had 2 patients (4.4%) with previous history of SAH from the culprit aneurysm but did not seek surgical intervention. They presented with re-bleed from the same cerebral aneurysm.

About half of the patients (51%) had size of the ruptured cerebral aneurysm dome <7mm (Table 3). In reviewing large prospective cohort studies which followed unruptured cerebral aneurysm till they had SAH from its rupture found that the majority of unruptured cerebral aneurysm were <7mm (60%-70%), though they rarely ruptured [1, 7, 8]. These studies revealed that the size of the unruptured cerebral aneurysm <7mm has rupture rate of almost 0%. These articles also concluded the size of the aneurysm is directly proportion to risk of rupture. Current neurosurgical practice in the world for UIA <7mm is conservative management. These patients are annually screened with repeat angiogram to evaluate any increase in the size or configuration of aneurysm, which might necessitate intervention. Only unruptured cerebral aneurysm >8-10mm are managed surgically or by interventional procedures like coiling.

It is evident from current study that about half of the subjects had ruptured aneurysm size <7 mm. This is an interesting finding and may raise serious questions among neurosurgeons about the management of small sized UIA. Many studies like Korja et al. [24] had mentioned sporadic rupture of small aneurysm, but conservative management for these small size unruptured cerebral aneurysm still stands. As one author put it [24], the risk factor burden in patients with unruptured aneurysm should be considered in addition to the size of aneurysm in decision making process for further management of these patients.

The most common locations for ruptured cerebral aneurysm in our study are ACOM, MCA and PCOM in descending order with percentage of 51.1%, 28.9% and 6.7% respectively (Table 4). In western studies, it is ACOM, PCOM and MCA in the descending order with frequency of 30%, 25% and 20% respectively [25]. Hence ACOM aneurysm was the most common location in this study in concordance with previous literature.

Previous studies clearly delineates that abnormal cerebral aneurysm dome configuration other than smooth contour of the dome with no out-pouching is an independent risk factor for its rupture [2, 7, 24]. In our study, we had 60% of the patients with abnormal configuration (Murphy's tit and daughter sac/lobulated) as compared to 40% saccular aneurysms with smooth contour. In two seminal articles [7, 24], it has been quoted be about 20-25%. Thus we have significantly high percentage of patients with abnormal aneurysm dome configuration which may be a contributory factor for rupture of even small aneurysm in our study.

Presence of multiple aneurysm is considered a risk factor in itself for rupture of cerebral aneurysm [1, 7, 24]. In this study, 13% (6 patients) had multiple aneurysms. Hence it falls within the range of 10-30% as quoted in Western studies as the incidence of multiple cerebral aneurysm [2].

Please refer to Table 5 and Table 6 for Hunt and Hess grading of SAH on admission and Fischer grading of SAH based on CT scan of the head respectively pertaining to our study. Less than 50% had Hunt and Hess Grade I and II combined, making their surgical morbidity for securing aneurysm low. However, over 60% of patients had Fischer grading of IV, increasing the likelihood of cerebral vasospasm, intraventricular hemorrhage may cause hydrocephalus and necessitating CSF diversion procedures and urgent evacuation of intracerebral hemorrhage. 75% of the patient had surgical interventions, while the rest had conservative management due to very poor neurological status or patient/patient's relative refusing surgery despite strongest medical advice.

Hunt and Hess Grading of SAH [19, 20] on admission has been clearly indicated in its role in determining surgical morbidity and chances of developing cerebral vasospasm, which increases with increment in the grading scale. Fischer Grading of SAH [22] based on CT scan of the head has shown to have direct relationship with the risk of cerebral vasospasm. However, it is not amply evident from the existing literature with utilization of test of significance that Hunt and Hess Grading or Fischer Grading of SAH has definite relationship with patient's clinical outcome. Current study employed Glasgow Outcome Scale (GOS) [21] as a measure of patient's clinical outcome at the time of discharge from the hospital (see Table 7). This study ascertained the strength of association between Hunt and Hess Grading and

Fischer Grading of SAH on admission individually with GOS, to determine whether these grading systems on admission of aneurysmal SAH patients has any bearing on the patient's clinical outcome.

Statistically significant association was found between Fischer Grading of SAH on CT head with GOS at the time of discharge from the hospital (p value of 0.03) (Table 7). Strong association but not reaching statistical significance was found between Hunt and Hess Grading of SAH on admission with GOS at the time of discharge from the hospital (p value of 0.07) (Table 7).

The authors of this study strongly recommends abstaining from alcohol, smoking, use of illicit drug like cocaine, control of hypertension to name a few to reduce the incidence of aneurysmal SAH.

The limitations of the study are: 1) small sample size 2) cross-sectional observational study, basically a descriptive study on patients with aneurysmal SAH who presented to the hospital, rather than a case control study or more robust prospective cohort study of UIA derived from the population at risk 3) there may be interview bias based on patient's or their relatives educational and cultural norms 4) inter-observer variability may exist among neuro-radiologists in angiographic measurement and morphological characterization of cerebral aneurysms.

The authors of this study strongly recommends abstaining from alcohol, smoking, use of illicit drug like cocaine, control of hypertension to name a few to reduce the incidence of aneurysmal SAH.

5. Conclusion

Current study on aneurysmal SAH patients in Bangladesh, there were certain similarities and dissimilarities with predominantly white based western studies. Among similarities, predominance of female gender, maximum number of affected patients were in the age group 40-60 years, ACOM is the most common cerebral aneurysm, and frequency of multiplicity of aneurysm was similar. Among the dissimilarities, HTN was the most common risk factor in our study compared to smoking in western studies. OCP use ranked 2nd as the common clinical risk factor in our study which is less prevalent risk factors in western studies. This study had higher percentage of cerebral aneurysm with abnormal dome configuration as compared to western studies. Interestingly, 50% of the patients had cerebral aneurysm <7mm in size, which are known to rarely rupture and should provoke serious thoughts among neurosurgeons about management of these small sized aneurysms. There was statistically significant v association between Fischer Grading of SAH based on CT scan of the head with GOS at the time of discharge.

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Conflict of Interest

None.

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