STUDY OF THE PREDICTORS OF RUPTURE OF A SPECIFIC ANEURYSM IN A PATIENT DIAGNOSED WITH MULTIPLE ANEURYSMS - A PROSPECTIVE EXPLORATORY OBSERVATIONAL STUDY

By

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Submitted by : Dr. YOGESH MADHUKAR SAWAKARE

Programme : MCh Neurosurgery

Month & year of submission : July 2019

CERTIFICATE

This is to certify that the thesis entitled **"Study of the predictors of rupture of a specific aneurysm in a patient diagnosed with multiple aneurysms - a prospective exploratory observational study"** is a bonafide work of **Dr. Yogesh Madhukar Sawakare** conducted in the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram (SCTIMST), under my guidance and supervision.

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Department of Neurosurgery

SCTIMST, Thiruvananthapuram

DECLARATION

This thesis titled **"Study of the predictors of rupture of a specific aneurysm in a patient diagnosed with multiple aneurysms - a prospective exploratory observational study"** is a consolidated report based on a bonafide study of the period from January 2018 to July 2019, done by me under the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram. This thesis is submitted to SCTIMST in partial fulfilment of rules and regulations of MCh Neurosurgery examination.

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Dr. Yogesh Madhukar Sawakare

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ABBREVIATIONS

ACA	–	Anterior cerebral artery
AVM	–	Arteriovenous Malformation
CTA	–	Computerised Tomogram Angiography
DACA	-	Distal Anterior cerebral artery
DSA	–	Digital substraction angiogram
EEG	–	Electro encephalogram
GCS	–	Glasgow Coma Scale
ICA	–	Internal Carotid artery
Lt	–	Left
MCA	–	Middle cerebral artery
MRA	–	Magnetic resonance angiography
MRI	–	Magnetic Resonance Imaging
NCCT	–	Non contrast computerised tomogram
PCA	–	Posterior cerebral artery
PCOM	–	Posterior communicating artery
Rt	–	Right
SAH	–	Subarachnoid haemorrhage
VBA	–	Vertebral aneurysm
WFNS	–	World federation Neurological Scale

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INTRODUCTION

Cerebral aneurysms rupture leads to subarachnoid hemorrhage which leads to significant morbidity and mortality.

The outcome after subarachnoid hemorrhage due to aneurysmal rupture is still poor; mortality rates ranges from 40-50%, severe disability in 10-20% and only 40% reach independent status[1,2]. Contributing causes to mortality and morbidity is bleed, rebleed, vasospasm and cerebral ischemia.

Thereby "prevention is better than cure" can be applied for cerebral aneurysms if causative factors are known and will result in effective treatment of this patients.

Predictive factors for bleeding in aneurysm are studied well in literature series. Multiple intracranial aneurysms occur in approximately one third (15–45%) of patients presenting with Subarachnoid hemmorhage.[3,4,9] The exact mechanism of intracranial aneurysm formation per se remains obscured; however, congenital and/or acquired degenerative changes in the arterial wall have been implicated.[5,6,7]

The presence of multiple aneurysms is sometimes associated with poor outcome because of the complex management issues that are involved and the higher incidence of complications arising from both the hemorrhage and any treatment [6].

It follows, therefore, that the identification of modifiable risk factors for formation of multiple aneurysms is important and has implications both for the prevention of SAH and a more detailed understanding of the pathogenesis of multiple cerebral aneurysms. It is also important to know which aneurysm has bled so as to deal with it at first.

Consideration of radiological and clinical parameters is necessary for the assessment of the rupture. Many criteria on the basis of radiology i.e angiographic studies has been taken into account such as shape, size, location . neck, aspect ratio, etc have been evaluated in various studies. [6,7,8]

Clinical assessment is also carried out in many studies for the same such as age, gender, cigarette smoking, alcohol, familial, hypertension, collagen vascular diseases, etc.[3,4 ,5]

Cerebrovascular disease risk factors such as hypertension, cigarette smoking, and alcohol consumption have been shown to increase the risk of SAH and spontaneous intracerebral hematoma.[5]

However, the role of these risk factors in the formation of multiple, as opposed to single, aneurysms is less well defined. To have an insight of this factors determining rupture of specific aneurysm we carried out a prospective exploratory study of multiple aneurysm in our institute.

AIMS AND OBJECTIVES

AIMS:-

To understand the various clinical, radiological and operative findings of multiple aneurysms with subarachnoid hemorrhage.

OBJECTIVES:-

1. To study the various clinical, radiological and operative findings of multiple aneurysms with subarachnoid hemorrhage.

2. Predictive factors influencing the rupture of these aneurysms.

REVIEW OF LITERATURE

Since many centuries before intracranial aneurysms have been recognized. The word aneurysm: 'aneurys' means "dilatation" is derived from Greek and probably from the Sanskrit word 'uru' meaning 'wide". In 1765 Biumi of Milan described the unruptured cavernous carotid aneurysm in 53-year-old lady in an autopsy

In 1830 Blackhail described the first account of ruptured intracranial aneurysm. In Brinton 1850 collected 52 cases from literature and systematically analysed the symptomatology due to rupture of intracranial aneurysm. In 1859 Guu stressed headache as an important symptom. In 1923 Symonds first described the clinical picture of subarachnoid haemorrhage in detail. He divided it into three groups a) signs of leakage from the aneurysm, b) those of disease causing the aneurysm, c) those of local compression caused due to aneurysm.

In 1931 Collier coined the term “Berry aneurysm”. In 1937 Dandy did the first successful clipping of aneurysm. In 1939 the technique of cerebral angiography was demonstrated aneurysm by Egaz Moniz for the first time.

With further advancements in radiology, surgical management, anaesthetic care and intensive care the outcome of this difficult entity improved in terms of morbidity and mortality.

Neurological grading systems evolved namely “FISHERS” and “WFNS” over years of research and meticulous observations.

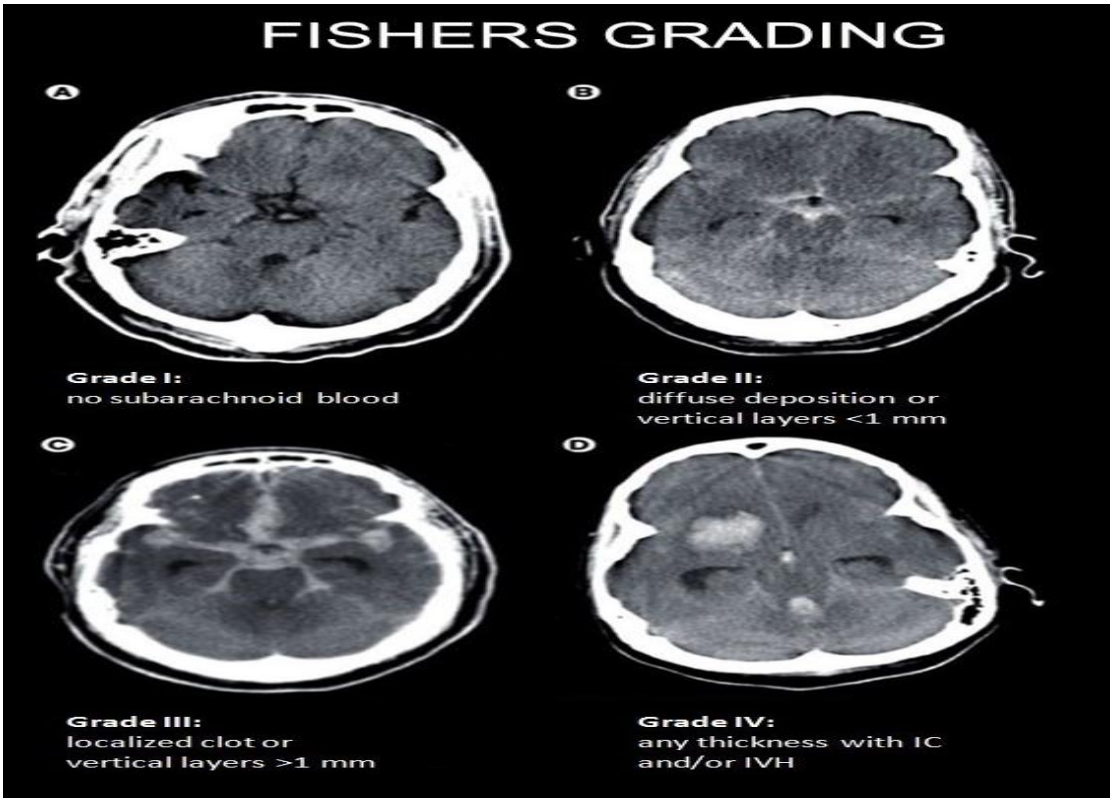


Figure 1 : Fishers grading

GLASGOW COMA SCALE

Eye(s) Opening	
Spontaneous	4
To speech	3
To pain	2
No response	1
Verbal Response	
Oriented to time, place, person	5
Confused/disorientated	4
Inappropriate words	3
Incomprehensible sounds	2
No response	1
Best Motor Response	
Obeys commands	6
Moves to localised pain	5
Flexion withdraws from pain	4
Abnormal flexion	3
Abnormal extension	2
No response	1
Best response	15
Comatose patient	8 or less
Totally unresponsive	3

A

WFNS SAH Grade		
WFNS Grade	GCS Score	Major Focal Deficit
0**		
1	15	-
2	13-14	-
3	13-14	+
4	7-12	+ or -
5	3-6	+ or -
*aphasia, hemiparesis or hemiplegia ** intact anseurysm		

B

Figure 2 : (A) Glasgow coma scale (B) WFNS SAH Grade

Theories implicated for the pathogenesis are classified as congenital, acquired, genetic and familial.

Pathological studies have proved that internal elastic lamina is the most important layer of the vessel wall maintaining the integrity. The cerebral vessels are predisposed to aneurysm formation because of thin wall and lack of abundant elastic tissue including absence of internal elastic lamina.

Factors altering the blood flow, such as vessel occlusion and those that cause increased blood flow such as in AVM's, and hypertension and the factors, which will affect connective tissue, such as smoking and connective tissue disorders, may accelerate the degenerative process.

Crompton examined 149 cases at autopsy and found medial defects, internal cushions and even changes in the internal elastic lamina in cerebral arterial junction at birth, although he noted that all these changes subsequently increase with increase in age. Arterial hypertension and renal polycystic disease were found to be associated with increased number of large medial defects. The present overall consensus is that atherosclerosis does not lead directly to the aneurysm formation. Funnel shaped dilatation; areas of thinning and small evagination were thought to be essential pre-aneurysmal lesions, as they were associated with severe degenerative changes in the internal elastic lamina.

The role of abnormalities of type- 3 collagen in the aetiology of saccular aneurysms is implicated and researched extensively.

Ostergarrd and Onlund found deficiency in type - 3 collagen in middle cerebral arteries of patients who died of subarachnoid haemorrhage.

In 1967 Pakarinen published the natural history of aneurysms after reviewing six series. The incidence of cerebral aneurysms in general population is about 1% while the autopsy series revealed an incidence of 2 to 6%. Nakagawa and Hashi et al found 6.5% incidence of asymptomatic cerebral aneurysms.

The group with a family history of SAH had an incidence of 18%. There are many theories proposed for the formation of cerebral aneurysms including congenital, acquired over congenital and acquired, apart from the genetic and familial factors.

Now it is widely accepted that it is mainly acquired and that the internal elastic lamina is the most important layer of the vessel wall maintaining the integrity. The cerebral vessels are predisposed to aneurysm formation because of thin wall and lack of abundant elastic tissue including absence of external elastic lamina. Factors that alter blood flow, such as vessel occlusion and those that cause increased blood flow such as in AVM's, and hypertension and the factors, which affect connective tissue, such as smoking and connective tissue disorders, may accelerate the degenerative process.

Morphologically aneurysm can be saccular, fusiform and dissecting. Yasargil divided them according to size by into baby (<2mm), small (3-6), medium (7-14), large (15-25) and giant (>25), according to the location, anterior and posterior circulation aneurysms. The relative frequencies of aneurysm at different anatomic site vary in various series. The commonest site is anterior circulation.

Use of routine 4-vessel angiography has increased detection of posterior circulation aneurysm from 5% to more than 8%. Ninety-five aneurysms occur close to the circle of Willis, in relation to anterior and posterior communicating arteries and the bifurcation of internal carotid artery, middle cerebral and basilar arteries.

Location of aneurysms in various studies

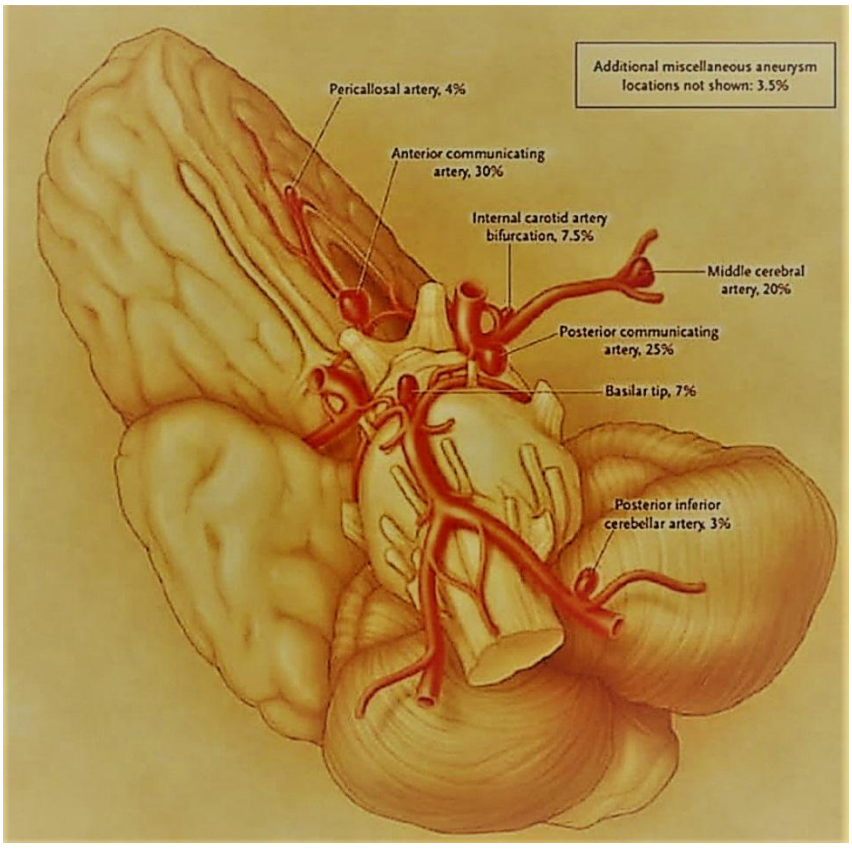


Figure 3 : Location of aneurysms in various studies

Ruptured aneurysm tends to be larger than unruptured aneurysm and symptomatic aneurysms are larger than asymptomatic aneurysms. Size at which aneurysm usually begin to rupture is about 3 mm in maximum diameter and the size at which they begin to produce symptom by means other than rupture is around 7mm.

INCIDENCE

The incidence of multiple aneurysms is exactly not known in the literature: it varies from study to study.

Incidences between 6 and 44% have been described[10], with most authors reporting an incidence between 20-30%.[11] In the autopsy studies incidence of multiple aneurysms is generally higher in clinical studies[12,13]. In clinical studies, the incidence of multiple aneurysms has ranged from 6-44%. Previously angiographic technique being in the development phases reported fewer multiple aneurysms. With newer angiographic techniques (Wilson and co-workers) have reported 49% of incidence of multiple aneurysm.

Multiple aneurysms are reported more common in women. Nehls et al,[14] noted a female male ratio of 5:1 in patients with two aneurysms, and 11:1 ratio in patients with three or more aneurysm. Others have also reported that multiple aneurysms are two or three times more common in women. It is not known that why the incidence is higher in women, but theories include the influence of hormone and higher prevalence of collagen vascular disease in women [15,16.] Age alone does not correlate with increased risk of multiple aneurysms above that for single aneurysm. Although several studies have shown an increased rate of multiple aneurysms in patients of 45 to 65 years age old.

In a study of 435 patients, lnagawa[17] found a similar ratio of multiple and single aneurysm in patients over 50 years of age.

CONDITIONS ASSOCIATED WITH MULTIPLE ANEURYSM

HYPERTENSION

An association between hypertension and multiple aneurysms is noted by several authors[15,18].

Andrews and Spigel[19] reported that in patients less than 55 years of age, multiple aneurysms were twice as common in hypertensive patients. They attributed this incidence to accelerated atherosclerosis.

Housepian and Pool[20] also found arteriosclerosis to be more common in patients with multiple aneurysms than in single aneurysms.

SMOKING

Smoking has been demonstrated to be risk factor for subarachnoid haemorrhage. The effect of smoking on intracranial aneurysm formation is not well understood.

One hypothesis is that smoking promotes degradation of elastin in blood vessel wall making the wall susceptible to dilatation. Patients with increased elastin degradation such as deficiency of α-1 antitrypsin may be higher risk for aneurysm formation. Cigarette smoking has been shown to decrease the activity of α-1 antitrypsin[16].

Another hypothesis is that aneurysm formation represents degenerative processes similar to atherosclerosis. Smoking has multiple effects on endothelial cells promoting atherosclerotic changes in vessel wall. The intracranial aneurysm was significantly higher in active and previous smokers, compared to non-smoker[21,22].

The other mechanism by which cigarette smoking may increase risk for SAH is by a transient elevation in blood pressure. Blood pressure values are generally lower in smokers than in nonsmokers,[23] but smoking a cigarette causes an acute increase in blood pressure for 3 hours.[19] This transient increase may contribute to the rupture of an aneurysm. The theory that cigarette smoking causes formation of aneurysms through atherosclerosis is unlikely because atherosclerosis promoting factors such as

hypertension, age, and diabetes, as well as cardiovascular and ischemic cerebrovascular diseases, did not correlate with multiple aneurysms.

CONNECTIVE TISSUE AND CONGENITAL DISORDERS:

There are many connective tissue and congenital disorders associated with intracranial aneurysms such as Ehler-Danlos syndrome, Marfans syndrome, Fibromuscular dysplasia, Coarctation of aorta, Adult polycystic kidney disease, Moya-Moya disease ,Tuberous sclerosis . Multiple aneurysms have been associated with these disorders[14,24.]

In fibromuscular dysplasia, polycystic kidney disease and tuberous sclerosis, renal hypertension is also thought to contribute by creating haemodynamic stress that accelerates damage to the arteries. Pope et al[23] demonstrated that patients with intracranial aneurysms had a type 3 collagen vascular deficiency. The Ehlers Danlos syndrome is characterized by fragmentation or absence of elastic tissue in small arteries and also by defects of type -3 collagen. Intracranial aneurysms associated with Moya-Moya disease are relatively rare and are common in the posterior circulation, 23 cases has been mentioned in literature (Yoshidide)[25] Bennet and coworkers[26] described an association of intracranial aneurysms and tuberous sclerosis. The cause of aneurysmal formation in fibro muscular dysplasia and polycystic kidney disease (adult type) is a defect in tunica muscularis of the arterial wall. Both fibromuscular dysplasia and polycystic kidney diseases are transmitted as an autosomal dominant trait, as may be in tuberous sclerosis.

SICKLE CELL DISEASE:

Recently, an association between sickle cell disease and multiple aneurysms has been reported with an incidence of 42%. Mechanism of aneurysm formation in this disorder is thought to be due to endothelial damage from rigid red blood cells. These patients tend to be younger and have a high frequency of posterior circulation aneurysms[22].

FAMILIAL ANEURYSMS:

Familial intracranial aneurysms are defined as "the presence of two or more family members among first and second degree relative with proven aneurysmal subarachnoid haemorrhage or incidental aneurysm[27]. Norrgard et al[28] reported a multiple aneurysm incidence of 53% in familial cases, compared with 21% in non-familial cases, this rate concerns with an incidence of about 50%, reported in other studies of familial aneurysms.[14,16,27,29]

In familial cases such patients tend to be younger by approximately 10 years and have different distribution of aneurysms. There is lower incidence of anterior and posterior communicating artery aneurysms and higher incidence of middle cerebral artery aneurysms. According to Andrews et al the incidence of anterior communicating artery aneurysms is lower than that of the middle cerebral aneurysms. The incidence of anterior communicating artery aneurysms in familial cases was 16.4% and in siblings was 13.6 %, compared with a 33.5 % incidence of anterior communicating artery aneurysms in general population. The incidence of middle cerebral artery was 32% in sibling, 25.5% in familial cases and 19.8% in the general population. Female patients with a cerebral aneurysm outnumbered male patients by ratio of 3:1 (76.6%).[30] Other reports also have identified a similarly higher incidence of familial aneurysms. Andrews also indicated that in siblings, the occurrence of intracranial aneurysms at identical sites and that mirror aneurysm are more than twice as frequent as expected in general population. The mean age of the patients with familial aneurysms is 39 years as compared to 52 years for those with non-familial ones.

ARTERIOVENOUS MALFORAMTIONS

The association of arteriovenous malformations and intracranial aneurysms has been well documented. There are many reports of arteriovenous malformations associated with multiple intracranial aneurysms.[31,32]

Walsh and King in 1942 reported the first example of patient having an aneurysm and AVM.[19] Batjer and associates found that 11 of 22 patients with arteriovenous malformations and aneurysm had multiple aneurysms. In these patients 82% of the aneurysms were located on vessel feeding the AVM. In all of their cases

of aneurysmal SAH the responsible aneurysm were located in an atypical distal site on a feeding vessel.

Multiple aneurysms of posteroinferior cerebellar artery associated with AVM has been reported in the literature.[32] Several published reports have suggested that between 2.7% & 9.3% of patients with AVM have associated aneurysm .[19]

IDENTIFYING THE SITE OF ANEURYSMAL RUPTURE:

Multiple aneurysms occur at the usual sites of single aneurysms. The most common site for multiple aneurysms is along the internal carotid artery and middle cerebral artery bifurcation. Bilateral aneurysms are common in patients with multiple aneurysms. Mirror aneurysms are reported in up to 40% of cases and are especially common at the MCA (Andrews).[33]

The distribution in various series is as follows: -

lnagawa:[34] ICA- 44%, MCA- 28%, ACOM - 17% and VBA- 6%.

Bjorkesten and Halonen:[35] MCA - 34%, ICA & PCA- 24% each and VBA- 1 0%.

Heiskanen:[36]ICA- 20%, MCA- 21% and ACOM- 19%.

Wilson:[10] MCA- 24%, PCOM- 23%, ICA- 21%, ACOM -19%, VBA- 10% and ACA- 4%.

Suzuki:[37] Two aneurysm - 77%, three aneurysms - 15%, and four or more aneurysm - 6%. 47% of multiple aneurysms were on opposite site. 21% are on same side. 29% are in midline and one on the side. 3% have both in midline.

When two internal carotid aneurysms coexist, the chance of having mirror aneurysm is three times greater than that of their both being on same side. When two middle cerebral artery aneurysms co-exist, the chance is four times greater. When anterior circulation aneurysm is found the chance of having second aneurysm in the posterior circulation is between 3-5%.

The following series quotes regarding the number of aneurysms found -

T.Inagawa:[34] 2 aneurysms 72%, 3 aneurysms 20%, 4 aneurysms 6% , 5 aneurysms 1.5% , 6 aneurysms 0.5%

Yaz and Kobayashi:[38] 2 aneurysms 81% ,3 aneurysms 15.8%,

4 aneurysms 3.2%

PROBABILITY OF RUPTURE BY ANEURYSM SITE:

The sites where multiple aneurysm ruptures are not necessarily the sites where they most commonly occur. Among most of the series the most common site of aneurysm rupture was anterior communicating artery aneurysms as follows: -

Heiskanen28: ACOM artery aneurysm 83%, MCA aneurysms 43%, ICA aneurysm 41%.

T. lnagawa8: ACOM artery aneurysm 68%, ICA aneurysm 40%, MCA aneurysm 38%, VBA aneurysm 20%.

T. lnagawa26: ACOM artery aneurysm 50%, MCA aneurysm 57%, ICA aneurysm 46%, VBA aneurysm 67%.

Nehls et al 5: ACOM artery aneurysm 62% ,PCOM aneurysm 50% ,ICA aneurysm 38% ,VBA aneurysm 50% ,MCA aneurysm 27%.

Inagawa[13] noted higher probability of rupture among patients over the age of 59yrs (79%) compared to those younger than 59 (59%). Other aneurysms having a high probability of rupture were along internal carotid artery and vertebrobasilar distribution. Most authors reported a relatively low probability of rupture for middle cerebral artery aneurysms[14].

CLINICAL SIGNS

The headache in ruptured aneurysm cases is described characteristically as "the worst headache of my life".[39,40]The symptoms can be due to the mass effect of a large aneurysm, or possibly from minimal leakage of blood which irritates the meninges; symptomatology being headache, unilateral third cranial nerve palsy (from a posterior communicating artery aneurysm), bilateral temporal hemianopsia (from an anterior communication artery aneurysm impinging on the optic chiasm) ischemic cerebrovascular disease, poorly defined spells, and seizures[41,42]. Such symptoms may be a warning sign of an impending rupture, as 10% to 43% of patients with SAH do a sentinel headache in the 2 months preceding the rupture.[43]

In majority of the cases, the neurological examination is not helpful in localizing the site of aneurysm rupture. Nehls et al [14] noted that focal signs were present in only 9 of 94 patients. In only two of the nine patients were the clinical finding of value in helping to localize the site of aneurysrn rupture. Almaani and Richardsorn[10] found the ciinical examination to be of value in only 30% of patients with lateralising findings, for example optic nerve in ophthalmic segment aneurysm, oculomotor nerve in Pcom aneurysm, 3rd,4th,and 6 th nerve in cavernous sinus aneurysm and weber's sign in superior cerebellar artery aneurysm They also reported that when EEG was combined with clinical examination, the site of rupture could be predicted with a 62% of accuracy.

CT SCAN:

Computed tomography can provide key information in localizing the site of aneurysm rupture. Non-contrast computed tomography could detect up to 90% of sub-arachnoid haemorrhage, when performed within 24 hour of rupture and is presently the best method for evaluating aneurysmal subarachnoid hemorrhage[14]. Focal collection of blood hematoma or intraventricular haemorrhage correspond to specific aneurysm site, when multiple aneurysms are present. Recent reports found that computed tomography could localize the site of aneurysm rupture in only 45 to 55 % of cases[14].

NCCT has high sensitivity but should not be applied as a sole diagnostic modality in the diagnosis of SAH. Moreover, NCCT sensitivity decreases with time

since haemorrhage; it has close to 100% sensitivity within 12 hours, 93% within 1 day, and less than 60% within 1 week of haemorrhage [44].

Middle cerebral artery aneurysms account for up to 55% of all aneurysmal hematomas. These hematomas typically appear as coma shaped lesions in the sylvian fissure. Hematoma from proximally located MCA aneurysm and ICA aneurysm occur at temporal lobe and basal ganglia.

Posterior communicating artery aneurysms are typically oriented directly posterior, slightly lateral and downward and medial to the tentorial edge.

Bleeding from aneurysms located in this position usually does not cause intracerebral hematoma, but produces a pattern of subarachnoid blood with in the suprasellar, peri-mesencephalic and ambient cisterns.

Anterior communicating artery aneurysms can produce a variety of hematomas. Blood may enter the third ventricle, through the lamina terminalis or it may enter the septum pellucidum directly through the midline creating a cavum septum hematoma. Bifrontal intraventricular hemorrhage can occur, after rupture through the infero-medial frontal lobe or less commonly, the corpus callosum. Unilateral gyrus rectus hematomas tend to occur opposite the side of dominant A - 1 as the aneurysm projects to opposite side. Basilar bifurcation aneurysms can also produce intraventricular haemorrhage when blood enters through the floor of the third ventricle. These aneurysms may also produce focal haemorrhage in interpeduncular region. PICA aneurysm rupture will cause bleed in the cerebella-pontine angie, or along the cerebellar vermis. Classical CT Scan picture is isolated blood in fourth ventricle.

MRI:

Role of MRl in the evaluation of patients with sub arachnoid haemorrhage is limited. MRI is unable to image acute sub arachnoid haemorrhage well, due to presence nonparamagnetic properties of oxyhaemoglobin. Its usefulness is in studying sub-acute or chronic sub arachnoid hemorrhage[45].

MRI can reveal local oedema and blood clot. Study by James and Robert et al demonstrated that MRI could disclose multiple aneurysms as filling defects. MRl has revealed intraluminal clot in symptomatic cerebral aneurysm as small as 16 mm[45].

DIGITAL SUBSTRACTION ANGIOGRAPHY(DSA):

Cerebral angiography, pioneered by Egas Moniz in 1927[46,47] which evolved and highly towards a digital technique, is still considered the gold standard for detecting vascular abnormalities of the brain and especially cerebral aneurysms.

DSA is the gold standard in the evaluation of intracranial aneurysms offering both dynamic and morphological information on the intracranial circulation[46,47].

There are various signs for localizing the site of rupture are as follows - dye extravasations (smoking gun), focal mass effect, focal vasospasm, aneurysm change on serial angiogram, aneurysm teat, irregular shape, proximal aneurysm and large aneurysm.

Nowadays DSA remains strongly indicated in all those cases in which the diagnosis has not yet been established such as :- SAH with a negative CTA, discrepancy between the distribution of SAH on CT scan and the display of the aneurysm on CTA, doubtful cases of CTA showing small aneurysms, CTA with suboptimal quality, to evaluate giant aneurysms to obtain haemodynamic information, to evaluate aneurysms very close to bone structures, to evaluate SAH supported by dissecting aneurysms, to evaluate multiple aneurysms, to better evaluate the correlations between the aneurysmal sac and the arteries surrounding or originating from the sac and last but not least, DSA is mandatory before endovascular treatment[48,49].

The principal drawback of DSA is its potential risk. The combined transient and reversible neurologic complication rate of cerebral angiography has been reported to be as low as 0.4% and as high as 12.2%[50].

Some aspects of cerebral haemodynamics, such as collateral flow and flow direction, cannot be demonstrated by CTA or even by MRA[51,52]. Rotational DSA, with 3D reconstructions, may improve diagnostic accuracy particularly if no

aneurysms are demonstrated by 2D-DSA. 3D DSA offers much more detailed information on the spatial relations between the aneurysm and surrounding vessels and structures for evaluation of the cerebral circulation allowing better patient management planning.

Aneurysm size and shape has also been analysed in predicting the site rupture. Some studies consider site only as the most important factor in determining the site of aneurysm rupture[21]. Nehl et al [14] found that the shape was the more consistent predictor of site of rupture in an analysis of size versus irregularities. Irregular aneurysm was the site of rupture in 93.3% of cases and whereas the large aneurysm was responsible in 83.3% of cases. They recommended weighing the relative difference in the size and shape when trying to localize the site of haemorrhage. Nehls et al[14] found that the site of rupture could be determined with a 97.5% accuracy using the following criteria:- use of focus of haemmorhage to locate source of bleeding, angiographic signs, sizes and shape of aneurysm,clinical or EEG finding to localize the side, MRI to look for focal edema or clot, repeat the angiogram at a later date to see if there is a serial change in any aneurysm and choose the aneurysm with highest probability of rupture. Akihoko Hino and Fugimeto et al [53] reported the site of prediction of rupture correctly in only 91% of cases before surgery.

MATERIALS AND METHODS

We have performed a prospective exploratory observation analysis of all patients with multiple aneurysms operated in our institute from Jan 2018 onwards ;

Data collection included the following.

Individual factors

Age

Sex

Duration of symptoms:

Symptoms: Vomiting/headache/raised ICP/ Motor/sensory/Visual/ cognitive/seizures/others.

Neurological Deficits.

Glasgow Coma Scale, WFNS and FISHERS grade on admission

Hypertension

Smoking

Alcohol

Diabetes Mellitus

Family history of cardiovascular disease (Angina, Myocardial Infarction or Peripheral vascular disease)

Family history of cerebrovascular disease (Transient ischemic attack or Stroke)

Menopausal state of female

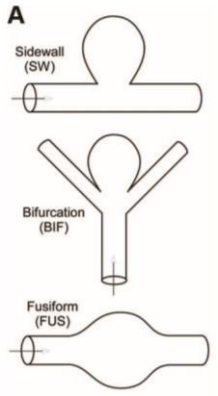
Surgical intervention

Radiological parameters

DSA / CT Angiogram /MR Angiogram on presentation

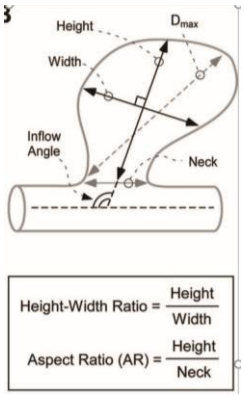
Size of aneurysm

Shape of aneurysm



Pattern of hemorrhage - Diffuse / focal

Aspect ratio [neck-to-dome length / neck-width]



Parent artery configuration (side wall and branching)

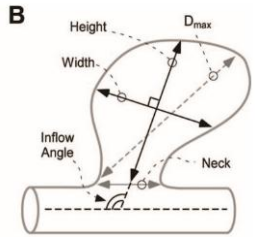
neck-width,

neck to dome length (length from the neck center to the dome of the aneurysm),

and aneurysm width (measured perpendicular to the neck to dome length)

Flow angle

The main branching angle was defined as the angle of the parent artery (in case of a sidewall aneurysm) or the angle between the parent artery and the daughter branch most approaching 180°



Contact between the aneurysm wall and bone

Adjuvant treatment

Need for Shunt

Inclusion criteria

All patients with SAH and multiple aneurysms (>1 aneurysm) proved on radiological investigations.

Exclusion criteria:

1. Insufficient radiological investigations quality to evaluate aneurysm geometry and morphology;

2. Inability to identify the location of the ruptured aneurysm based on the pattern of hemorrhage on CT/DSA/CTA/MRA or neurosurgical findings.

RESULTS

Table 1 : Age distribution

Age in years	Frequency	Percent
≤ 40	4	12.1
41 - 50	12	36.4
51 - 60	6	18.2
61 - 70	10	30.3
>70	1	3
Total	33	100

Our study was undertaken from under the department of Neurosurgery in Sree Chitra Tirunal Institute of Medical Sciences and Technology. The study is a prospective exploratory observation study and is going to continue till a significant number of patients are included.

All patients admitted in Neurosurgery department presenting with subarachnoid hemorrhage and having more than one aneurysm i.e. multiple aneurysms were included.

A total number of 33 patients presented with subarachnoid hemorrhage having multiple aneurysms in our study. Majority of patients in our study was having age more than 40 years about 87.9%.

Male to female ratio of 1:2.3 was seen in our study implying more of female patients.

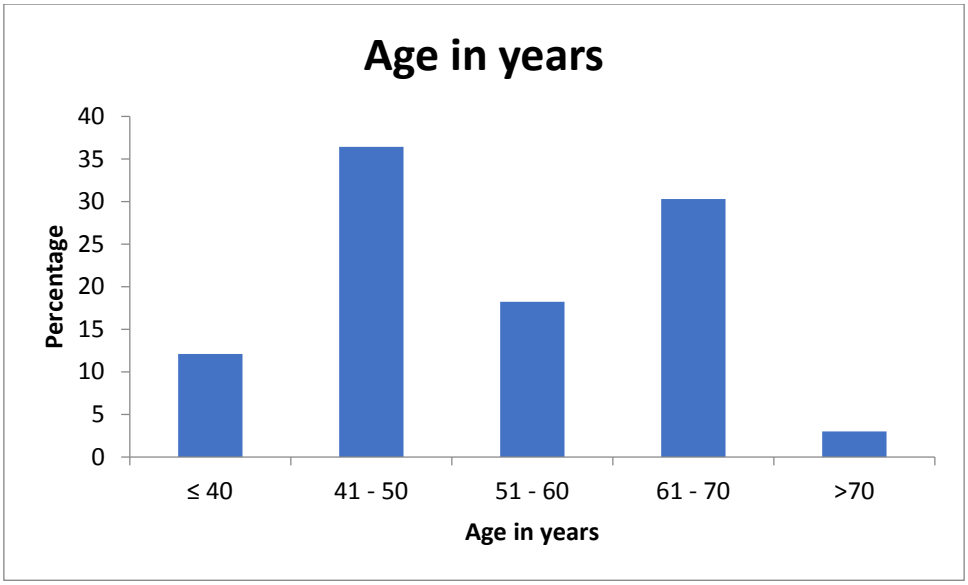


Figure 4 : Age distribution

Table 2 : Gender distribution

Sex	Frequency	Percent
Male	10	30.3
Female	23	69.7
Total	33	100

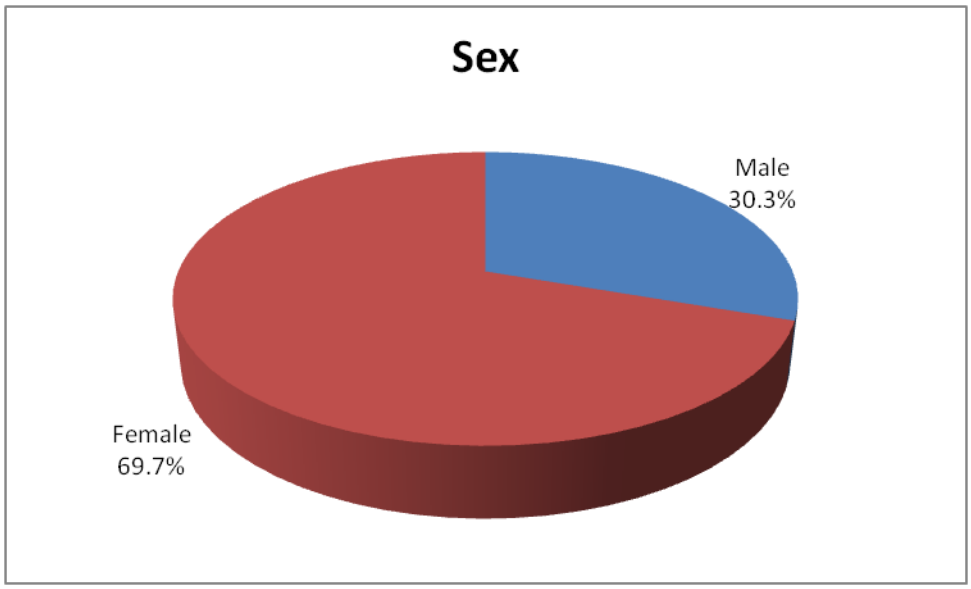


Figure 5 : Gender distribution

Most common symptom was headache which was present in all of the patients followed by vomiting (75.8%), loss of consciousness (30.3%), seizure (15.2%), and weakness (12.1%).

Table 3 : Symptoms

Symptomatology	Frequency	Percent
Head ache	33	100
Vomiting	25	75.8
Seizure	5	15.2
LOC	10	30.3
Weakness	4	12.1

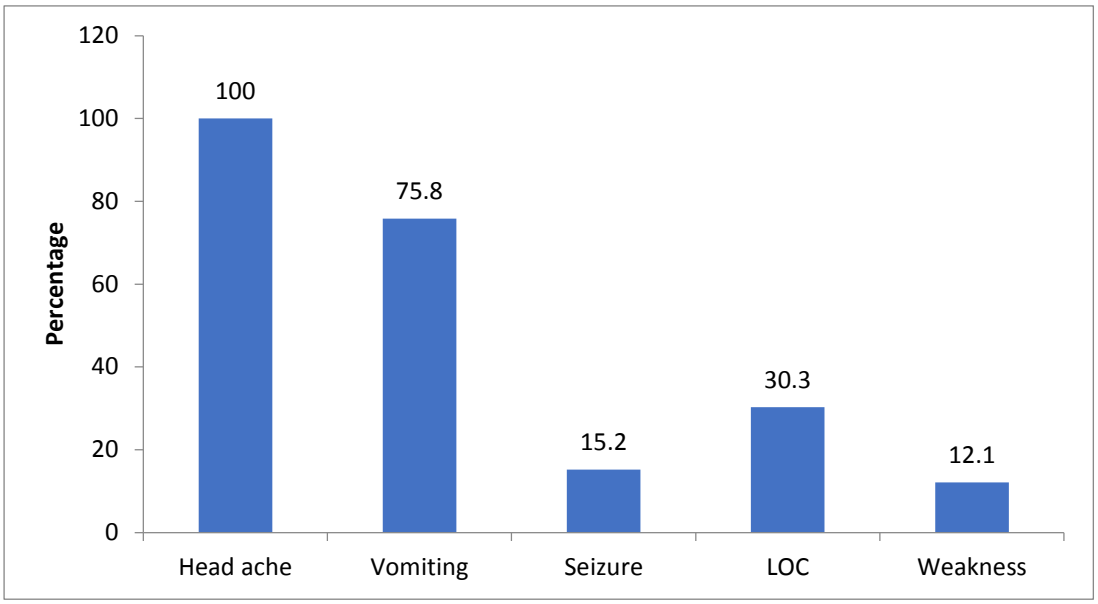


Figure 6 : Symptoms

Most common location of bleed seen in our study was Slyvian fissure (48.5%) followed by basal cisterns (30.3%).

IVH was seen in about 21.2 % of cases.

Table 4 : Pattern of hemorrhage

Pattern of hemorrhage	Frequency	Percent
Rt Slyvian	16	48.5
Lt Slyvian	16	48.5
Interhemispheric	15	45.5
Perimesencephalic	9	27.3
Supraseller	8	24.2
Interpeduncular	10	30.3
Basal cisterns	10	30.3
IVH	7	21.2

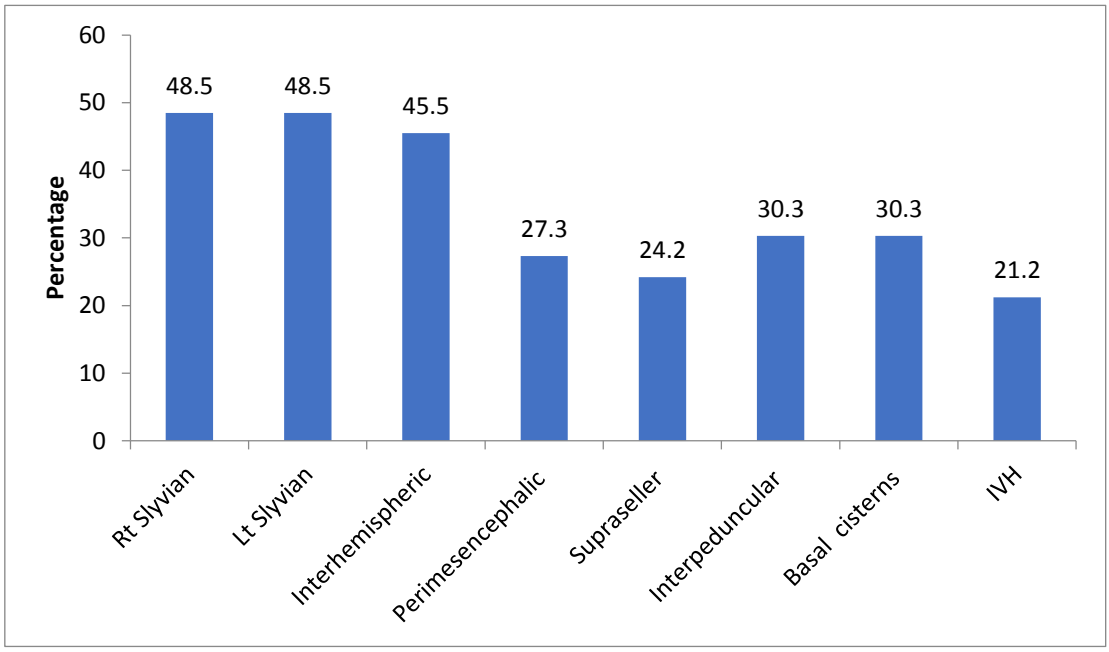


Figure 7 : Pattern of hemorrhage

Table 5 : WFNS grade

WFNS grade	Frequency	Percent
Grade 1	27	81.8
Grade2	2	6.1
Grade3	3	9.1
Grade4	1	3
Total	33	100

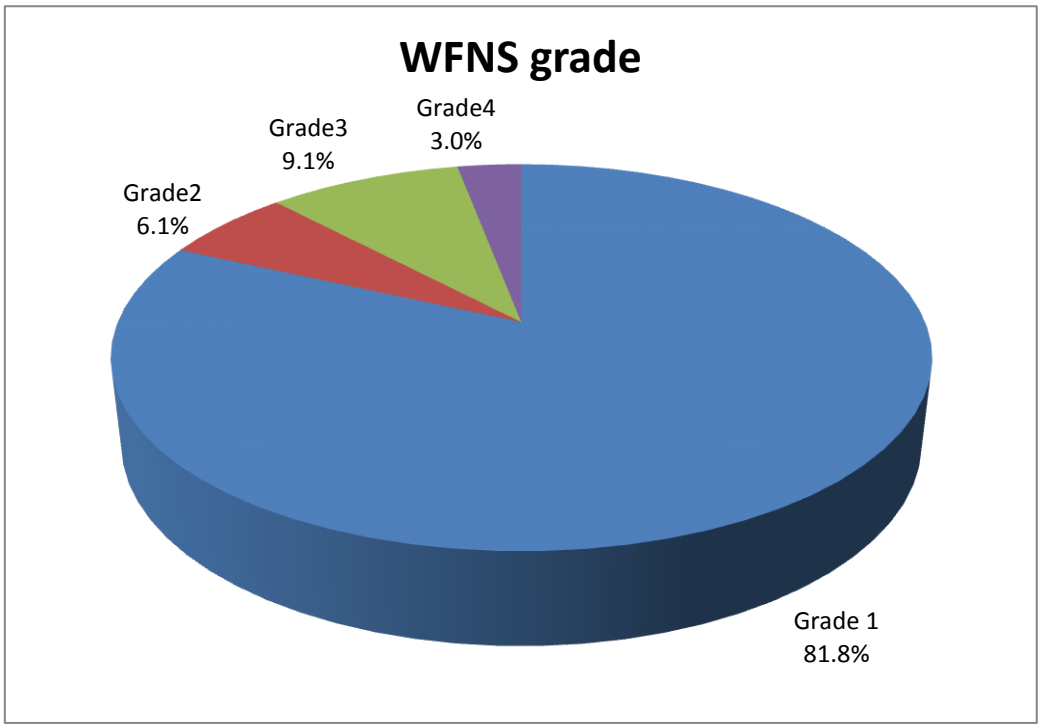


Figure 8 : WFNS grade

Majority of patients seen were in grade I 81.8 % followed by grade 3 (9.1%), grade2(6.1%) and then grade 4 (3%) as per WFNS grading.

Table 6 : Fishers grade

Fishers grade	Frequency	Percent
Grade1	8	24.2
Grade2	9	27.3
Grade3	6	18.2
Grade4	10	30.3
Total	33	100

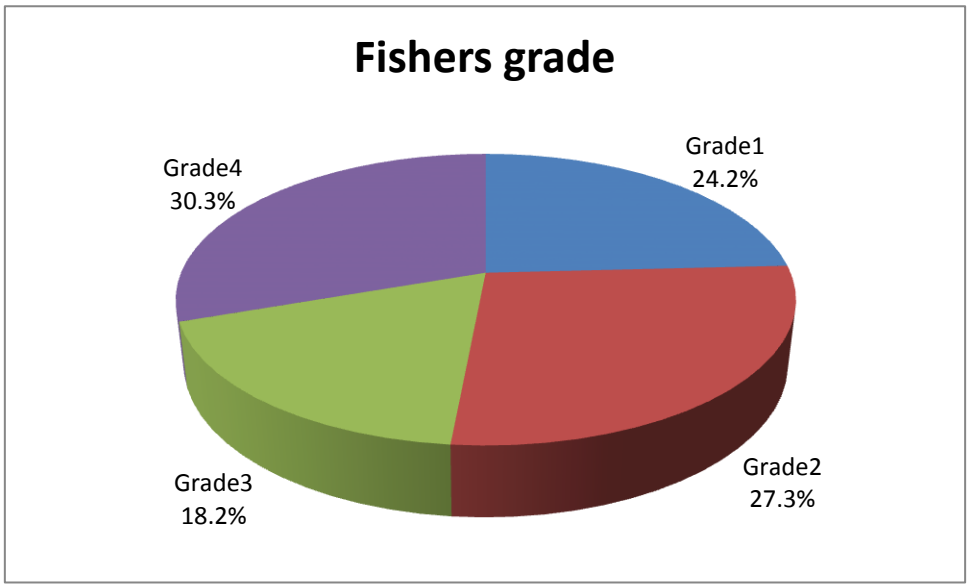


Figure 9 : Fishers grade

Majority of patients seen were in grade 4 (30.3%) followed by grade 2 (27.3%), grade 1 (24.2%) and then grade 3 (18.2%) as per FISHERS grading.

Table 7 : Comorbidities

	Frequency	Percent
Hypertension	21	63.6
Smoking	8	24.2
Alcohol	6	18.18182
Diabetes Mellitus	7	21.2
Trauma	0	0
Menopausal state of female	17	51.51515

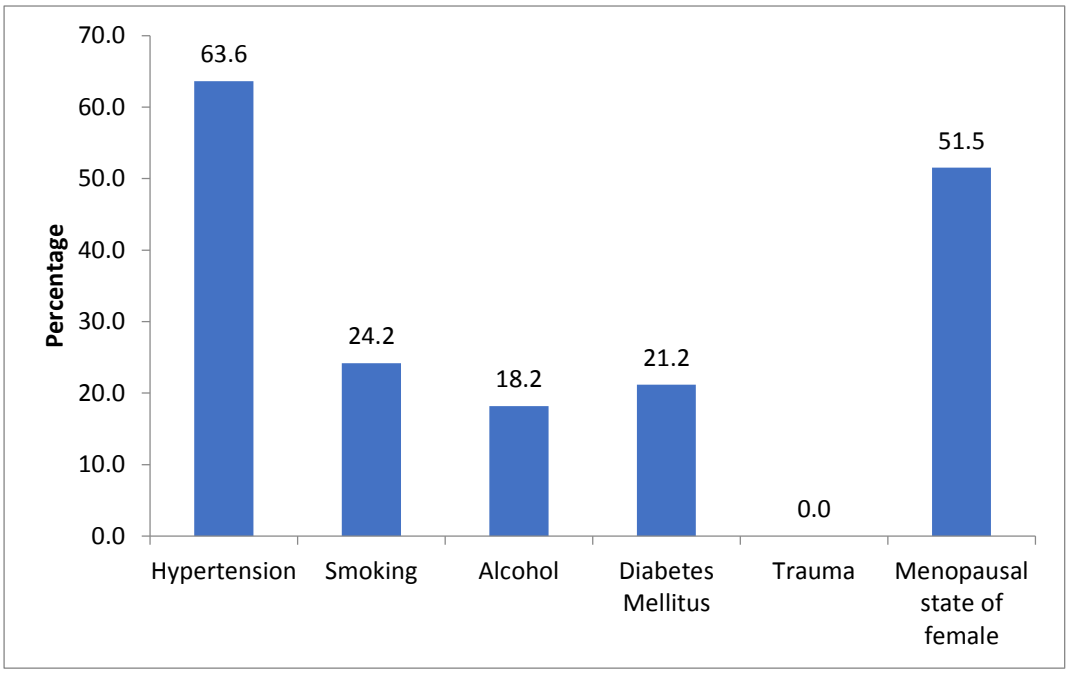


Figure 10 : Comorbidities

Most common predisposing factor seen was hypertension (63.6%), smoking (24.2%), alcohol (18.8%), diabetes (21.2%).

None of the cases had trauma as one of the causative factors. 51.5% of females were menopausal.

Most common ruptured aneurysm was MCA aneurysm 8 cases followed by 6 Acom, 6 p-com, 1 para p-com,3 basilar top,2 anterior choroidal,2 DACA ,1 ICA bifurcation,1 V4 vetebral segment,1 superior hypophyseal,1 SCA and 1 hypoglossal artery aneurysm.

Most common ruptured aneurysm was MCA aneurysm 11 cases followed by 4 Acom, 5 p-com, 6 carotid cave, 2 PCA,2 DACA, 2 supraclinoid, 1 para p-com,1 para clinoid,2 V4 vertebral,2 anterior choroidal,2 cavernous,1 basilar,1 pro-atlantal,1 ophthalmic,1 PICA,1 terminal ICA.

Table 8 : Side of ruptured aneurysm

Side of ruptured aneurysm	Frequency	Percent
Right	14	42.4
Left	11	33.3

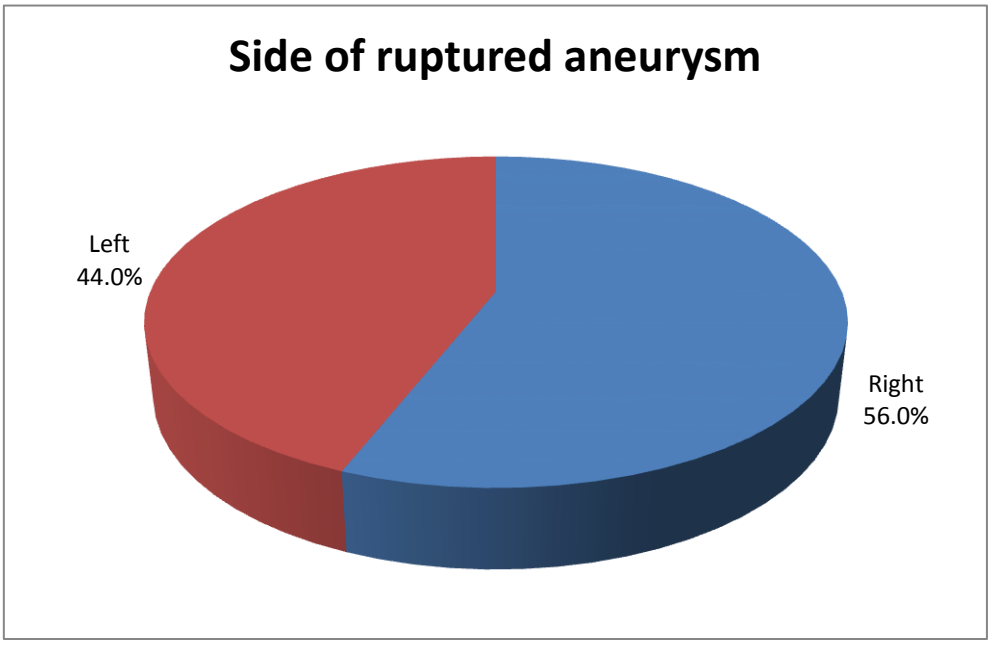


Figure 11: Side of ruptured aneurysm

Ruptured aneurysms were more common on the right side 56.0% and 44% on left side.

Table 9 : Cross flow across acom

Cross flow across acom	Frequency	Percent
-	21	63.6
+	11	33.3
present on left ICA , absent on rt ICA	1	3
Total	33	100

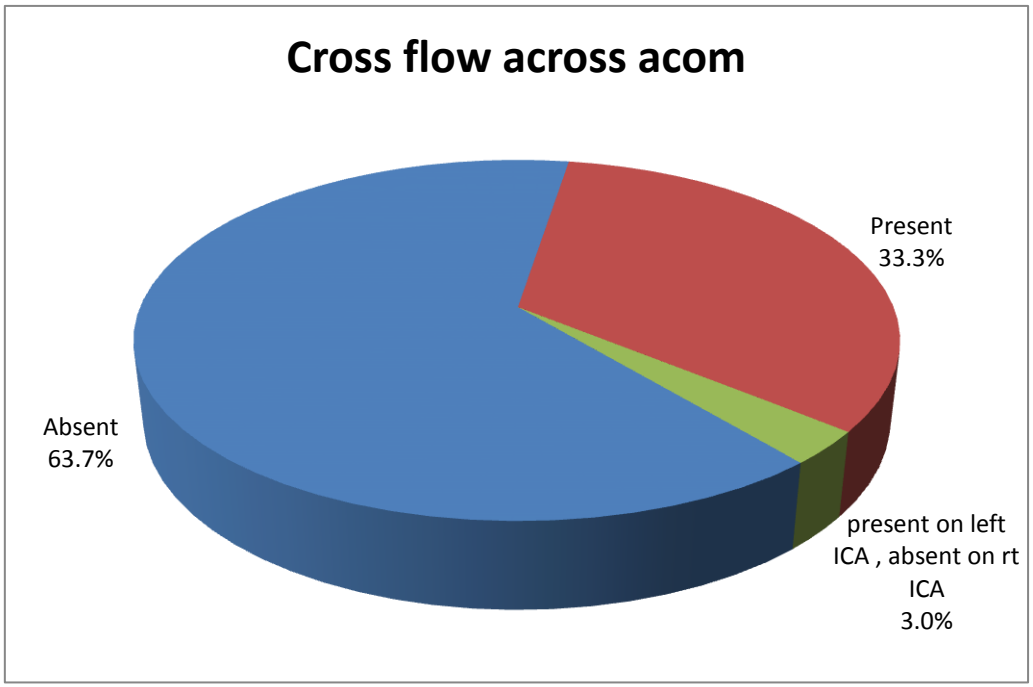


Figure 12 : Cross flow across acom

Cross flow across acom was present in 33.3%, absent in 63.7%.

One patient with Vertebral V4 segment aneurysm had cross flow present on left ICA, absent on rt ICA.

Table 10 : cross flow across pcom

cross flow across pcom	Frequency	Percent
-	19	57.6
+	8	24.2
ltpcom+ , rt pcom-	5	15.2
poor	1	3
Total	33	100

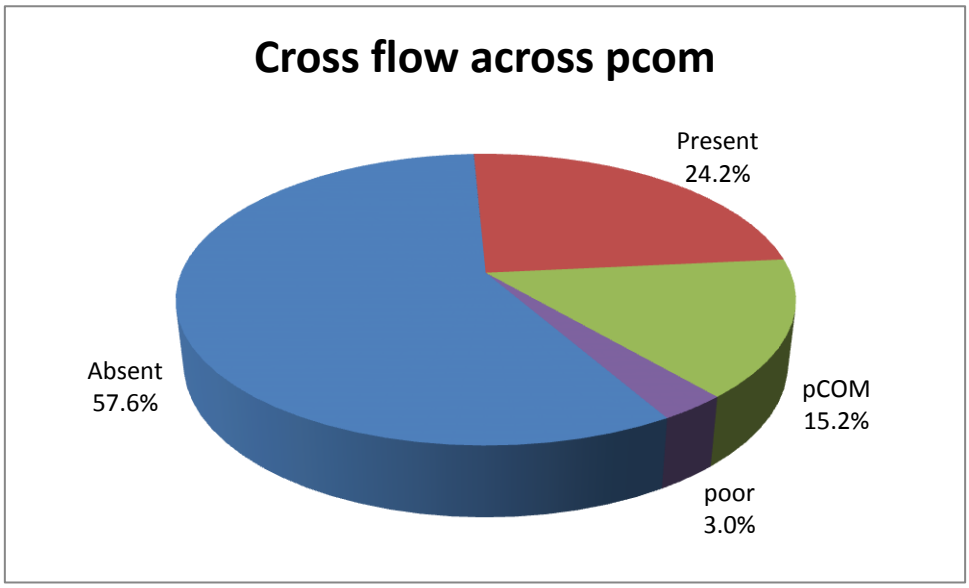


Figure 13 : cross flow across pcom

Cross flow across p-com was present in 24.2% , absent in 57.6% had an cross flow on p-com, present on left p-com and absent on rt p-comm in 15.2% of cases .

Table 11 : Shape of ruptured aneurysm

Shape of ruptured aneurysm	Frequency	Percent
Saccular	28	84.8
Fusi-saccular	5	15.2
Total	33	100.0

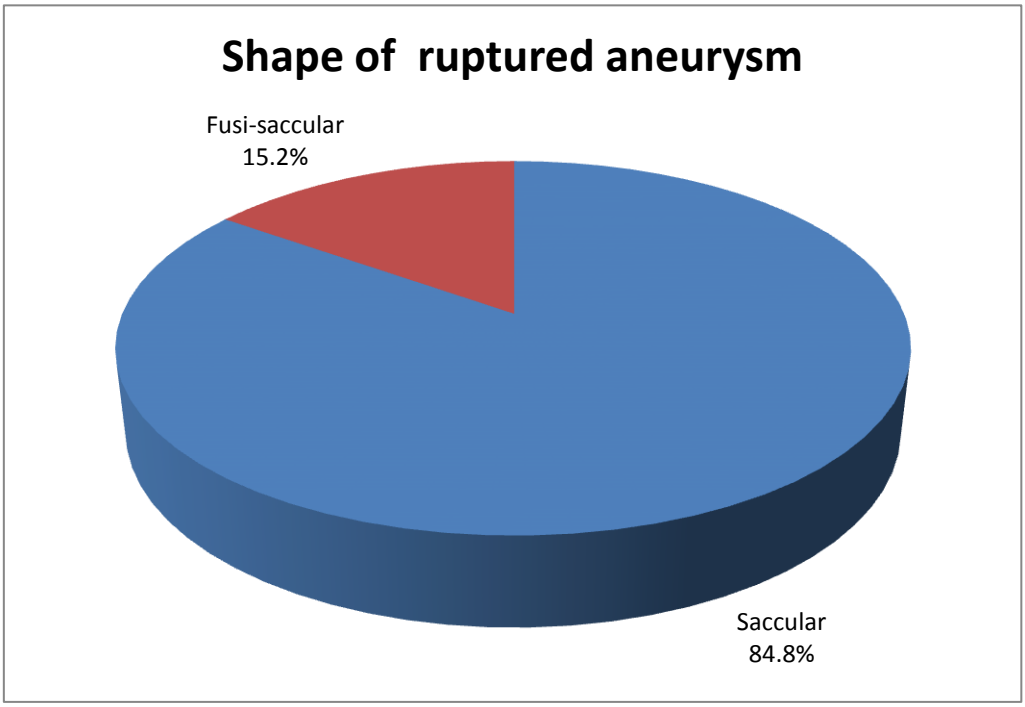


Figure 14 : Shape of ruptured aneurysm

Most common ruptured aneurysms were saccular 84.8% as compared to fusi-saccular in unruptured in 15.2%.

Table 12 : Shape of unruptured aneurysm

Shape of unruptured aneurysm	Frequency	Percent
Saccular	24	72.7
Fusiform	2	6.1
Fusi-Saccular	2	6.1
Total	28	84.8

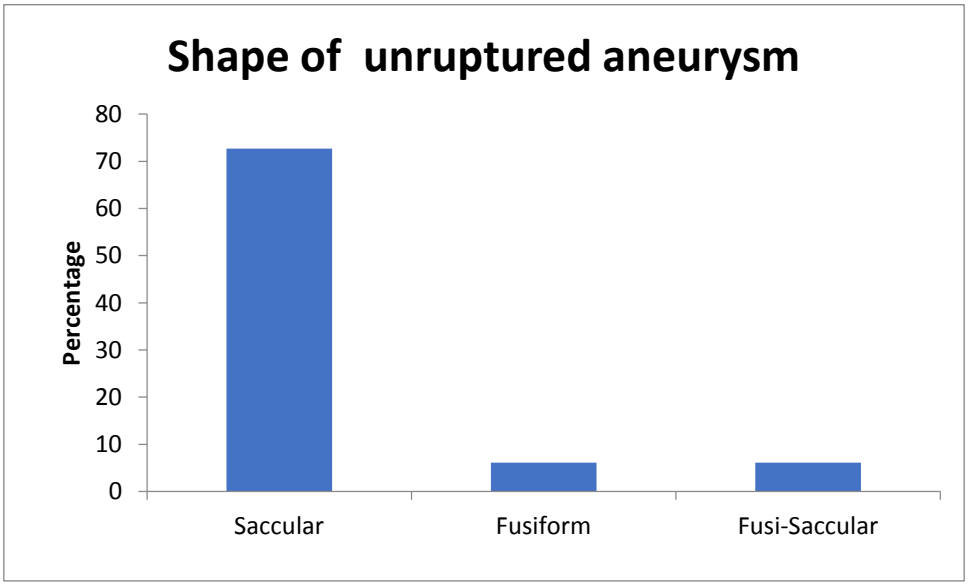


Figure 15 : Shape of unruptured aneurysm

Saccular aneurysm (72.7%) most common amongst unruptured cases followed by fusiform (6.1%) and fusi-saccular (6.1%).

Table 13: Pattern of hemorrhage

Pattern of hemorrhage	Frequency	Percent
Diffuse	12	36.4
Focal	21	63.6
Total	33	100

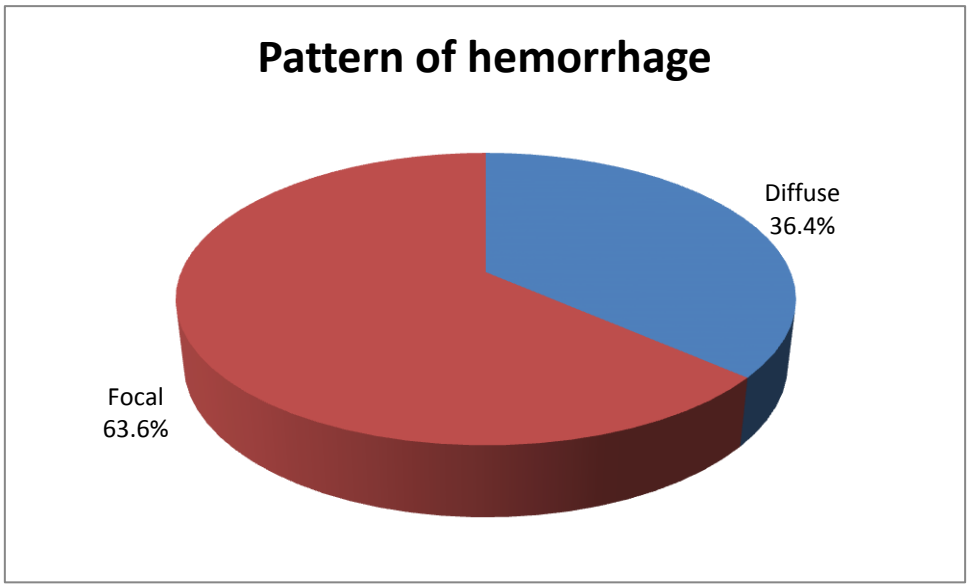


Figure 16: Pattern of hemorrhage

Most of the hemorrhage pattern was focal in 63.6% and diffuse in 36.4 % in the observed cases.

Table 14: Ruptured Aneurysm type

Ruptured Aneurysm type	Frequency	Percent
Bifurcation	26	78.8
Side wall	7	21.2
Total	33	100

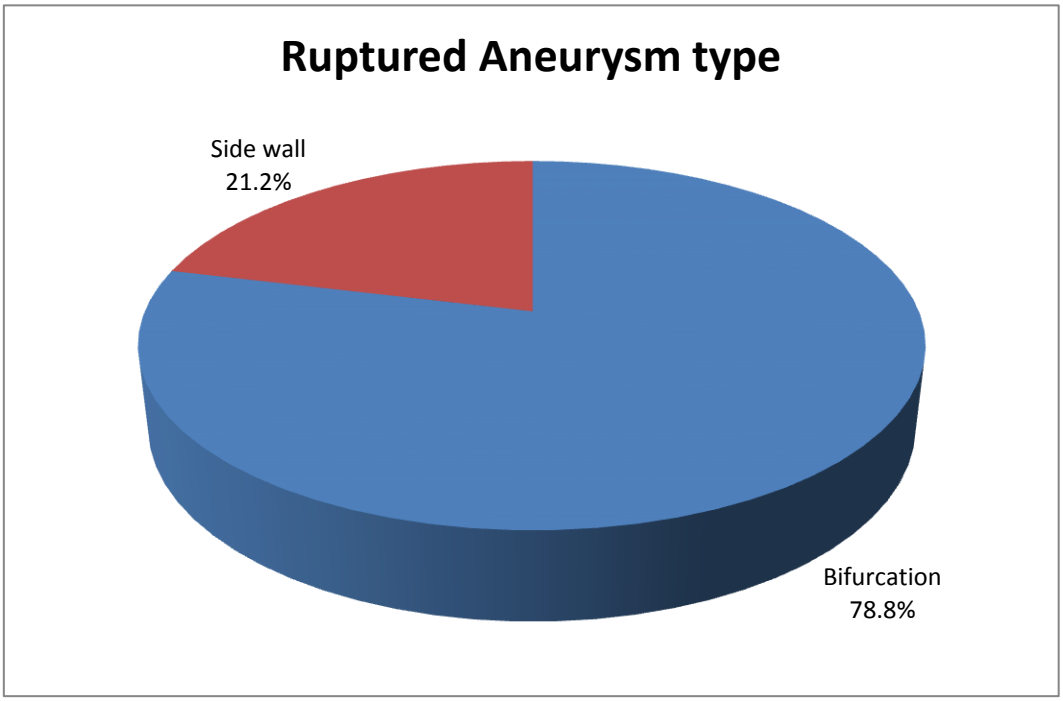


Figure 17 : Ruptured Aneurysm type

Majority of the aneurysms which ruptured were present on the bifurcation (78.8%) than sidewall (21.2%).

Table 15: Unruptured Aneurysm type

Unruptured Aneurysm type	Frequency	Percent
Bifurcation	13	39.4
Sidewall	20	60.6
Total	33	100.0

Majority of the aneurysms which were unruptured were present on the bifurcation (39.4%) than sidewall (60.6%).

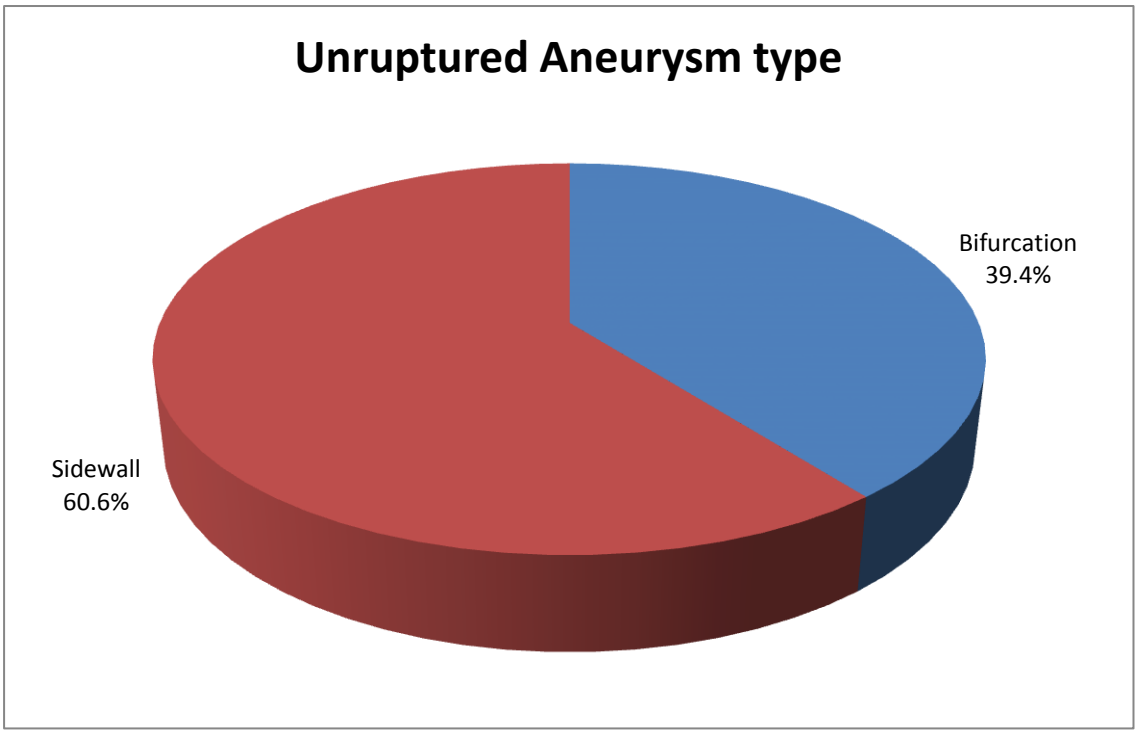


Figure 18: Unruptured Aneurysm type

Table 16: Post op Angioplasty

Post op Angioplasty	Frequency	Percent
None	18	54.5
Once	9	27.3
Twice	6	18.2
Total	33	100.0

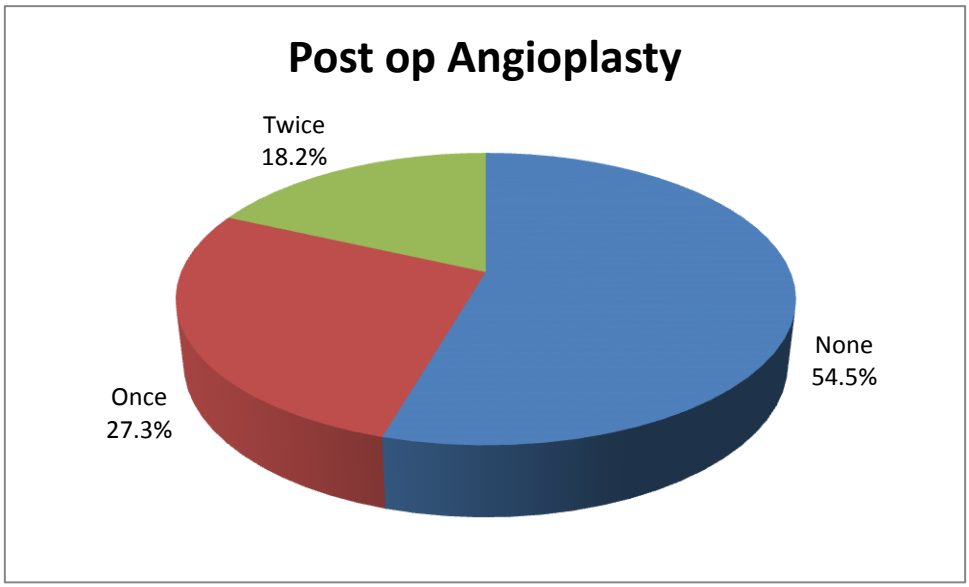


Figure 19: Post op Angioplasty

Chemical angioplasty sos balloon angioplasty was required in 45.5 % of cases out of which 27.3% required only once while 18.2% required on twice occasion.

Table 17: Width of aneurysm

	N	Width of aneurysm		p
		Mean	sd	
Bleed aneurysm	33	5.07	2.60	<0.001
Un-bled aneurysm	33	2.94	1.27	

Width of bled aneurysm (5.07 mm) in our study was more than un-bled(2.94 mm).

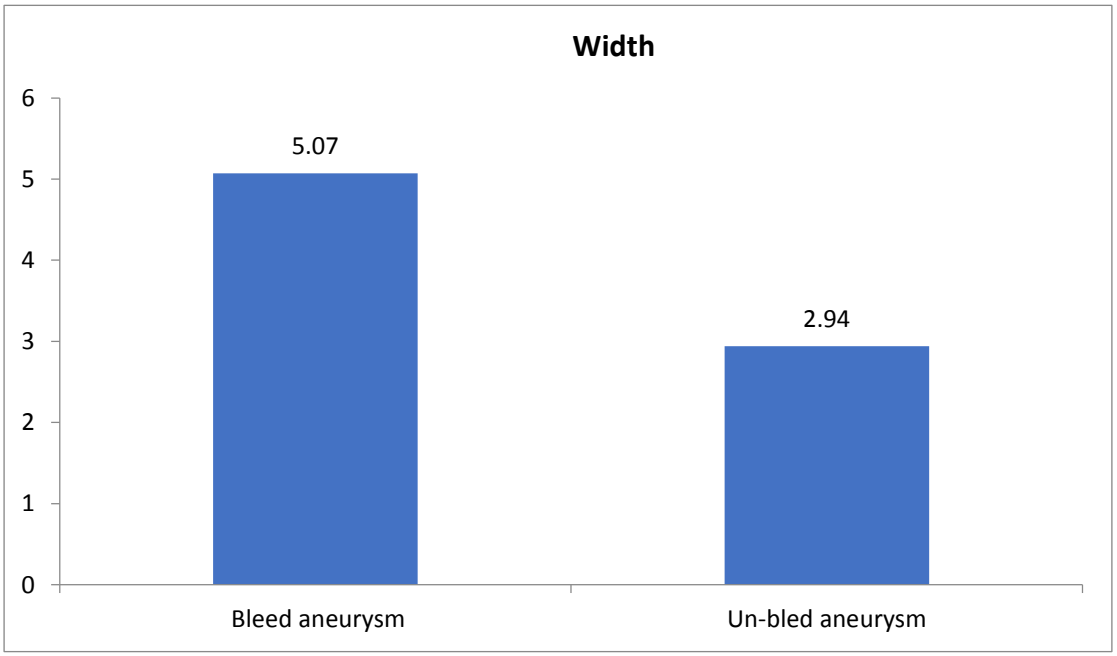


Figure 20 : Width of aneurysm

Table 18 : Aspect ratio

	N	Aspect ratio		p
		Mean	**sd**	
Ruptured aneurysm	28	2.01	1.12	0.122
Unruptured aneurysm	28	1.66	0.62	

Aspect ratio in ruptured aneurysm (mean2.01) was greater than unruptured aneurysms(mean1.66).

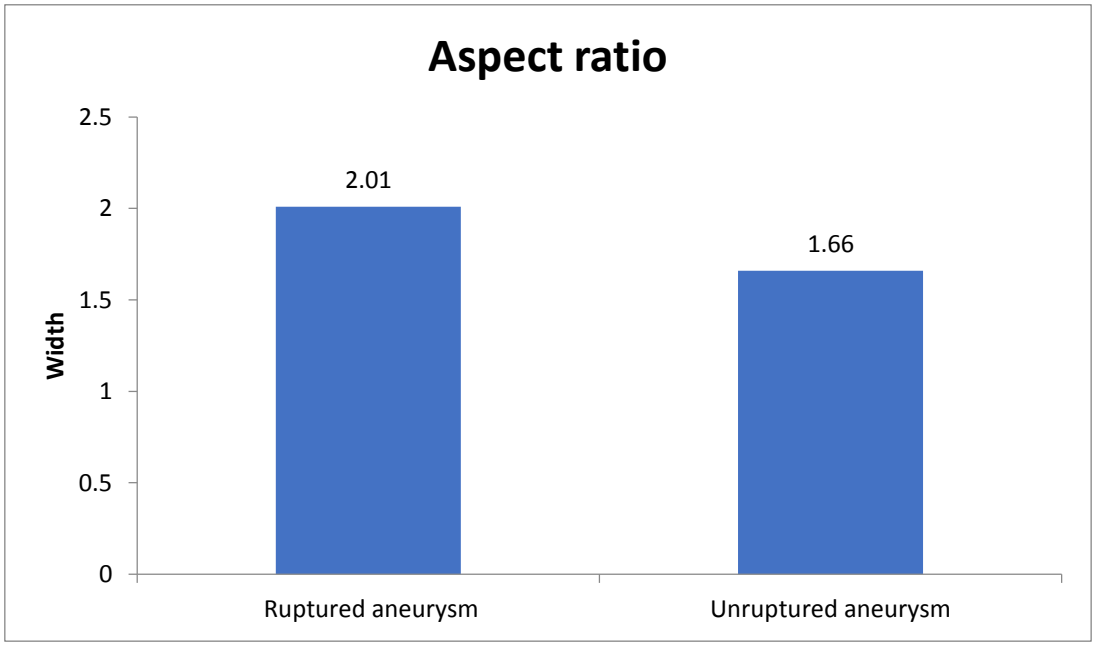


Figure 21: Aspect ratio

Table 19 : Neck of aneurysm

	N	Neck of aneurysm		p
		Mean	sd	
Ruptured aneurysm	29	2.87	1.32	0.003
Unruptured aneurysm	29	1.89	0.86	

Neck in ruptured aneurysm (mean of 2.87 mm) was greater than unruptured aneurysms (mean of 1.89 mm).

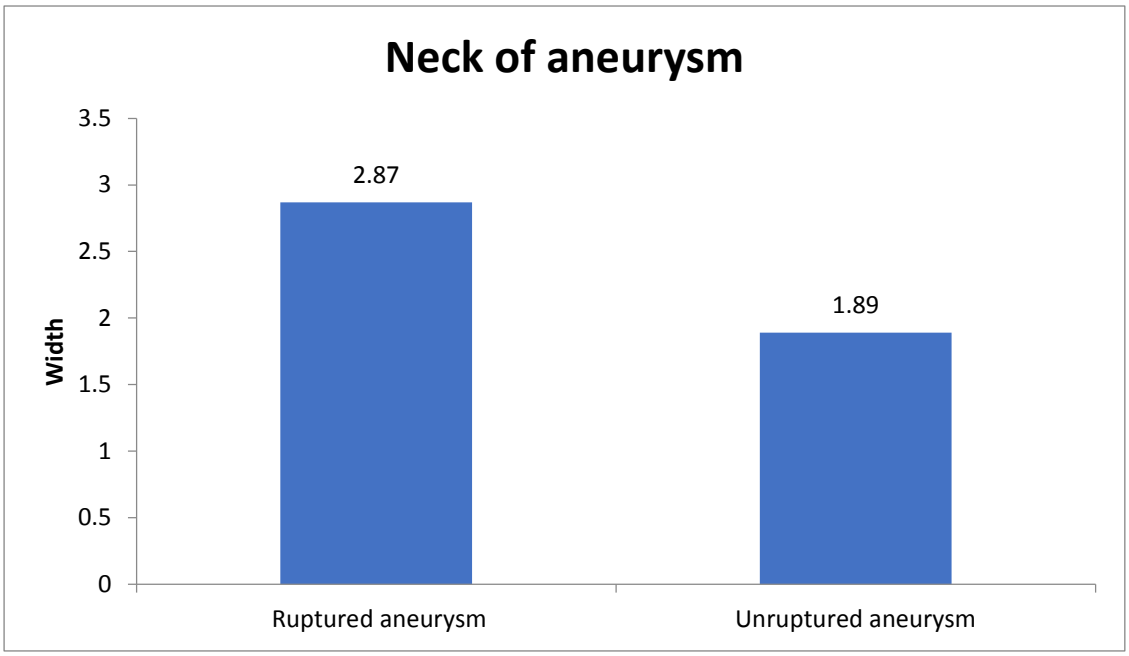


Figure 22 : Neck of aneurysm

Table 20 : Presence of blebs on ruptured aneurysm

Presence of blebs on ruptured aneurysm	Frequency	Percent
Yes	26	78.8
No	7	21.2
Total	33	100.0

Presence of blebs (78.8%) were present in ruptured aneurysms

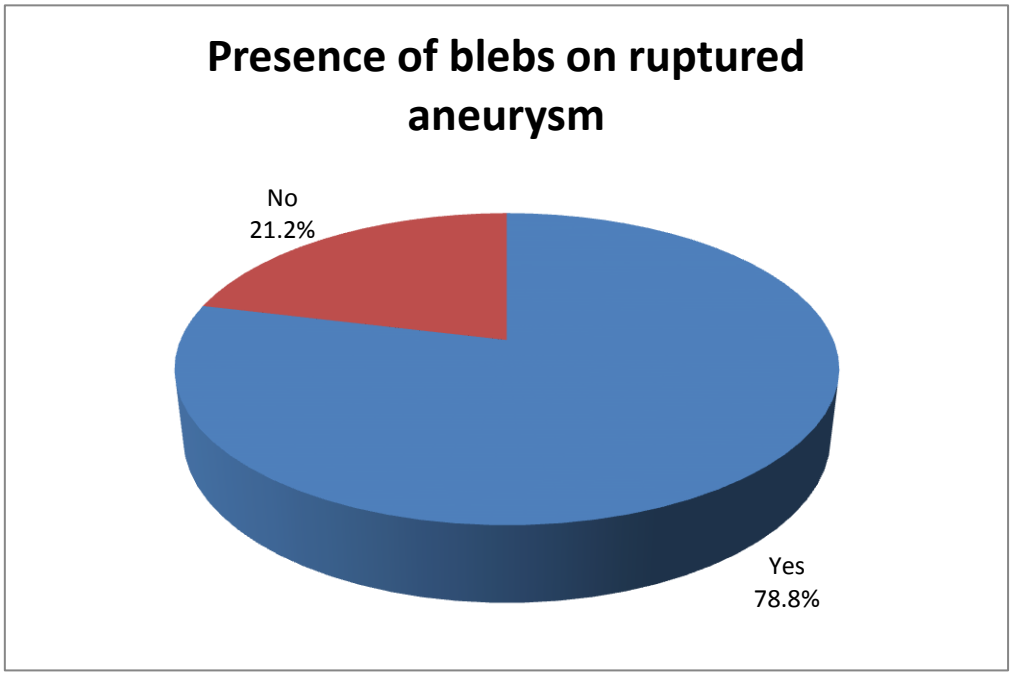


Figure 23 : Presence of blebs on ruptured aneurysm

Table 21 : Flow angle

		Flow angle		t	P
	N	**Mean**	**sd**		
Ruptured aneurysm	33	124.4	26.3	3.525	0.001
Unruptured aneurysm	43	102.7	26.8		

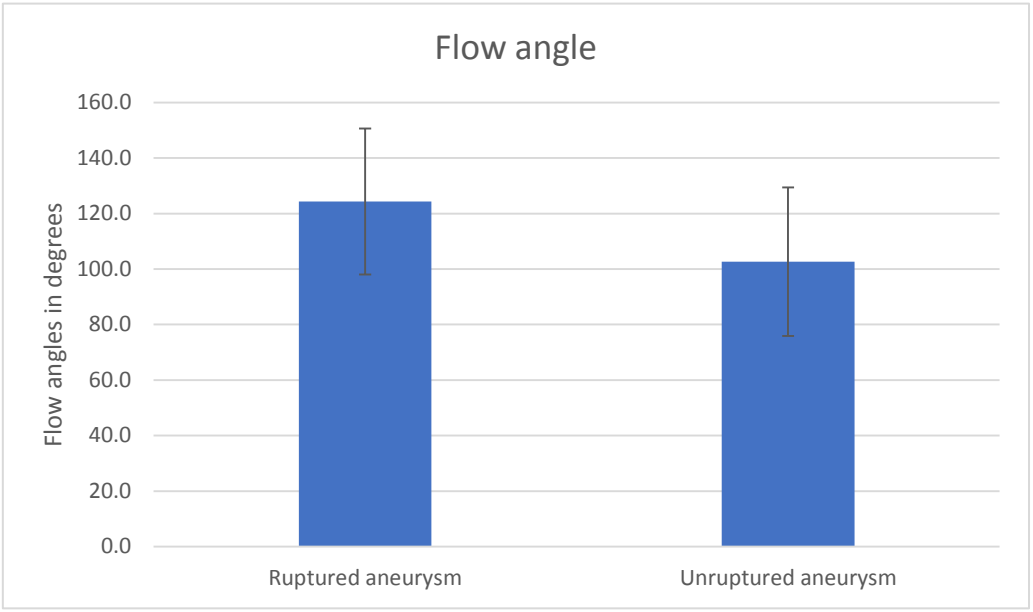


Figure 24 : Flow angle

Flow angles in our study which are found to be more obtuse in ruptured mean (124.4 degrees) than in unruptured cases (mean 102.7 degrees).

Table 22 : Contact of aneurysm with bone

Contact of aneurysm with bone	Ruptured aneurysm		Unruptured aneurysm		Total		χ^2	df	P
	n	%	n	%	n	%			
Yes	16	48.5	19	41.3	35	44.3	.402	1	.526
No	17	51.5	27	58.7	44	55.7			
Total	33	100.0	46	100.0	79	100.0			

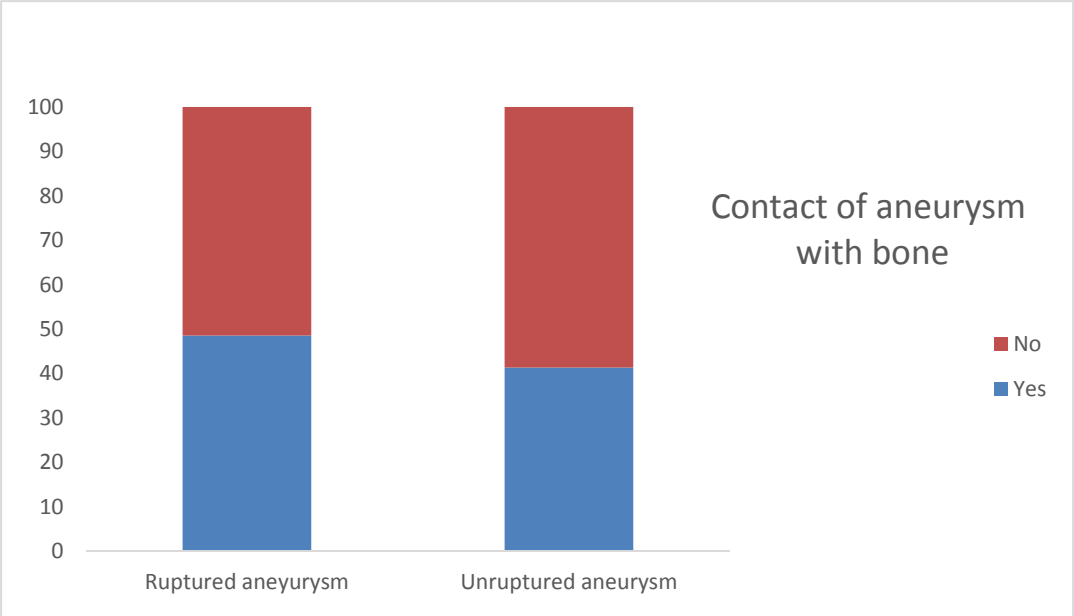


Figure 25 : Contact of aneurysm with bone

There was more incidence of bone wall contact in ruptured aneurysm 48.5% as compared to unruptured in 41.3 % of cases.

DISCUSSION

Our study was undertaken from under the department of Neurosurgery in Sree Chitra Tirunal Institute of Medical Sciences and Technology. The study is a prospective exploratory observation study and is going to continue till a significant number of patients are included.

Most common symptom was headache which was present in all of the patients followed by vomiting (75.8%), loss of consciousness (30.3%), seizure (15.2%), and weakness (12.1%).

The headache in ruptured aneurysm cases is described characteristically as "the worst headache of my life".[39,40]

Risk factors have been extensively studied in various longitudinal studies which have enhanced our understanding regarding this complex condition.

Most common predisposing factor seen was hypertension (63.6%) in 21 patients, smoking (24.2%) in 8 patients, alcohol in 6 patients (18.8%), diabetes in 7 patients (21.2%). None of the cases had trauma as one of the causative factors.51.5% (17 out of 23 females) females were post-menopausal.

Intracranial aneurysms are symptomatic in only 10-15% of cases maximum number detected incidentally[54, 55]. The symptoms can be due to the mass effect of a large aneurysm, or possibly from minimal leakage of blood which irritates the meninges; symptomatology being headache, unilateral third cranial nerve palsy (from a posterior communicating artery aneurysm), bilateral temporal hemianopsia (from an anterior communication artery aneurysm impinging on the optic chiasm) ischemic cerebrovascular disease, poorly defined spells, and seizures[41,42].

These symptoms can be considered as a warning sign of an impending rupture, as 10% to 43% of patients with SAH report experiencing a sentinel headache in the 2 months preceding the rupture [43]. So therefore, the presence of headache even in asymptomatic patients is to be considered seriously and needs to be investigated further as it may signify an underlying pathology as an aneurysm.

In a study by Seppo Juvela et al[56], the study was designed to identify independent risk factors for multiple intracranial aneurysms in patients with subarachnoid hemorrhage. Cigarette smoking, age, hypertension and female sex were found to be the risk factors for multiple intracranial aneurysms. Anatomic risk factors such as increased aneurysm size, the presence of a daughter sac and posterior circulation location are associated with increase risk of rupture.

In another study by Seppo et al he stated that the cessation of smoking is very important for the unruptured aneurysms to grow in size as growth of aneurysm was observed more in the smokers group.

In a study by HABIB et al revealed that, as opposed to the occurrence of a single aneurysm, there was a significant association between the presence of multiple aneurysms and hypertension, cigarette smoking, family history of cerebrovascular disease, female sex, and postmenopausal state in female patients[57].

Most common location of bleed seen in our study was Sylvian fissure (48.5%) followed by basal cisterns (30.3%). Intra-ventricular haemorrhage was seen in about 21.2 % of cases.

Non contrast head CT has a nearly 100% sensitivity for the presence of acute SAH in the first 6-24 hours following symptom onset. NECT scan was used as a primary screening tool in our patients to understand the pattern of hemmorhage[58].

Sylvian fissure bleed was noted in our cases of all ruptured MCA aneurysms, interhemispheric bleed was noted in all cases of ruptured A-com aneurysms, basal cisterns bleed was noted commonly in cases of p-com, basilar, SCA, PCA and vertebral artery aneurysm.

These findings corroborated with various patterns of SAH studied in the literature. In a study by Carrie et al[59] the various patterns of subarachnoid haemorrhage are mentioned. Aneurysm ruptures from branch points in the circle of Willis and produce a large volume of SAH when they rupture. Accordingly, aneurysmal SAH often fills the suprasellar, central, anterior, lateral, posterior, and lower basal cisterns and may extend to the cerebral sulci. Associated intraventricular hemorrhage sometimes occurs, such as with anterior communicating artery aneurysms

that rupture into the third ventricle through the lamina terminalis. The epicenter of SAH occasionally suggests the location of an underlying ruptured saccular aneurysm. For example, SAH in the interhemispheric fissure suggests an anterior communicating artery aneurysm, whereas sylvian fissure SAH suggests a middle cerebral artery aneurysm.

All patients admitted in Neurosurgery department presenting with subarachnoid haemorrhage and having more than one aneurysm i.e. multiple aneurysms were included. A total number of 33 patients presented with a total of 79 aneurysms were included presenting with subarachnoid haemorrhage. Total number of aneurysms ruptured were 33 and unruptured were 46. Out of 79 total aneurysms - 55 were clipped ,10 were wrapped and 10 were unclipped. Ruptured aneurysms were all treated - 32 clipped and 1 was coiled.

Dissection and Clipping of a bifurcation aneurysm

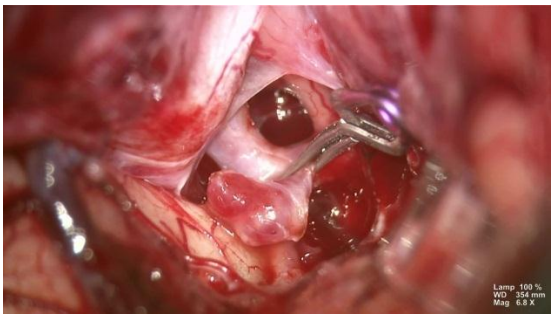


Figure 26 : Clipped bifurcation aneurysm

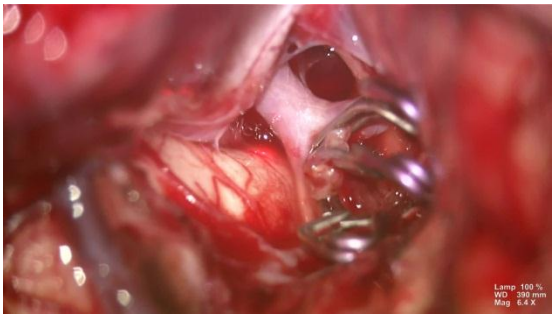


Figure 27: Reconstructed bifurcation aneurysm

Total 32 of 33 ruptured aneurysms were clipped, one basilar ruptured case was coiled. Total of 10 aneurysms were wrapped out which 5 were ruptured cases in addition to clipping; 5 remaining aneurysms which also wrapped were of unruptured cases not amenable to clipping.

So most of the aneurysms has been tackled and the remaining ones were kept on follow up imaging. Most of the aneurysms 23 were of anterior circulation exclusively, posterior circulation exclusively in 5 cases; both anterior and posterior circulation in 5 cases.

Most common aneurysm seen was MCA aneurysm.

Most common ruptured aneurysm was MCA aneurysm 8 cases followed by 6 Acom, 6 p-com, 1 para p-com,3 basilar top,2 anterior choroidal,2 DACA ,1 ICA bifurcation,1 V4 vetebral segment,1 superior hypophyseal,1 SCA and 1 hypoglossal artery aneurysm.

Majority of patients in our study was having age more than 40 years about 87.9% with 10 male and 23 female patients. Male to female ratio of 1:2.3 was seen in our study suggesting more of females presenting with subarachnoid haemorrhage.

Majority of patients seen were in grade I (81.8%) followed by grade 3 (9.1%), grade2(6.1%) and then grade 4 (3%) as per WFNS[60] grading. As per FISHERS[61] grading majority of patients seen were in grade 4 (30.3%) followed by grade 2 (27.3%), grade1(24.2%) and then grade 3 (18.2%).

Ruptured aneurysms were more common on the right side 56.0% and 44% on left side. Cross flow across A-com was present in 33.3%, absent in 63.7%. One patient with Vertebral V4 segment aneurysm had cross flow present on left ICA, absent on rt ICA. Cross flow across p-com was present in 24.2%, absent in 57.6%, present on left p-com and absent on rt p-comm in 15.2% of cases.

Saccular aneurysm (72.7%) most common amongst unruptured cases followed by fusiform (6.1%) and fusi-saccular (6.1%). Most of the hemorrhage pattern was focal in 63.6% and diffuse in 36.4 % in the observed cases. Majority of the aneurysms which ruptured were present on the bifurcation (78.8%) than sidewall (21.2%). Majority of the aneurysms which were unruptured were present on the sidewall (60.6%) than bifurcation (39.4%).

Surgical interventions -

All ruptured aneurysm were tackled with craniotomy and clipping sos wrapping as necessary in one sitting.

Single stage surgery with clipping of maximum accessible aneurysms was done for most of the patients except a few. Most common craniotomy was pterional craniotomy which was mainly done for the anterior circulation aneurysms.

- RSSO craniotomy was preferred in cases of vertebral V4 segment aneurysms.

Dual staged surgery was done for the following aneurysms: -

- One case of Bilateral MCA aneurysm with the ruptured aneurysm clipped first.
- One case of Left MCA aneurysm with Rt MCA aneurysm and Rt ICA aneurysm.
- One case of Rt communicating segment aneurysm with Lt MCA bifurcation aneurysm.

These all cases with dual staged procedure was interval period of almost 1 year.

- Once a left sided approach was used to clip bilateral MCA aneurysms successfully.
- One case of bilateral MCA bifurcation mirror aneurysm was tackled with bilateral pterional craniotomy done in the same sitting.
- For DACA aneurysm peri-coronal parasagittal craniotomy was done for the access.
- Only one basilar aneurysm was coiled and the unruptured PCA aneurysm was kept on follow up.

The aneurysms which were not accessible were kept on follow for monitoring clinical signs like headache, neurological deficits or interval growth in size of aneurysms.

None of the untreated aneurysms had presented with bleed or any other deficits or interval growth

It has always been challenging regarding the management of multiple aneurysms.

Questions which are needed to addressed are –

- Whether all the aneurysms should be clipped in one sitting or two sittings?
- Whether to operate and clip all aneurysms?
- When to operate in an acute setting to have a better outcome?

  Currently, there are several studies which throw light on these aspects in order to have better outcomes.

Mc Kissock et al [35] in 1964 and Paterson and Bond [36] thought that operation for unruptured aneurysm were not indicated.

Heiskanen and Marttila [37] in 1970 advocated that only those unruptured aneurysms, which could be reached, through the same approach as for the ruptured aneurysm should be operated upon, and that a second operation would not be indicated.

Hamby in 1959, Poppen and Fager in 1959, Moyes in 1971, Mount and Brisman in 1971 and in 1977 and Samson et al in 1977, recommended that if conditions were satisfactory, all surgically accessible unruptured aneurysms should be operated.

Suzuki and Sakurai in 1979 and Solazar in 1980 and in 1983 insisted that all the multiple aneurysms should be considered for operation even if a second operation was necessary to clip the unruptured aneurysm.

The aneurysm which has been detected unruptured in a cases of multiple aneurysms presenting with subarachnoid haemorrhage should be evaluated for factors which may be responsible for the increased future risk of rupture in the future.

The risk of bleed from untreated unruptured aneurysm is quoted to be 1-2% per year in the literature[30].

A yearly risk of rupture of 1% in 61 patients with multiple aneurysms in whom at least one asymptomatic lesion had not been clipped was noted by Heiskanen[28].

An annual rupture rate between 1 & 2 % was also quoted by Winn et al[38] for similarly unsecured aneurysms and the mortality rate is said to be > 4% over a 5-year period.

The morbidity and mortality have been implicated for patients with the ruptured aneurysm i.e. the symptomatic lesion more than the unruptured ones. So, it is very important to identify the ruptured one early and treat on priority basis the same.

In a study by Brisman et al had noted an overall mortality of 56 % in patients with multiple aneurysm compared to 59% in patients with single aneurysm.

There was a similar rate of rebleeding of 30% in patients with single or multiple aneurysms in a study by Winn[38] (1983). The site of second haemorrhage was found to be from the original ruptured aneurysm and never from an asymptomatic aneurysm. Therefore, it was suggested that treatment should first be directed towards the symptomatic lesion.

The location of multiple aneurysms and the serious risks of operating on asymptomatic unruptured aneurysms determines the choice of surgical approach.[37,39,40]

There is a con-census that in a single operation maximum number of aneurysms should be tackled with foremost target being the ruptured aneurysm. The remaining asymptomatic aneurysms can be dealt at a later stage with the second operation. [41,42]

Most authors opine that all accessible aneurysms should be clipped; to start from the deepest one progressing to most superficial one's (Nehls and Armenda et al[5]).

The technical difficulties in such cases as regards to clipping of symptomatic superficial aneurysm first is the interference with deeper view and thereby causing difficulty in clipping them.

There are some opinions in these situations as follows –

- Clip the superficial symptomatic lesion and attempt for the deeper, asymptomatic lesion for clipping.
- To clip the deeper lesion first taking care not to disturb the ruptured aneurysm, which can be clipped second.
- Asymptomatic lesion which cannot be accessed in the first operation can be left untreated to be dealt with through another approach.
- When additional aneurysm cannot be clipped through a single approach, the unsecured lesions are treated like another incidental aneurysm if it has not ruptured.

A number of large series have carried out research on the role of one and two stage operations for patients with multiple aneurysms[26,39,43.]

The advantage of a single stage is that no further surgery is needed for dealing with asymptomatic aneurysm at a later date. The risk of haemorrhage from the asymptomatic aneurysm is also decreased or virtually eliminated in single staged approach. So, the patient is less exposed to repeated surgical interventions and thus less of anaesthesia related complications, vasospasm, infection and bleeding risks. The advantage of two-stage approach is that the aneurysm exposure and clipping may be technically easier when subarachnoid blood has cleared and brain swelling has decreased.

In a study by Mizoi et al [43] reported their experience in 372 cases of multiple aneurysms, patients with multiple anterior circulation aneurysms or anterior communicating artery aneurysms in combination with anterior or posterior circulation 90 % of them were treated through single craniotomy.

In our study 43 patients, aneurysm was bilateral and in 27 patients was unilateral.

A single staged surgery was successful in 60 % of patients with bilateral aneurysms and 42% of patients with vertebrobasilar and anterior circulation aneurysms.

In a study by lnagawa[26] single staged surgery was done in 71 % two staged surgery was done in 16%. Ruptured aneurysm was treated in the first stage followed by the unruptured aneurysm in the second stage.

In a study by Lester & Brisman[39] reported 70 patients of multiple intracranial aneurysms with total of 160 aneurysms, 110 aneurysms on internal carotid artery ,10 being on intra-cavernous ICA, 31 on middle cerebral artery, 16 on anterior cerebral artery or on anterior communicating artery and 4 on posterior circulation.

There were 56 patients with 2 aneurysms, eight with 3, five with 4 and one with 5 aneurysms. There were 20 patients with bilateral symmetrical aneurysm. (17 on ICA, and 3 on MCA).17 patients had nonsurgical treatment, and 22 had one aneurysm surgically treated. Twenty-five patients had both aneurysms treated by surgery, four had all three, one had all four and one had all five. 46 patients did not have all their aneurysms treated including 17 who had no surgical procedure at all. In this group good results are in 44%, poor in 35%, and death in 21 %. Of the 24 patients who had all their aneurysms surgically treated by intracranial clipping, muscle wrapping, plaster spraying or extra cranial carotid ligation, 88% had good result, 8% had poor result and 4% died. The risk of subarachnoid haemorrhage from an originally asymptomatic aneurysm is in between 10 - 20% in this series.

Chemical angioplasty or as required balloon angioplasty was required in 45.5% of cases out of which 27.3% required only once while 18.2% required on twice occasions.

Vasospasm is a known cause of morbidity and mortality in most of the cases either treated surgically or medically which accounts for 50% of deaths among those surviving initial ictus[62].Vasopsasm has a predictable time course which comes between 3-21 days post bleed, maximum between 5-14th days[63]. Incidence of symptomatic CVS varies between 17 % and 48 % of aneurysmal rupture cases[64,65].

Vasospasm early detection can be done by vigilant monitoring of clinical signs such as drop in sensorium, slurred speech, restless and irritable behaviour. Strategies for the treatment of vasospasm are medical i.e. nimodipine which has a class I evidence and intervention i.e. angioplasty either chemical or balloon using Milrinone which has class II evidence[66]. Relief of vasospasm has a direct impact on the morbidity and mortality of these patients and should be relieved as urgently as possible. In a study by Z.Q. Huang et al[67] 2361 patients with 2674 aneurysms were studied at 4 medical centers. Geometric and morphologic parameters examined for symmetric bilateral intracranial aneurysms comprised aneurysm wall regularity, size, neck width, aspect ratio, size ratio, neck-to-parent artery ratio, and area ratio which proved increased neck width, aspect ratio, neck, width and irregular size was associated with increased rupture risk.

A metanalysis by W. Brinjikji et al[68] twenty-one studies including 3954 patients with 4990 aneurysms with 13,294 aneurysm-years of follow-up were included found that growth and thereby rupture risk was associated with increasing age, female sex, smoking, irregular aneurysm shape, location in the posterior circulation, cavernous carotid artery or MCA bifurcation, and larger aneurysm size.

Width of bled aneurysm (5.07 mm) in our study was more than un-bled (2.94 mm). There was significantly greater width in case of ruptured aneurysms as compared to unruptured group. In studies quoted by Giordan et al Z.Q. Huang et al[67] more than 5 mm of width were noted in the ruptured group[69].

Aspect ratio in ruptured aneurysm (mean2.01) was greater than unruptured aneurysms(mean1.66) which was similar to study quoted by Daan et al[70].Aspect ratio is found to be greater in ruptured cases than unruptured cases studied in literature and now in recognised parameter for evaluation for the rupture of aneurysm [71,72].

Neck in ruptured aneurysm (mean of 2.87 mm) was greater than unruptured aneurysms (mean of 1.89 mm). Blebs/daughter sacs were present in 78.8% cases of ruptured aneurysms.

In many studies as supported by hemodynamic models aneurysm blebs have been identified as a risk factor for increased risk for future rupture and is corroborated by being more common in ruptured aneurysm cases than in unruptured ones .[73,74,75].

In studies by Tateshima et al[76] it is proven that the wall shear stress is more near to blebs alters the intra-aneurysmal flow dynamics. This finding was later confirmed in a similar study with PCMR imaging[77].These blebs do contribute to altered flow dynamics and thereby increased risk of rupture of aneurysms. So early identification of such aneurysm holds a prime importance in these cases.

Flow angles were found to be more obtuse in ruptured mean (124.4 degrees) than in unruptured cases (mean 102.7 degrees).

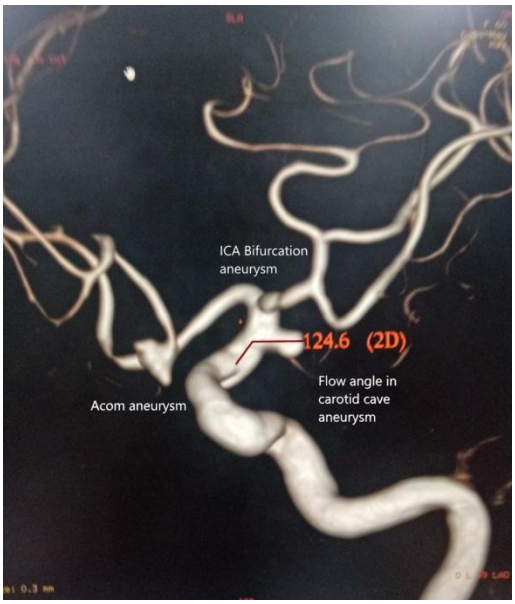


Figure 28 : Flow angle in carotid cave aneurysm

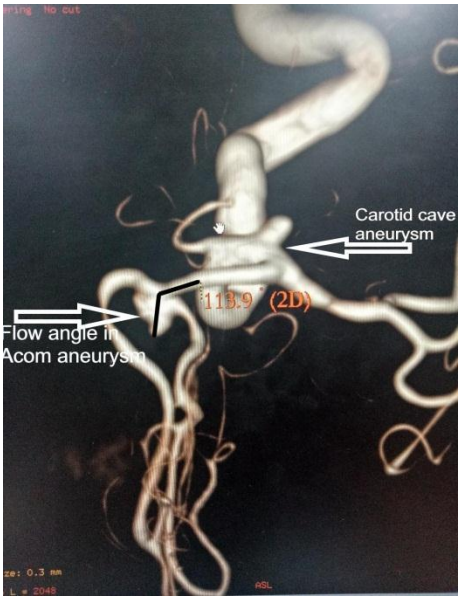
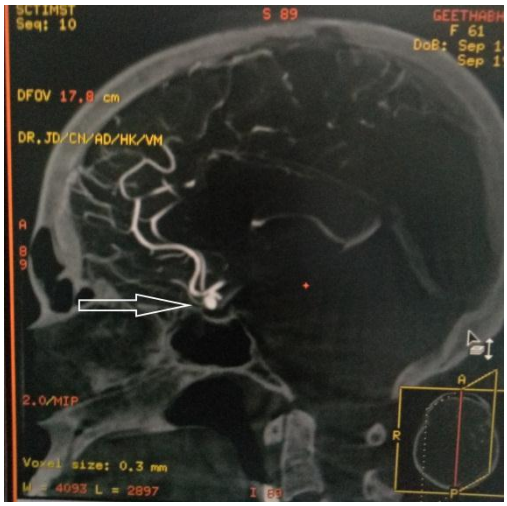


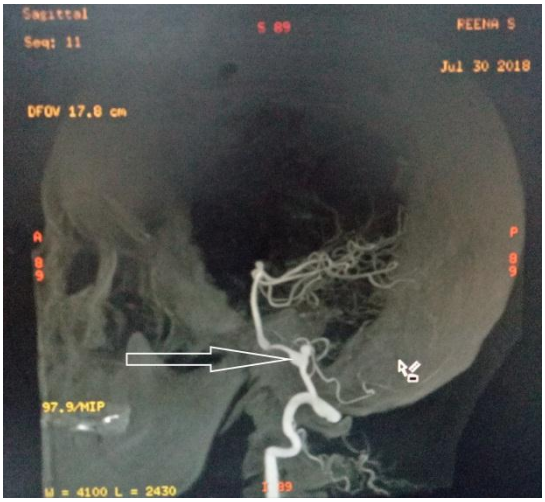
Figure 29 : Flow angle in A-com aneurysm

In a study by Merih et al[78] and Baharoglu et al[79] inflow angle, aspect ratios, maximal dimension was used to discriminate between ruptured and unruptured cerebral aneurysms. The inflow-angle were found to be significantly more obtuse in ruptured subset of patients, similarly, maximal dimension, height–width ratio, and dome–neck aspect ratio was significantly greater in the ruptured subset.

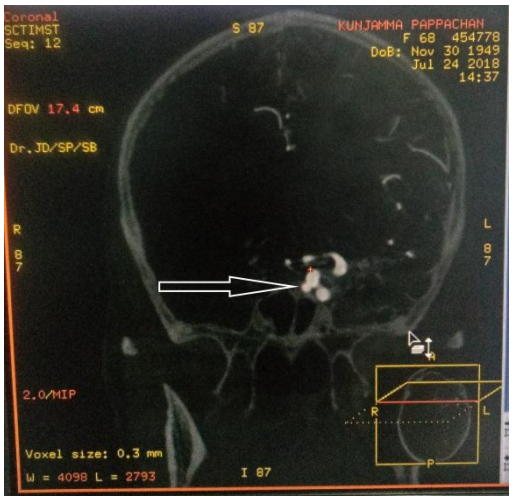
Bone wall contact was present in more cases of ruptured aneurysm (48.5%) as compared to unruptured cases (41.3%) signifying a constant insult to the aneurysm wall and thereby contributing to more rupture.



A



B



C

Figure 30 : (A) Bone wall contact of A-com aneurysm (B) Bone wall contact of vertebral V4 aneurysm, sagittal view (C) Bone wall contact of vertebral V4 aneurysm coronal view

Studies by Daan et[70] al and D Saan[80] et al clearly state the role of perianeurysmal environment in the rupture of aneurysms with bone wall contact as one of the factor responsible.

Blebs or daughter sacs were seen in 78.8% cases of ruptured aneurysms.

Presence of blebs or daughter sacs giving rise to irregular shape of aneurysms has been implicated in rupture of aneurysms as in studies quoted by Bjorkman et al[81] and P Bhojal et al[82].

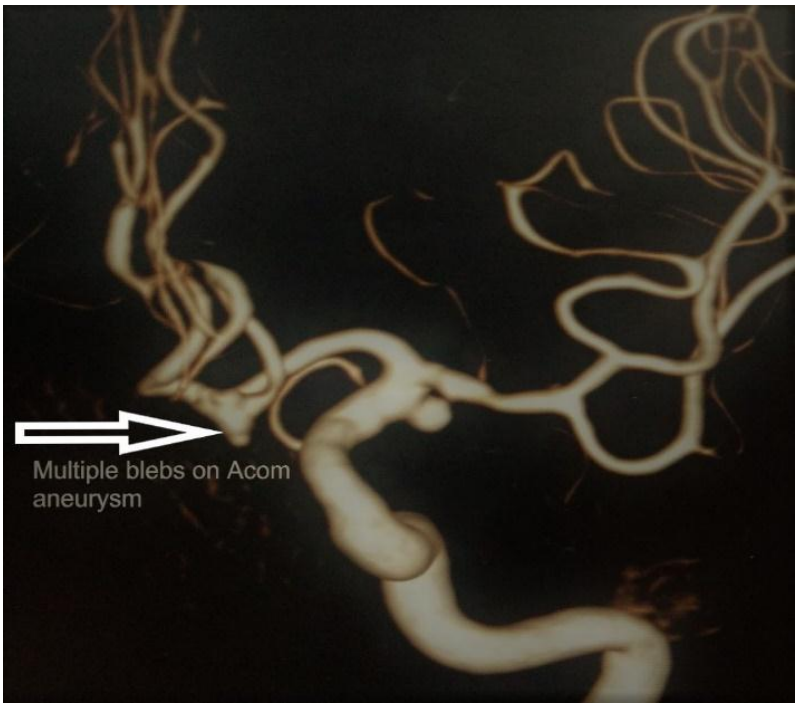
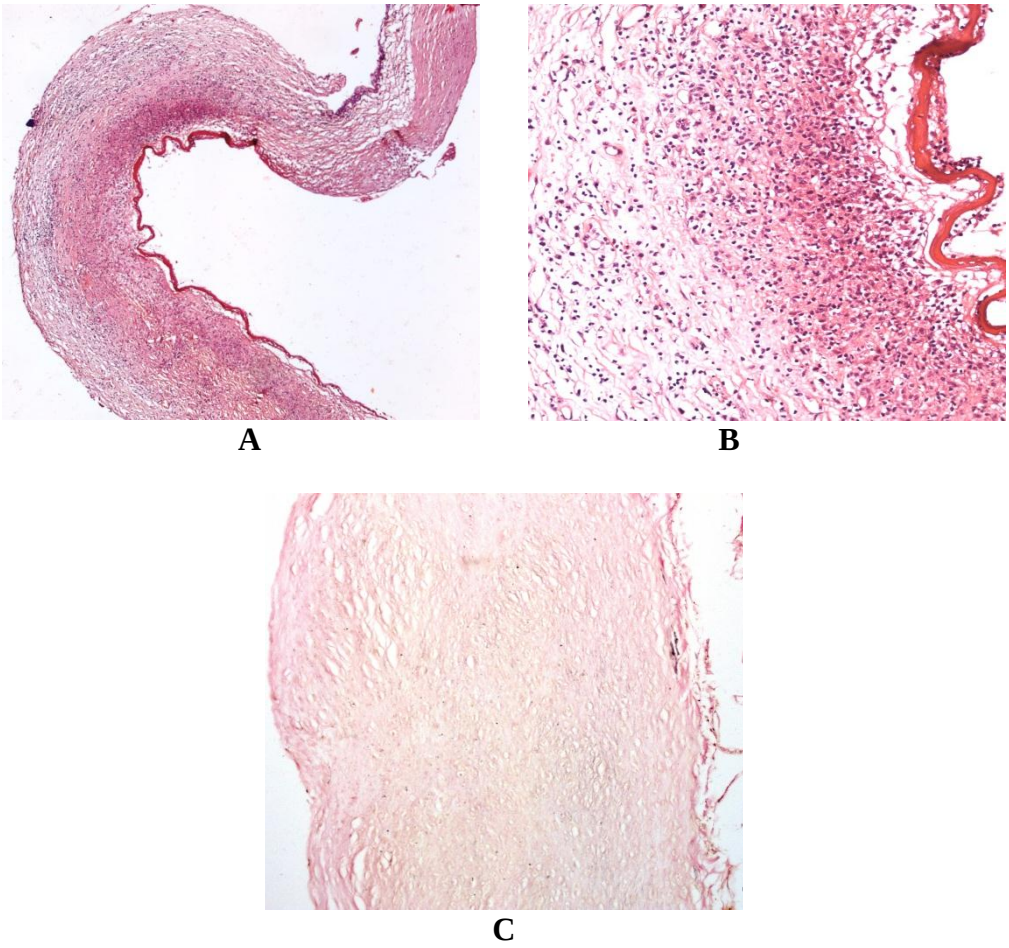


Figure 31 : Multiple blebs seen on A-com aneurysm with carotid cave aneurysm

The aneurysms which has more of irregular shape with blebs has more incidence of rupture in our study which corroborates with the literature series available currently.



A **B**

C

Figure 32 : Sections from wall of aneurysm (A) show the luminal aspect covered with fibrin. The wall is fibrotic with moderate infiltrates of lymphocytes and histiocytes (B) with absence of internal elastic lamina (C). [A&B: Haematoxylin and Eosin, original magnification 50X and 200X, C: Elastic van Gieson, original magnification 200X]

8 out of 33 patients were suspected to have intra operative abnormal pathology and were sent for pathological examination all of the specimens showed absence of internal elastic lamina corroborating with the established pathology of formation of aneurysms.[10,50,80]

Complications

All of the patient was ambulant post-op except a few cases for which physiotherapy was given and they had significant improvement in ambulation thereafter.

One patient was quadriparetic post-op, a case of basilar top aneurysm. One patient has third nerve palsy in a case of ruptured anterior choroidal aneurysm which improved with steroids.

Post op only one patient had hydrocephalus for which VP shunt was done. Patient was a case of Ruptured a-com aneurysm presenting with a diffuse haemorrhage. Patient improved significantly after CSF diversion procedure.

One patient had lower limb DVT post op in a case of mirror MCA aneurysm which was treated with anticoagulation and Bard Denali filter.

Patients with vasospasm were detected on the basis of deterioration of clinical signs such as decreased sensorium and were immediately subjected to angioplasty (chemical or balloon). Most of the patients improved significantly post angioplasty. There was no mortality noted in our study.

CONCLUSIONS

In our study there were more of females presenting with multiple aneurysm as compared to males with lower grades of haemorrhage (WFNS and FISHERS scale). Age group was > 40 years in most of the patients. Smoking and Hypertension were more common comorbidities found. GCS on presentation was >10 in most of cases.

The epicentre of haemorrhage was according to location of aneurysm. Maximum number aneurysms had been clipped in our study.

Radiological parameters in ruptured aneurysm were having more of flow angles (obtuse), increased neck, width and aspect ratios as compared to unruptured aneurysms. Bone wall contact was found in significant number of cases of ruptured aneurysms. Daughter aneurysms and blebs were more common findings in ruptured cases. None of the cases have rebled and on regular follow up.

There was an immediate action taken if vasospasm was suspected in the patients for which angioplasty was done. Relief of spasm relieved symptoms and ultimately surgical outcome significantly.

So, patients with addiction habits as smoking and alcohol need to be advice for discontinuation of the same. Comorbidities such as hypertension need to be controlled to prevent any future rebleed event. Epi-center of haemorrhage investigated with NECT and DSA can predict the exact site of aneurysm and targeting the therapeutic options like clipping or coiling towards the ruptured aneurysm.

To conclude meticulous clinical and radiological evaluation predicts the bled aneurysm thereby helping in the treatment for the same.

Limitations

The number of cases is a limiting factor in our study and will be ultimately overtaken by a further continuation of the study.

As it is a prospective study to be continued in future a solid conclusion is not expected at this point, although majority of findings are corroborating with the various studies in the literature.

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ANNEXURE I

Individual factors

Age

Sex

Duration of symptoms:

Symptoms: Vomiting/headache/raised ICP/ Motor/sensory/Visual/ cognitive/seizures/others.

Neurological Deficits.

Hypertension
Smoking
Alcohol
Diabetes Mellitus
Trauma
Family history of cardiovascular disease (Angina, Myocardial Infarction or Peripheral vascular disease)
Family history of cerebrovascular disease (Transient ischemic attack or Stroke)
Collagen vascular disorders / Polycystic kidney disease/others
Menopausal state of female

ANNEXURE II

Radiological parameters DSA / CT Angiogram /MR Angiogram on presentation

Size of aneurysm

- Anterior circulation or Posterior circulation
- Proximal upto A1, M1 ,Acom ,P1, MCA Bifurcation
- Distal beyond proximal are the distal sites

Shape of aneurysm

Pattern of hemorrhage

Presence of blebs / blisters / thrombus

Aspect ratio [dome length-to-neck / neck-width]

Flow angles
Aneurysm type - sidewall or bifurcation type

Parent artery configuration (side wall and branching)

- neck-width,
- aspect ratio -neck to dome length (length from the neck centre to the dome of the aneurysm)
- aneurysm width (measured perpendicular to the neck to dome length)

Involvement of circumference of vessel

Flow angle

Location Contact between the aneurysm wall and bone/dura/parenchyma.

Adjuvant treatment

Need for Shunt

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Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SCT/IEC/1162/DECEMBER-2017 07.02.2019

Dr. Mathew Abraham
Professor
Department of Neurosurgery
SCTIMST, Thiruvananthapuram

Dear Dr. Mathew Abraham,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "STUDY OF THE PREDICTORS OF RUPTURE OF A SPECIFIC ANEURYSM IN A PATIENT DIAGNOSED WITH MULTIPLE ANEURYSMS - A PROSPECTIVE EXPLORATORY OBSERVATIONAL STUDY (IEC/1162)" on 16th December, 2017.

The following documents were reviewed:

Original submission

1. *Covering letter addressed to the Chairman, IEC, SCTIMST dated 15.11.2017 with check list*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Proforma*
6. *Information Sheet and Consent Form in English and Malayalam*
7. *CV of Principal Investigator and Co-Principal Investigator*

Revised submission

1. *Covering letter addressed to the Chairman, IEC, SCTIMST dated 31.01.2019 with check list*
2. *IEC Application Form*
3. *Project Proposal*
4. *Proforma*
5. *Information Sheet and Informed Consent Form in English and Malayalam*
6. *CV of Principal Investigator and Co-Principal Investigators*

The following members of the Ethics Committee were present at the meeting held on 16th December, 2017 at G. Parthasarathi Board Room, AMCHSS, SCTIMST

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
3.	Dr. S S Giri Sankar	LL.M. Ph.D.	Male	Legal Expert	No
4.	Dr. Aneesh V Pillai	BA. LLB (Hons.), LLM, Ph. D, SET (Law)	Male	Legal Expert	No
5	Mr. Satheesh Chandran	MSW, PGDPM	Male	Lay person/ NGO/ Social Scientist	No
6.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
7.	Dr. P. Manickam	BSMS, MSc (Epid).,PhD	Male	Health Science Expert/ Social Scientist	No
8.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
9.	Dr. Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
10.	Dr. V. Raman Kutty	M D, M Phil, M P H	Male	Health Sciences Expert/Clinician	Yes
11.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC