"*A RETROSPECTIVE STUDY OF ANGIOGRAM NEGATIVE SUBARACHNOID HAEMORRHAGE: ASSESSMENT OF CLINICAL PROFILE, BLEEDING PATTERN AND LONG-TERM OUTCOMES*"

THESIS

SUBMITTED IN PARTIAL FULFILLMENT FOR DEGREE OF

M.Ch NEUROSURGERY

(2016 – 2018) OF THE

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL

SCIENCES AND TECHNOLOGY,

TRIVANDRUM, INDIA

DR. PALAK JAISWAL

DEPARTMENT OF NEUROSURGERY

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

TRIVANDRUM, INDIA

"A RETROSPECTIVE STUDY OF ANGIOGRAM NEGATIVE SUBARACHNOID HAEMORRHAGE: ASSESSMENT OF CLINICAL PROFILE, BLEEDING PATTERN AND LONG-TERM OUTCOMES"

Submitted by : ***Dr. PALAK JAISWAL***

Programme : MCh Neurosurgery

Month & year of submission : July 2018

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

TRIVANDRUM, INDIA

CERTIFICATE

This is to certify that the work incorporated in this thesis titled

"*A RETROSPECTIVE STUDY OF ANGIOGRAM NEGATIVE SUBARACHNOID HAEMORRHAGE: ASSESSMENT OF CLINICAL PROFILE, BLEEDING PATTERN AND LONG-TERM OUTCOMES*"

for the degree of

M.Ch NEUROSURGERY

has been carried out by ***DR. PALAK JAISWAL***

under my supervision and guidance. The work done in connection with this thesis has been carried out by the candidate himself and is genuine.

Dr. Mathew Abraham
Professor& Head
Principal Guide
Department of Neurosurgery,
SCTIMST, Trivandrum.

Dr. MATHEW ABRAHAM M.S, M.Ch, F.R.C.S (Edin)
Professor and Head
Department of Neurosurgery
Sree Chitra Tirunal Institute for
Medical Sciences and Technology
Thiruvananthapuram - 695 011

Dr. Easwer H. V.
Professor
Co - Guide
Department of Neurosurgery,
SCTIMST, Trivandrum.

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
Thiruvananthapuram

DECLARATION

This thesis titled ***"A RETROSPECTIVE STUDY OF ANGIOGRAM NEGATIVE SUBARACHNOID HAEMORRHAGE: ASSESSMENT OF CLINICAL PROFILE, BLEEDING PATTERN AND LONG-TERM OUTCOMES"***, is a consolidated report based on a bonafide study of the period from January 2005 to December 2016, 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 fulfillment of rules and regulations of MCh Neurosurgery examination.

Date: 30th July 2018

Place: Trivandrum

Dr. Palak Jaiswal,

Department of Neurosurgery,

SCTIMST, Trivandrum

ACKNOWLEDGEMENT

The guidance of **Prof. Mathew Abraham,** Professor and Head of the Department of Neurosurgery, has been invaluable. I am extremely grateful and indebted for his contributions and suggestions, which were of invaluable help during the entire work. His critical remarks, suggestions, helped me in achieving a high standard of work.

I, also owe a deep sense of gratitude to **Prof. Suresh Nair**, former Head, Department of Neurosurgery for his invaluable advice and guidance, without which this work would not have been possible. He will always be a constant source of inspiration to me.

I express my sincere and deepest gratitude to my co-guide, **Prof. Easwer H. V.** His expertise, invaluable guidance, constant encouragement, affectionate attitude, understanding, patience and healthy criticism has added considerably to my experience. Without his constant inspiration, it would have not been possible to complete this study.

I am deeply indebted to Prof. Krishnakumar K., Dr. George Vilanilam, Dr. Jayanand Sudhir, Dr. Prakash Nair, Dr. Tobin George and my colleagues. I thank them for their constant encouragement and support.

I am very grateful to my **wife and family** for their constant encouragement and moral support.

Last but not the least, I owe gratitude to all the patients who put their faith in us and without whom this work would not have been possible.

TABLE OF CONTENTS

INTRODUCTION

Spontaneous subarachnoid haemorrhage [SAH] is an acute and potentially fatal neurosurgical emergency. Patient mortality approximates 45% within a month after SAH. Hence, identification of a treatable cause of SAH is necessary.

Spontaneous, non-traumatic SAH is most commonly caused by rupture of saccular aneurysms. Less commonly, it results from rupture of arteriovenous malformations, arterial dissections, tumours, or other vascular abnormalities. Occasionally, no structural cause for the haemorrhage can be identified on radiographic imaging. These haemorrhages, termed idiopathic SAH or angiogram-negative SAH [anSAH], represent approximately 15% of all SAHs (1–6).

This group of patients pose a difficult management proposition. This is so because these patients run the risk of re-bleed and its consequences, if a structural lesion had been missed on the initial angiogram. Such patients, on additional vascular studies in delayed fashion, reach a definitive diagnosis over a range of 2 to 20% (7–10). However, most patients with anSAH have a more favourable outcome, and a minimal chance of recurrent SAH. Also, recent studies suggest that certain bleeding pattern on admission computed tomography [CT] of head, are more likely to be diagnosed with a definitive bleeding source in additional vascular studies and are more likely to eventually undergo intervention(8,9,11–13).

The present study reports the outcome data of all the consecutive patients admitted at our institution who met the criteria for anSAH. This study also focused on clinical features, complications, relationship between initial bleeding pattern and outcome, and role of repeat imaging.

AIMS AND OBJECTIVES

1. To identify patients presenting with spontaneous non-traumatic subarachnoid haemorrhage in whom the initial 4-vessel cerebral digital subtraction angiogram[DSA] showed no evidence of any vascular pathology.

2. To study the clinical profile, complications and long-term outcomes of anSAH patients.

3. To study the bleeding pattern of subarachnoid haemorrhage on CT and determine its relationship clinical features, complications and outcomes.

4. To study the role of follow up imaging in angiogram negative subarachnoid haemorrhage

REVIEW OF LITERATURE

Epidemiology

SAH is one of the most feared neurological events due to its associated high mortality and tendency to cause dependence. Its economic impact is more than twice that estimated for ischaemic stroke (14). Spontaneous SAH cases account for 5% of all strokes (15,16). According to the European Registers of Stroke study, the incidence of SAH has found to be 9 cases/100, 000 inhabitants per year (15). These non-traumatic SAH affects approximately 20,000–30,000 people in the USA each year(17) and carries up to 45% 30 day mortality as well as poor functional outcome among survivors (4,18–20).

Although trauma is the most common cause of SAH, ruptured saccular aneurysms are the most common cause of non-traumatic SAH, accounting for approximately 85% of cases of spontaneous SAH (3,4). Of the remaining 15% of cases, two thirds are due to idiopathic perimesencephalic haemorrhage [PMSAH] (21,22). The remaining cases result from a wide variety of causes.

History

Hayward RD in 1977 first reported cases of subarachnoid haemorrhage of unknown aetiology (23). He in his 51 cases out of 592 cases of (22%) SAH, found no cause that could be determined after four vessel angiogram and CT scan. He demonstrated that subarachnoid haemorrhage is mild in such patients. All his patients were of clinical grades 1 to 3. He did not report any case of re-bleed and there were no deaths. His study also emphasized the good prognosis of those patients.

Prior, Mckissack in 1959 also stressed the better prognosis in his cases of subarachnoid

haemorrhage of unknown aetiology (24).

However, the concept of a benign, non-aneurysmal form of SAH with a distinct radiographic appearance was first crystallized by Van Gijn and colleagues in 1985 (21). Since then, multiple studies have confirmed that the outcome following PMSAH and anSAH are different than those for aneurysmal SAH and are good, with minimal risk of re-bleeding.

Bleeding pattern & their causes

According to the pattern of haemorrhage on initial CT scan, it is possible to identify subsets within the larger group of patients in whom the initial angiogram reveals no aneurysm (25–27). This differentiation has crucial implications for prognosis and management of these patients and allows selection for repeated angiography of only those patients who are at risk of re-bleeding.

SAH can be classified into at least three distinct patterns by location on initial unenhanced CT. Proper classification depends on unenhanced CT evaluation within 3 days of symptom onset, because substantial redistribution occurs thereafter, fundamentally altering the pattern (28).

Rarely, a fourth scenario is encountered, in which no blood is visible on unenhanced CT and SAH is diagnosed by lumbar puncture.

A) <u>Diffuse or anteriorly located haemorrhage in the basal cisterns</u>

Several causes of bleeding should be considered in patients with normal angiogram who show a diffuse or anteriorly located haemorrhage in the basal cisterns.

1) Insufficient examination of posterior circulation:

Despite the widespread use of four-vessel angiography & technical improvement, angiography of the posterior circulation remains a difficult procedure and the angiogram should be reviewed for proper visualization of the branches of both vertebral arteries if no aneurysm is found.

2) Occult or missed aneurysm:

The possible causes of unrecognized ruptured aneurysms included (1) an initial overlooking, (2) thrombosis or vasospasm and (3) the presence of a blister aneurysm i.e., aneurysms with a thin wall and no neck, arising from non-branching sites along the circle of Willis.

3) Vertebral/carotid artery dissection:

The patterns of haemorrhage on the CT scans of patients with carotid/vertebral artery dissection can be indistinguishable from those of patients with ruptured aneurysms. The diagnosis should be considered in patients in whom the angiogram shows localized nonspecific narrowing of artery, signs of intimal flap, a pseudo-aneurysm, or a double lumen. However, these features may be absent on an initial angiogram. Repeat angiograms may disclose the true cause of the haemorrhage in these patients.

4) Dural & spinal AVMs:

Dural arteriovenous malformations [AVMs] of the tentorium can give rise to a basal haemorrhage that is indistinguishable from aneurysmal haemorrhage (29). A history of head injury with skull fracture should raise the suspicion of a dural shunt, since healing of a skull fracture may be accompanied by the development of a dural AVM. In

patients in whom CT scan suggests a tentorial origin of the haemorrhage and in whom the angiogram seems to be normal, the angiogram should be reviewed/repeated again, with the possibility of a tentorial AVM in mind.

SAH can be a mode of presentation in approximately 10 % of patients with spinal AVM. The patterns of haemorrhage on the CT scans are indistinguishable from those of patients with ruptured aneurysms. Vertebral or spinal angiography may demonstrate the lesion, but this procedure is not always diagnostic (30,31). Re-bleed occur in half of these patients who survive the initial bleed(32).

B) <u>Peripheral convexity subarachnoid haemorrhage</u>

SAH may be localized to a few sulci of the cerebral convexities or to one of the sylvian fissures, without basal cistern or ventricular involvement. In the absence of trauma, isolated peripheral convexity SAH is rare and may be under recognized with an estimated incidence of 7% of all cases of spontaneous SAH (33).

Various causes include reversible cerebral vasoconstriction syndrome, cerebral amyloid angiopathy, posterior reversible encephalopathy syndrome, cerebral venous thrombosis, infectious causes, sickle cell disease, coagulation disorders and Moya-moya disease. Rarely ruptured superficial vascular malformations, cervical tumours, cerebral vasculitis, cocaine abuse, and rupture of a small circumferential artery in pontine cistern may present similarly. No cause is identified in 14–35% of cases (33–35). Few important surgical causes are:

1) Infectious Causes:

SAH complicates approximately 1–2% of cases of infectious endocarditis. The distribution of SAH is usually peripheral sulci or localized within one sylvian fissure,

but may be diffuse or occult on CT. Patients may have a history of injectable drug use and present with fever, headache, mental status changes, and physical examination signs of systemic emboli.

Associated imaging findings include embolic infarcts, micro-haemorrhages, or micro abscesses. Although some cases are secondary to rupture of septic [mycotic] aneurysms, angiography may be normal in 10 % cases (36). In these cases, SAH may result from focal endarteritis, vessel rupture at the site of embolic occlusion, or occult septic aneurysm. In patients with septic aneurysms, most aneurysms are located on the distal branches of the middle cerebral artery and approx. 10 % cases are more proximally located. In patients with aspergillosis, most aneurysms are located on the proximal part of vertebrobasilar or carotid artery (37). The aneurysms can be found on repeat angiograms (38), but, if angiography is repeated after long interval, it may be normal because mycotic aneurysms can resolve after antibiotic therapy.

2) Pituitary Apoplexy:

It has been proposed as a rare cause of SAH of unknown cause. Bjerre in 1986 presented a series of 10 cases who presented with anSAH. Among them, one had panhypopitutarism with partly empty sella, 3 had plain X-rays showing an enlargement of sella with low growth and gonadal hormones (39). The rest 6 had a mild fall in the hormonal levels. He suggested that haemorrhagic necrosis might be an important cause of subarachnoid haemorrhage with normal angiography.

C) **<u>Haemorrhage confined to cistern around the mid brain</u>**

Idiopathic Perimesencephalic haemorrhage:

A definite pattern of bleed has been identified as perimesencephalic non-aneurysmal

SAH [PMSAH] that constitutes approx. 10 % of all patients with SAH and two thirds of those with a normal angiogram (26,40). Van Gin and Rinkel et al defined PMSAH as extravasated blood that is confined to the cisterns around the mid brain, with centre of the bleeding immediately anterior to the midbrain. There is no extension of blood to the lateral sylvian cisterns or interhemispheric fissure. Some sedimentation in the posterior horns may be seen but frank intraventricular haemorrhage or extension into the parenchyma rules out that the patients belong to this category.

A quadrigeminal variant to PMSAH have been described in which there is SAH centred in the quadrigeminal cistern without pretruncal blood (41).

It is imperative to definitely diagnose these benign entities as the management protocol may not warrant further evaluation to try and pinpoint a source of bleed. Although 20 % of the patients have acute hydrocephalus on their admission CT scan, only a few are symptomatic and even then an excellent outcome can be anticipated (40).

Rinkel's definition of PMSAH had high interrater reliability and high specificity (97%) with low sensitivity and a low positive predictive value. So many new definitions have been proposed.

Weyerbrock et al in 2009, classified SAH bleeding patterns according to their anatomical blood distribution into 5 types ranging from Type 0 having a negative CT (SAH confirmed by lumbar puncture); type 1 shows prepontine or perimesencephalic bleeding; type 2 shows blood in the prepontine cistern extending to the medial Sylvian fissure. Extensive bleeding involving the basal cisterns, lateral Sylvian fissure, and hemispheric sulcal relief is observed in type 3. Type 4 SAH shows massive SAH with intracerebral haemorrhage. (42) Type 0 and 1 are subcategorized as a "typical PMH" type SAH compared to types 2, 3 and 4 which are considered "non-typical". They

concluded that DSA should remain the gold standard as it allows detection non-aneurysmal bleeding sources at low-risk. However, repeat angiography may be omitted in the case of type 0 and 1 bleeding if a complete, high quality DSA was obtained initially.

Nayak et al in 2011 also suggested a new classification system for the non-aneurysmal SAH that correlated the initial cranial CT imaging findings with the clinical outcome which was measured by the discharge Modified Rankin Scale [mRS] (43). The classification system ranged from Type 1a: Blood in basal cisterns only. Type 1b: Blood in basal cisterns with extension into the sylvian fissures only. Type 2: Type 1 (including 1a & 1b) with extension of blood into cortical sulci ± ventricles. Type 3: SAH without blood in basal cisterns. Type 4: any type of SAH + subarachnoid blood in the posterior fossa/cerebellar vermis. Based on this classification they concluded that the Type 1 category of haemorrhages are usually benign and do not warrant extensive battery of clinical and radiological investigations. Type 2 haemorrhage have a varying prognosis and need to be investigated and managed in similar lines to that of an aneurysmal haemorrhage with emphasis towards radiological investigation. Type 3 and Type 4 haemorrhages are usually more sinister and have a poor outcome. These group of patients need to be extensively investigated both clinically and radiologically in an attempt to find an underlying cause. If a cause is found and treated, the clinical outcome in such patients may turn positive and favourable.

Recently in 2016, Wallace et al gave an anatomic definition of PMSAH that correlated with a low risk of brain aneurysm and was applied with excellent inter-observer agreement(44). The criteria was essentially the same as those used by Rinkel et al(40) with three key exceptions. It stated as (1) centre of bleeding located immediately

anterior and in contact with the brainstem in the prepontine, interpeduncular, or posterior supra-sellar cistern; (2) blood limited to the prepontine, interpeduncular, supra-sellar, crural, ambient, and/or quadrigeminal cisterns and/or cisterna magna; (3) no extension of blood into the Sylvian or interhemispheric fissures; (4) intraventricular blood limited to incomplete filling of the fourth ventricle and occipital horns of the lateral ventricles (i.e. consistent with reflux); (5) no intraparenchymal blood.

Aetiopathogenesis

The cause and mechanisms of PMSAH has not been determined despite magnetic resonance imaging [MRI] studies with particular attention given to the perimesencephalic cisterns. Various theories proposed for the source of bleed are: capillary leak, a tear in the basal vein of Rosenthal or one of its tributaries, anterior longitudinal pontine or interpeduncular and posterior communicating veins, lenticulostriate or thalamoperforating arteries, intraluminal basilar dissection, cryptic brainstem AVMs and capillary telangiectasia and cavernous malformations (45). Most authors have postulated a non-arterial source of the haemorrhage due to a slower onset of headache, infrequent loss of consciousness, lack of blood in the brain parenchyma or ventricular system, limited amount of blood in the adjacent chiasmatic cistern, and low complication rate as compared with patients suffering from aneurysmal SAH (46,47). Rinkel et al. on the other hand, suggested a venous or capillary source for patients with perimesencephalic SAH (48). Extensive involvement of the cisterns, parenchyma, and more acute clinical presentation suggests an arterial source (49).

Some studies reported a possible contribution of a primitive variant of the basal vein of Rosenthal in the pathogenesis of PMSAH(22,50). There is also an interesting debate about the possible relation between PMSAH and venous system variants or anomalies

(51). However, a recent study reviewing the venous phase of the DSAs of 59 patients with PMSAH, Daenekindt et al. (52) were unable to confirm a contribution of a primitive variant of the basal vein of Rosenthal in the pathogenesis of PMSAH. Several authors have described an association between PMSAH and abnormal venous drainage pattern. The hypothesis is that SAH may have resulted from venous rupture secondary to central cerebral venous hypertension caused by sinus stenosis or abnormalities in venous outflow (46,47,53). Physical exertion including components of the Valsalva manoeuvre can be an important predisposing factor for PMSAH. Some kinds of physical exertion produce increased intrathoracic pressure, which may block jugular venous return, resulting in elevated intracranial venous pressure. This may cause mechanical swelling of the intracranial veins and lead to venous or capillary breakdown. The SAH was associated with the Valsalva manoeuvre in 37 % of the patients with PMSAH and in 16 % of those with non PMSAH in one series (54). However, it remains unclear why the venous or capillary network would be more vulnerable in patients with PMSAH compared with healthy persons.

The etiology of angiogram-negative aneurysmal SAH remains elusive. Numerous theories have been proposed, which are difficult to validate, due to the paucity of post-mortem studies. Angiography may yield false negative results due to vasospasm, vascular thrombosis, mass effect by an adjacent hematoma, or a technically inadequate examination. The technical quality of an angiogram must be considered as an incomplete examination increases the chance of missing an aneurysm.

Another popular theory is bleeding due to a micro-aneurysm that undergoes thrombosis or is destroyed at the time of haemorrhage(23). In some patients, this small ruptured aneurysm can be demonstrated by three-dimensional (3D) rotational angiography (55).

To explain predominant involvement of the basal cisterns, Alexander et al. (56) postulated that SAH may be due to leakage from the lenticulostriate and thalamoperforating vessels. Furthermore, Park et al. (49) reported a tiny aneurysm on a perforator at its origin from the basilar artery in the interpeduncular cistern in 3 of 13 patients with presumed PMSAH. These aneurysms were seen only on 3D reconstructed angiographic images.

Several conditions can also produce a false appearance of SAH on CT or MRI, known as pseudo-SAH. The causes of pseudo-SAH include non-haemorrhagic subarachnoid space pathologic abnormalities, such as meningitis and leptomeningeal carcinomatosis, and imaging artefacts occurring in the absence of subarachnoid space abnormality.

1) Pathologic abnormalities affecting the subarachnoid space:

Acute bacterial leptomeningitis results in disruption of the blood-brain barrier and leakage of proteins into the CSF. In severe cases, the increase in CSF protein concentration may be sufficient to cause increased CSF attenuation on CT, giving the false appearance of SAH (57). Elevated CSF protein concentration also decreases the T1 relaxation time of CSF and creates hyper-intense CSF on FLAIR images, mimicking SAH (58,59). A similar increase in CSF signal intensity on FLAIR images has been described in leptomeningeal carcinomatosis(59,60), may be related to elevated CSF protein concentration.

2) Imaging artefacts on CT:

Patients with anoxic encephalopathy may exhibit diffuse hyper-density within the basal cisterns and subarachnoid spaces on CT, without SAH detected by lumbar puncture or autopsy (61,62). Pseudo-SAH in this situation results from a combination of diffuse

cerebral oedema, resulting in decreased attenuation of brain parenchyma, effacement of the subarachnoid spaces, and engorgement of venous structures on the pial surfaces. The apparent high attenuation of the subarachnoid spaces is largely perceptual, and the actual CT attenuation values within the basal cisterns measure lower than expected for blood products (62).

Spontaneous intracranial hypotension is reported to produce pseudo-SAH on CT, occurring in 10% of 40 consecutive patients in one series(63). The characteristic CT findings include increased attenuation of the tentorium, basal cisterns, and sylvian fissures. The corresponding MRI findings are pachymeningeal tentorial enhancement and obliteration of the basal cisterns and sylvian fissures due to brain sagging. Subdural fluid collections may be present.

Iatrogenic causes of pseudo-SAH on CT include recently administered intrathecal or IV contrast material, after endovascular procedures, like aneurysm coiling and stroke intervention (64,65). The presumed mechanism is contrast material extravasation in areas of blood brain barrier breakdown related to hyper-perfusion injury (65) or subclinical ischemia resulting from temporary vessel occlusion by micro-catheters or balloon inflation (64). Differentiating post procedural contrast extravasation from SAH is important because it may affect patient treatment. Extravasated contrast material typically clears within several hours, helping to confirm the diagnosis (65).

3) Imaging artefacts on MRI:

FLAIR imaging is sensitive to both acute and subacute SAH, making it a viable alternative when CT is equivocal. Several clinical conditions, however, can mimic SAH on FLAIR imaging. Patients receiving general anaesthesia for MRI may have diffuse FLAIR signal hyper-intensity in the basal cisterns and cerebral sulci. This finding

originally was thought to be due to effect of inhaled anaesthetic agents, but later shown to result from the T1-shortening effects of the administration of 100% oxygen (66–68).

CSF pulsation artefact can also produce FLAIR signal hyper-intensity in the ventricles or subarachnoid spaces that may mimic SAH. The artefact is caused by the inflow of non-nulled CSF in areas of high CSF flow rate, typically in the cervical or thoracic spinal canal, the third or fourth ventricles, cerebral aqueduct, and just superior to the foramen of Monroe. Occasionally, CSF pulsation artefact interferes with evaluation of the basal cisterns in the posterior fossa. Cross-referencing with coronal and sagittal imaging planes or with faster sequences, such as gradient-recalled echo or true fast imaging with steady-state precession, is helpful (69).

An even more troublesome artefact relates to patient motion on single-shot fast spin-echo FLAIR images, a sequence reserved for moving patients. In this scenario, head displacement between the inversion and acquisition pulses may result in areas of non-nulled CSF in regions not associated with high CSF pulsatile flow, such as in the sulci overlying the frontal convexities (70). The artefactual nature of the hyper-intense CSF FLAIR signal may be difficult to appreciate, because the images may otherwise appear free of motion artefact. Increasing the inversion pulse section width or using a non-section selective initial inversion pulse can help to reduce the artefact (70).

Pseudo-SAH on MRI has been reported in conditions associated with altered perfusion and blood brain barrier disruption, including acute ischemic stroke (71) and after carotid artery stenting (72) or balloon test occlusion (73). The hyper-intense acute reperfusion marker refers to hyper-intense CSF signal on FLAIR imaging, found in association with compromised perfusion or hyper-perfusion syndromes and caused by leakage of small amounts of gadolinium-based contrast material through a

compromised blood brain barrier (74). Leakage of gadolinium-based contrast material has also been associated with pseudo-SAH on FLAIR images in patients with renal failure, in patients receiving high concentrations of gadolinium-based contrast material, and in seemingly healthy patients with intact renal function and an intact blood brain barrier (75).

Evaluation of angiogram negative SAH

The most common cause for non-traumatic spontaneous SAH is aneurysm and principle management is immediate localization of the site of aneurysm so that a life-saving procedure can be offered to prevent re-bleed. Unenhanced CT is the best initial test for patients clinically suspected to have SAH. CT angiography [CTA] or digital subtraction angiography [DSA] is then performed to exclude underlying saccular aneurysm.

However, studies have shown that in 3–36% of cases the initial neurovascular examinations do not reveal a causative cerebral aneurysm or other vascular abnormality (76). Identification of such patients who have a vascular pathology as the cause of SAH despite negative initial neurovascular examinations is challenging for several reasons; firstly, there are many possible causes, secondly, the likelihood of finding the treatable cause is low and third, failing to detect a vascular lesion places the patient at risk for recurrent haemorrhage leading to increased morbidity and mortality (19).

Patients with anSAH are usually subjected to subsequent studies to identify the cause of SAH. However, there are no uniform, internationally accepted guidelines for performing diagnostic workup in such patients. It is not clear whether a second cerebral angiogram should be performed in patients with PMSAH.

Accuracy of DSA and need for repeat study

Although, 4-vessel cerebral digital subtraction angiography (DSA) is the gold standard radiological technique for aneurysmal localization, the false negative cerebral angiogram range in 3 %–15 %.

Perret in 1959 reported 89% accuracy for angiography compared with autopsy findings in 210 patients (77). He indicated that the lesions were missed because of the presence of vasospasm (2.5%), observer error (3%) or inadequate angiographic examination (2%). In addition, a ruptured aneurysm was missed in 2% after another aneurysm has been shown. He concluded that the potential accuracy of angiography is about 96%.

Forster (1978) repeated angiogram in 56 out of 150 patients whose initial angiogram was normal (78). Repeat angiogram detected aneurysms in 2 cases that had been previously missed. He suggested that a false negative rate of 5% is too low to routinely repeat four-vessel angiogram in those with subarachnoid haemorrhage of unknown etiology. Also, a routine spinal angiogram in these cases is not indicated because of the low yield and risks involved. He however, suggests that angiogram may be selectively repeated if the previous study is not absolutely satisfactory. Also, spinal angiograms for those who had spine signs or have repeated unexplained subarachnoid haemorrhage.

Juul et al in 1986, repeated angiographic studies in 17/34 patients of SAH in whom initial angiogram was negative and found aneurysm in 2 patients with the false negative rate of 5.8% among all patients whose initial angiogram was negative and 11.7% among those in whom angiographic study was repeated (79). Iwanaga et al in 1990, reported further high false negative angiogram rates of 16% (7). Urbach et al in 1998, reported false negative rates of 6% (80) while Inamasu et in 2003 found 36% false negative rate in a large retrospective series (81). Jung et al in 2006, reported false

negative rate: 17.5% overall,1.5% in PMSAH group, and 45.9% in non PMSAH group and advised repeat angiography, especially in non PMSAH group (82).

Similar to Forster, in 1990, Gilbert et al., suggested that repeat angiography was unnecessary if the original angiogram was adequately performed (83). This was contradicted by later authors who demonstrated a much higher pickup rate in repeat angiography for SAH, reporting that as many as 30% discover an aneurysmal aetiology (7,10,27,80,81,84–87). The most common aneurysms found on repeat angiography were of the anterior communicating artery (81).

Recently, Fontanella et al. have rejected this consensus supporting repeat imaging in all cases except those where the patient is particularly unwell (88).

In a recent study of 52 consecutive patients with non-traumatic SAH all of whom underwent DSA, the sensitivity, specificity and accuracy of DSA for detecting intracranial aneurysms were 98.1%, 98.1%, and 95.1% (89).

Rinkel examined 113 patients with anSAH during 1983–1990 (77 with PMSAH and 36 with non PMSAH) and found PMSAH make up two-third of all patients PMSAH and deferred the need for repeat angiogram (40,48).

Presently, with improved technique such as magnification angiography, the accuracy of diagnosis is higher. However, a negative four-vessel angiogram does not exclude an aneurysm or a micro-angioma.

Apart from the varied yield and accuracy of DSA, it is also associated with various complications. It requires the use of iodinated contrast material (with the attendant risks of nephrotoxicity) and ionizing radiation. Major complications are: a) local – groin hematoma, thrombosis of artery, local site infection; b) systemic - nausea, vomiting,

transient hypotension, chest pain, arrhythmia, urticaria, rhinorrhea, acute renal failure, anaphylaxis and death; c) neurologic - transient or reversible or permanent stroke. Despite this complication risks, majority of authors recommend repeat DSA in anSAH (90).

Timing and number of repeat angiography

Controversy surrounds the decision of number and timings of radiological examinations. Bradac et al 1997, had second angiogram performed 1-4 weeks later revealed an aneurysm in 5 of 40 cases (85). Little et al, 2007, have performed repeat DSA after 1 week of admission following negative initial DSA (5). Dalyai et al in 2013, performed 2 DSA at 1 week and 6 weeks after the initial negative angiogram and proposed a protocol of short-term and long-term angiographic follow-up in patients with non PMSAH and negative initial angiography (91). Almandoz in 2014, performed delayed neurovascular imaging at least 14 days after presentation with a negative initial and 7 day repeat DSA, found it valuable in the evaluation of patients with diffuse SAH demonstrating a causative vascular lesion in 8% of patients (92). Bakker et al in 2014, did meta-analysis and found DSA varied from 1 to 6 weeks after the initial DSA and concluded that the exact timing of the repeat DSA is subject to debate (93).

Role of 3D rotational angiography

3D rotational angiography has increased the diagnostic capability, detecting aneurysms smaller than 3 mm. In some patients with angiographically negative aneurysmal SAH, a small ruptured aneurysm or tiny aneurysm on a perforator at its origin can be demonstrated by newer three-dimensional (3D) rotational angiography(55).

Role of CT angiography [CTA]

CT angiography which is widely available, can be performed quickly, and is a non-invasive procedure. In comparison, DSA is invasive and time consuming and carries a risk of neurologic complications of up to 2.3%, even in patients without vascular disease. Furthermore (according to manufacturer data), CT angiography has a lower radiation exposure (1.0 mSv [at 200 mAs] with the Siemens Sensation 16 scanner and 1.8 mSv [at 380 mAs] with the Siemens Sensation 64 scanner) than selective cerebral angiography (3.5–6.5 mSv). Also, CTA is cheaper than DSA. The chance of missing a ruptured aneurysm at CT angiography is not more than 2%.

Considering the complications of DSA and advances in CTA, some authors postulate a more aggressive strategy to withhold even first DSA if initial CT angiography (CTA) is negative (9,28,94). Velthuis et al proposed that CTA is an adequate screening examination for vertebrobasilar aneurysms in patients with perimesencephalic pattern of haemorrhage, and DSA can be withheld in these patients (28). This issue was supported by the findings of Cruz and co-workers, who examined 41 patients with a PMSAH with CTA and DSA. They concluded that DSA brought no benefit detecting a bleeding source after an initial negative CTA and hence, it could be avoided (13).

In recent years, CTA has been studied as a primary method to confirm or exclude the presence of an aneurysm in patients with anSAH. Agid et al. reported 193 CTAs with negative findings of 912 studies performed for SAH. Of these patients, 93 had PMSAH, 50 patients had diffuse non PMSAH blood distribution, 32 had no blood on CT and 18 had peripheral sulcal/convexity distribution (9). Compared with the results of cerebral angiography, all of the findings of patients with PMSAH were true-negative for aneurysm, as were those of all of the 32 patients with no blood on the initial CT scan.

In the non PMSAH group, 5/50 patients (10 %) were eventually diagnosed with an aneurysm. This included 1 aneurysm seen on angiography (false-negative for CTA) and 4 patients were diagnosed with repeat angiography. Two of these 4 had aneurysms diagnosed on repeat cerebral angiography that were present on both initial angiogram and CTA, but were overlooked.

Unfortunately, even the most advanced CTA may not detect aneurysms smaller than 3–4 mm in diameter. Also, it lacks sensitivity for lesions involving the carotid artery at the skull base or within the contrast-filled cavernous sinuses (95).

Role of MRI and MR Angiography [MRA]

Three-dimensional time-of-flight (TOF) MRA is the most widely used MRI sequence. Advantages of TOF MRA include good spatial resolution, relatively insensitive to signal loss caused by turbulent flow, and can be performed within a time span that allows anatomic MRI during the same imaging session.

Despite advances in MRI, various factors limit it use in SAH patients. These includes artefacts related to spin saturation and flow which can simulate cerebral aneurysms. The sequences are sensitive to patient motion. A patient with acute SAH is in severe pain which limits the ability to remain relatively motionless, thus preventing it use in setting of acute SAH. The signal intensity of substances that are bright on unenhanced or contrast enhanced T1-weighted images, such as methemoglobin-containing (hematomas) and cystic lesions filled with proteinaceous material, can be transmitted onto TOF source images and simulate an aneurysm.

MRA has a sensitivity of 70% to 99%, and a specificity of 100% for aneurysms 3 mm or greater in diameter; however, the sensitivity diminishes for very small aneurysms (under 3 mm in diameter) to as low as 40%.(96)

Andaluz et al. assessed the yield of additional imaging in 92 patients with SAH in whom the initial angiogram failed to reveal the cause of SAH (8). Additional imaging studies included repeat angiography, cerebral magnetic resonance imaging (MRI), and MR angiography in all patients. Of these, 45 had PMSAH pattern on the initial CT scan, and 47 had non PMSAH. Interestingly, subsequent angiography demonstrated abnormal findings, such as saccular aneurysms, blister-like aneurysms, dysplastic cerebral arteries and fibromuscular dysplasia, in five (13.9 %) of the 36 patients in the PMSAH group and seven (14.9 %) of the patients with non PMSAH group. Furthermore, additional CTA showed unidentified aneurysms in 3 patients in non PMSAH group (of 21 patients who received CTA). Brain MRI, which was performed in all 92 patients, provided no information about the identification of the source of bleeding in either patient group. Spinal MRI, revealed a cranio-cervical dural arteriovenous fistula in one patient that was subsequently confirmed by angiography.

Complete examination can be defined as selective examinations of the internal and external carotid arteries and both vertebral arteries, with additional 3D rotational angiography plus 3D reconstructed angiographic images. Visualization of the cervical vessels is important to exclude a spinal vessel abnormality or fistula and the ECA with its branches to exclude a dural fistula.

Many investigators reported diagnostic and management algorithms that try to avoid false negative diagnosis of aneurysmal source of the spontaneous SAH (55,97,98). It is important to identify the patients who would benefit from extensive neuro-radiological

imaging and to omit unnecessary diagnostic studies when there is a low index of suspicion for the presence of an aneurysm.

Role of surgery after negative initial DSA

Another school of thought advocates exploratory surgery for anSAH patients. Jafar et al in 1993, reported six patients with SAH who, despite multiple negative cerebral angiograms, underwent exploratory surgery due to a high clinical and radiographic suspicion for the presence of an aneurysm(99). He found anterior communicating artery (AcomA) aneurysms in five cases (pick-up rate 80%) (99) and proposed that that exploratory aneurysm surgery is warranted, despite repeated negative cerebral angiograms, if the patient manifests the classical signs of SAH.

Similarly, Tatter et al took up nine patients for exploratory surgery among 40 patients were admitted to the Massachusetts General Hospital with angiogram-negative SAH and confirmed three aneurysms and four micro-aneurysms responsible for the SAH an astonishing pick up rate of 77.77% (100). He proposed that micro-aneurysms are the source of a significant percentage of non-perimesencephalic angiogram-negative SAH and suggest that these lesions may represent a forme-fruste of saccular aneurysms.

Later, Little et al in 2007, reported surgery for 1 patient with classic patterns of SAH highly suggestive of a focal pathology(5).

Complications and Prognosis

Although, the clinical presentation of non-aneurysmal SAH is often indistinguishable from that of aneurysmal SAH, the overall patients with anSAH tend to have a much better prognosis than those with ruptured cerebral aneurysms. In a retrospective study of 216 patients treated for spontaneous SAH with a mean follow-up of 29 months,

Woznica et al. reported good short-term outcomes (MRS 0–2) in 83.9 % of patients with non-aneurysmal SAH, compared with 36.5 % for those with aneurysms (101). Even within non-aneurysmal SAH group, subgroups stratified by bleeding pattern had significant differences in outcome. Patients with less extensive haemorrhage had significantly better short-term outcome than patients with extensive haemorrhage. On long-term follow-up, the number of patients with a good clinical outcome increased to 87.4 % in the non-aneurysmal SAH group and to 45.1 % in the aneurysmal SAH group. Long-term outcome was significantly worse in aneurysmal SAH patients compared to patients with non-aneurysmal SAH.

Generally, PMSAH is associated with an excellent clinical course that is rarely associated with complications and long-term neurological dysfunction and disability. However, non-PMSAH does not always follow the benign clinical course usually described for PMSAH, and significant morbidity and even mortality can be seen in the context of this disease(102). These often demonstrate a worse condition at admission, and a less favourable clinical outcome, probably due to higher incidence of complications such as subsequent bleeding, vasospasm, and hydrocephalus.

Subsequent re-bleeding:

Current studies of anSAH have reported a subsequent bleeding rate of up to 8.5 %, depending on the design of the study, the quality of the angiography, and the duration of follow-up. This is significantly lower than that of aneurysmal SAH. The risk of subsequent bleeding also seems to be significantly different in PMSAH and non PMSAH. Among patients with PMSAH, no case of rebleeding has been documented in some literature(98,103,104). However, fatal rebleeding can still occur and therefore, the incidence of rebleeding is never zero (105,106). For example, in one setting of

PMSAH, anticoagulation therapy started for acute coronary syndrome lead to subsequent re-bleeding(107). Up to 8.5 % of non PMSAH patients do rebleed, and 2.1–3.9 % die as the result of a fatal rebleeding (106).

Vasospasm:

Clinical vasospasm following anSAH has been reported in 3 %–30 % of patients, with much less frequently in PMSAH subgroup seen in 2 %–3 % of patients. Angiographic vasospasm, on the other hand, has been reported more frequently than clinical vasospasm. Although very rare, vasospasm in the setting of PMSAH may occur and become symptomatic(6,108–110). Samaniego et al. reported a case of symptomatic vasospasm with PMSAH, refractory to the traditional triple-H therapy, that required multiple endovascular intervention with intra-arterial nicardipine infusion and balloon angioplasty(111). They also concluded that a large cisternal haemorrhage was correlated with the development of delayed cerebral ischemia in this patient with anSAH(112).

Vasospasm is much more prevalent in patients with the non PMSAH pattern. Hui et al. compared a group of 31 patients who were treated for PMSAH with a group of 63 patients with non PMSAH(104). Overall, twenty-two patients had radiographic and clinical vasospasm; 19 of 63 (30.1 %) patients being treated for non PMSAH suffered from vasospasm compared to 3 of 31 (9.7 %) patients being treated for PMSAH.

Hydrocephalus:

The reported incidence of hydrocephalus in non-aneurysmal SAH is varied. The incidence of hydrocephalus in the recent studies ranges from 4.3 % to 38.3 %. Similar to vasospasm, acute hydrocephalus developed more frequently in the patients in the non PMSAH group. Kang et al. retrospectively reviewed the clinical outcome of 52 patients

with anSAH documented on CT scans and reported an 8.7 % incidence of acute hydrocephalus at presentation (98). They reported complete recovery and no VP shunts in patients with PMSAH. However, in the group of non PMSAH patients, acute hydrocephalus was found in 11 patients, of whom 3 required a ventricular shunting procedure due to refractory hydrocephalus.

Kostic et al in 2012, examined 36 patients with anSAH(113). In 22% of PMSAH and 37.5%non PMSAH patients, acute hydrocephalus occurred, which is a slightly lower percentage than in the study of Rinkel et al for PMSAH type (27.5%) (114). These authors found a statistically significant correlation between complete filling of all perimesencephalic cisterns and hydrocephalus occurrence. The presence of blood in the basal cisterns is a major blocker of the cerebro-spinal fluid circulation in the tentorial hiatus region, and therefore the direct cause of ventricular dilatation(114). However, the size of ventricles, amount of blood in the rest of subarachnoid space, natural route of CSF, can also be important in hydrocephalus genesis. This is an explanation of a higher incidence of ventricular dilatation in non PMSAH patients compared to PMSAH ones.

Although anSAH is generally considered a benign pathology with good prognosis, this event may influence the quality of life (115). After a mean follow-up of 101 months, Alfiere et al. reported that 9 of 38 (23.6 %) patients had not returned to work because of cognitive impairment as a sequel of PMSAH(116).

MATERIALS AND METHODS

This study has been carried out at Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum. During study period from 01/01/2005 to 31/12/2016, total 1086 cases were admitted with subarachnoid haemorrhage. 165 patients were diagnosed to have SAH of unknown etiology and 144 where available with initial 4-vessel cerebral DSA which did not reveal any abnormality.

Inclusion criteria

SAH documented by a non-contrast cranial CT within initial 72 hours from bleeding and a negative initial cerebral angiogram with imaging follow-up by repeat catheter angiography or MRI/CTA of circle of Willis. For long term follow up, patients with minimum 12 months follow up were included in the study.

Exclusion Criteria

Trauma, presence of a cerebral aneurysm, other intracranial vascular abnormalities, absence of follow up intracranial vascular imaging following the initial angiogram. The patients who had LP proven subarachnoid haemorrhage where CT scan failed to reveal any SAH were also excluded from the study.

Out of 144 patients, only 117 patients were available for a repeat study. Thus only 117 patients were included in the study that has undergone a repeat evaluation {CTA/DSA/MRI} after initial negative 4-vessel cerebral DSA.

Clinical data were obtained by reviewing medical records. Following clinical data was recorded.

A) Clinical Presentation:

Apart from demographic data like age and sex, a detailed account of patient's symptoms was recorded like headache, vomiting, altered sensorium, loss of consciousness, neck pain, motor & cranial nerve deficits, visual symptoms, speech abnormality, memory impairment and seizures. Any history suggestive of warning leaks or previous SAH was noted.

B) Associated Risk Factors:

Past history of migraine, hypertension, diabetes, CAD, stroke was noted. Personal history of smoking, alcoholism and addictions were also taken. Family history of SAH was also enquired.

C) Clinical Grade of SAH on admission: All the patients were clinically graded according to the WFNS grading system. (Annexure 1)

D) Hospital course and complications

Patients hospital course, length of stay, any complication of SAH- neurological, cardiovascular, pulmonary, thromboembolic, electrolyte imbalance and functional outcome at discharge using Glasgow outcome score(GOS) and modified Rankin scale (mRS) was noted. (Annexure 1) Delayed cerebral ischemia was defined as the occurrence of focal neurological impairment or a decrease of at least 2 points on the Glasgow Coma Scale not attributed to other causes by means of clinical assessment, CT or MRI of the brain, and appropriate laboratory studies based on the Vergouwen's definition(117).

The clinical outcome was measured by the discharge GOS score and mRS score: a

score of mRS ≤ 1, and GOS score = 5 was considered as a good outcome.

Imaging data was reviewed by retrieving images from PACS. Following imaging data was recorded

A) Non-contrast enhanced CT Head

1. Interval from haemorrhage to first CT scan:

The interval from time of the bleed to the time taken for the first CT Scan was recorded and were divided into four groups

1. 0 day (on the day of bleed)
2. 1-3 days
3. 4-6 days
4. After 6 days.

2. Pattern of haemorrhage on the initial CT scan:

All admission head CT scans were reviewed, and patients were assigned to 1 of 3 SAH groups:

i) **classic/diffuse haemorrhage pattern** consistent with aneurysmal rupture with blood in basal cisterns, Sylvian cisterns, or posterior fossa;

ii) **perimesencephalic haemorrhage (PMH)**, which was defined according to Rinkel an Van Gijn criteria and included a) centre of the haemorrhage located immediately anterior to the midbrain, with or without extension of blood to the anterior part of the ambient cistern or to the basal part of the Sylvian fissures; b) no complete filling of the anterior interhemispheric fissure and no extension to the lateral Sylvian fissures, except for minute amounts of blood; and c) absence

of frank intraventricular haemorrhage;

iii) **isolated peripheral/convexity/sulcal pattern of haemorrhage**

3) Other radiological features like extent of SAH, rebleed on repeat CT scans, hydrocephalus, infarct, intraparenchymal and intraventricular haemorrhage were also documented separately as present or absent. The extent of SAH on admission CT was graded using a modified Fisher scale (Annexure 1)

B. Digital Subtraction Angiography

Cerebral catheter angiography was performed using the Seldinger technique, with a 4- or 5-Fr introducer in the common femoral artery by the neuroradiologist. Selective bilateral carotid and bilateral vertebral injections were done and images were obtained in the anteroposterior, lateral and oblique directions in a two dimensional DSA machine. About 30 -50 ml of the contrast is used during the study. Additional views were taken in doubtful cases and in patients with repeat DSA. Following parameters were noted.

1. Time interval from haemorrhage to initial DSA
    a. Day 0
    b. 1-7 days
    c. 8-21 days
    d. after 21 days
2. Presence or absence of vasospasm was noted
3. Presence of any suspicious lesion on DSA like bulbosity, infundibulum, vascular malformation, aneurysms, ectasia of vessels, venous abnormality was noted.

4. Any complication associated with DSA was also noted.

Follow up

As per the institute protocol, after the initial negative, patients were advised to follow up after 6- 8 weeks for repeat vascular imaging either DSA, CTA or MRI on the discretion of OPD consultant. Clinical follow up at 6month and then yearly. Clinical follow up data was recorded from medical records and GOS and mRS score were recorded for functional outcome. Long-term follow up was defined as > 1year of follow up.

1. Follow up neurovascular imaging
    a. CTA
    b. DSA
    c. MRA
2. Interval for follow up imaging (in weeks)
3. Any abnormal findings on follow up imaging
4. Clinical parameters on follow up
    a. New event/attack
    b. New deficits
    c. GOS score
    d. mRS score
5. Duration for last clinical follow up from ictus (in months)
    a. 6months
    b. 6-12months
    c. 12-36 months
    d. 36- 60 months

e. >60months

Statistical Analysis:

Descriptive statistics were employed, with frequency & percentages calculated for categorical data, and mean & standard deviations calculated for continuous variables using annova test. The chi square was used to assess the significance of associations. The analysis was done using Statistical Package for the Social Sciences, version16.00 (SPSS Inc).

RESULTS

Of the 1086 patients with spontaneous SAH admitted to our hospital from January 2005 to December 2016, 144 patients (13.25%) had negative initial four-vessel angiography. These subjects consisted of 66 men and 78 women. The mean age was 50.2 years (range 20–73 years). Patients aged 50–59 years were the most common, comprising 37.5% of the study population, and patients aged 40–49 years were the second most common age group.

Table 1 Age and Sex distribution in angiogram negative SAH

	Male		Female		Total	
Age in years	N	%	N	%	N	%
<30	6	9.1	3	3.8	9	6.3
30-39	8	12.1	5	6.4	13	9.0
40-49	10	15.2	26	33.3	36	25.0
50-59	25	37.9	29	37.2	54	37.5
>60	17	25.8	15	19.2	32	22.2
Total	66	100.0	78	100.0	144	100.0

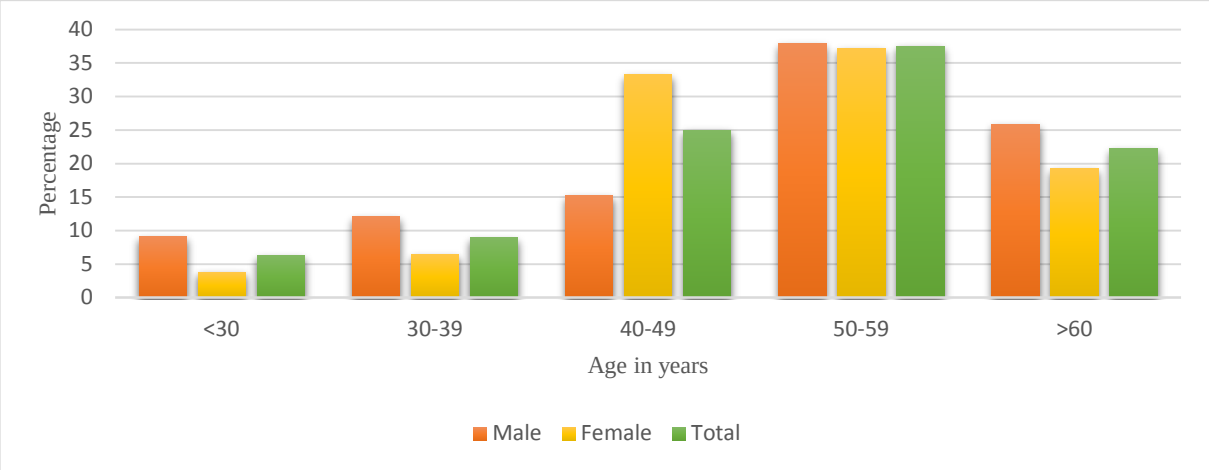

Figure 1: Age and sex distribution of patients with initial negative angiogram subarachnoid haemorrhage. Range 20 – 73years (mean of 50.6years). male: female ratio 1:1.18

Depending upon haemorrhage pattern on initial CT scan were classified into 3 groups. group I (diffuse), 61 patients (42.4%); group II (PMSAH), 64 patients (44.4%); and group III (convexity SAH), 19 patients (13.2%) Table 2, fig 2.

Table 2 SAH pattern on initial CT of patients with negative initial angiogram

Pattern of Haemorrhage	Frequency	Percentage
Diffuse	61	42.4
PMH	64	44.4
Convexity	19	13.2
Total	144	100.0

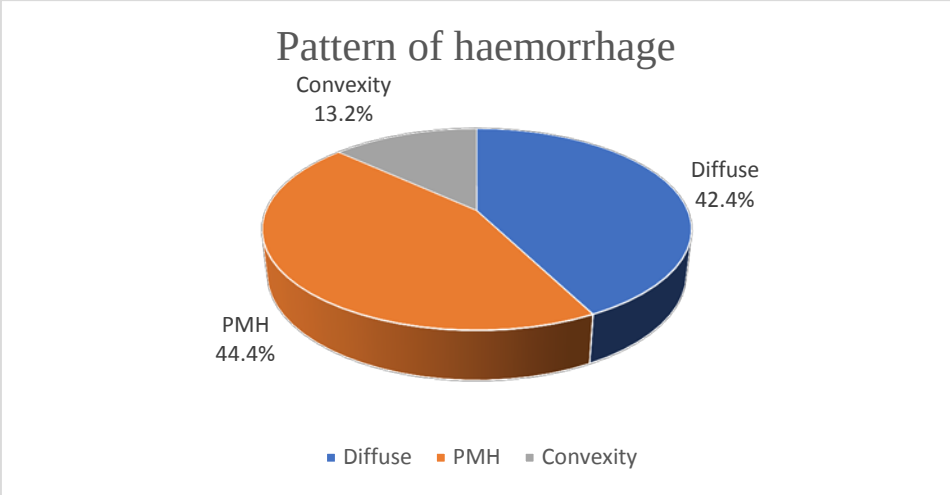

Figure 2: Subarachnoid haemorrhage pattern on initial CT with negative angiogram

Table 3 Age and Sex distribution depending upon haemorrhage pattern

		Areas of haemorrhage						Total		p
		Diffuse		PMH		Convexity				
		N	%	N	%	N	%	N	%	
Age	<30	4	6.6	0		5	26.3	9	6.3	
	30-39	5	8.2	4	6.3	4	21.1	13	9	
	40-49	18	29.5	15	23.4	3	15.8	36	25	
	50-59	22	36.1	27	42.2	5	26.3	54	37.5	
	>60	12	19.7	18	28.1	2	10.5	32	22.2	0.002
Sex	Male	29	47.5	28	43.8	9	47.4	66	45.8	
	Female	32	52.5	36	56.3	10	52.6	78	54.2	0.904

Age was statistically different in 3 groups, diffuse SAH occurred over wide spectrum, while PMSAH occurred in elderly with >60% above 50years and convexity SAH mainly in younger patients with >60% below 50 years. Table 3

Both genders were involved to similar extent in both the groups.

Table 4 Initial clinical manifestations of patient with angiogram negative SAH

	Areas of Haemorrhage on initial CT						Total		p
	Diffuse		PMH		Convexity				
	N	%	N	%	N	%	N	%	
Headache	56	91.8	63	98.4	14	73.7	133	92.4	0.002
Vomiting	45	73.8	56	87.5	10	52.6	111	77.1	0.005
Seizure	6	9.8	0		4	21.1	10	6.9	0.003
Short term LOC	21	34.4	5	7.8	4	21.1	30	20.8	0.001
Altered sensorium	11	18	3	4.7	2	10.5	16	11.1	0.060
Limb weakness	11	18	3	4.7	5	26.3	19	13.2	0.017
Cranial nerve palsy	4	6.6	6	9.4	3	15.8	13	9	0.468
Visual disturbances	1	1.6	5	7.8	4	21.1	10	6.9	0.014
Speech abnormality	2	3.3	0		1	5.3	3	2.1	0.255
Memory disturbances	1	1.6	0		0		1	0.7	0.504
Neck pain/ stiffness	25	41	17	26.6	3	15.8	45	31.3	0.065
Papilloedema	8	13.1	9	14.1	2	10.5	19	13.2	0.923

Headache and vomiting was the most common presentation among all the angiogram negative SAH patients, but significantly less common in patient with convexity type SAH.

Seizures and short-term loss of consciousness were seen significantly less in PMSAH group. Similarly, limb weakness was more commonly seen with diffuse and convexity subgroups.

Table 5 Comorbidities in patient with anSAH

Comorbidities	Areas of Haemorrhage						Total		p
	Diffuse		PMH		Convexity				
	N	%	N	%	N	%	N	%	
Diabetes	10	16.4	13	20.3	1	5.3	24	16.7	0.302
Hypertension	28	45.9	27	42.2	3	15.8	58	40.3	0.060
Others									-
Migraine	0		0		1	5.3	1	0.7	
Dyslipidaemia	1	1.6	2	3.1	1	5.3	4	2.8	
Cerebrovascular disease	1	1.6	0		0		1	0.7	
Heart disease	1	1.6	3	4.7	2	10.5	6	4.2	
Hypothyroidism	2	3.3	1	1.6	1	5.3	4	2.8	

No major comorbidities were significantly related to any particular pattern of bleed. However, hypertension was the most common comorbidity present in >40% case. No significant family history or history of addictions noted

Table 6 GCS, WFNS and MFG distribution at admission in different haemorrhage pattern

		Areas of Haemorrhage on Initial CT						Total		p
		Diffuse		PMH		Convexity				
		N	%	N	%	N	%	N	%	
GCS	<15	16	26.2	3	4.7	3	15.8	22	15.3	
	15	45	73.8	61	95.3	16	84.2	122	84.7	0.004
WFNS	1	45	73.8	60	93.8	16	84.2	121	84	
	2	14	23	4	6.3	0		18	12.5	
	3	2	3.3	0		3	15.8	5	3.5	<0.001
MFG	1	25	41.0	54	84.4	18	94.7	97	67.4	
	2	2	3.3	1	1.6	0	0.0	3	2.1	
	3	27	44.3	7	10.9	1	5.3	35	24.3	
	4	7	11.5	2	3.1	0	0.0	9	6.3	<0.001

Group II PMSAH had relatively lower WFNS grade and modified Fisher grade distributions compared with group I and III ($p < 0.001$) and more than 95% case were admitted with GCS score of 15. Table 6

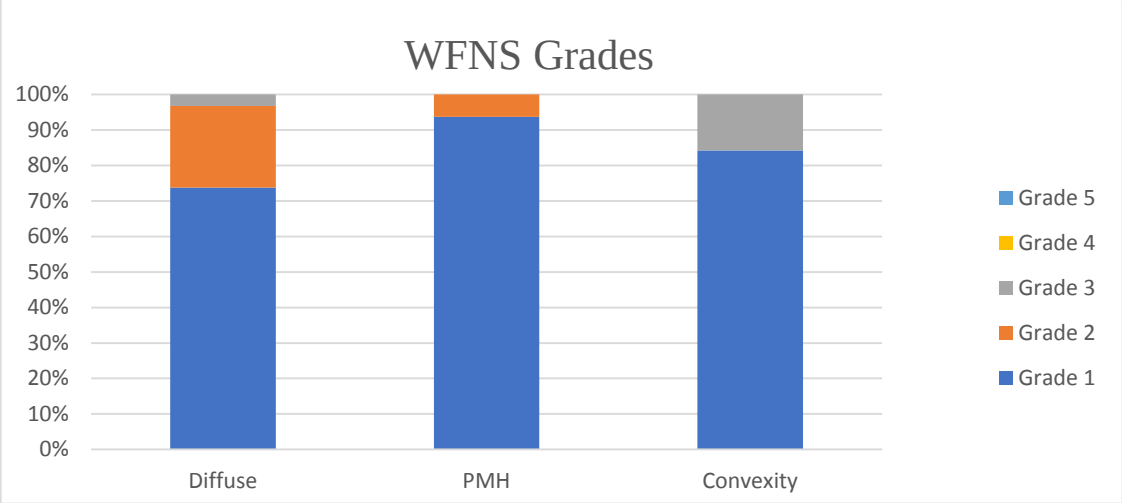

Figure 3 Graphical presentation of WFNS grades in different haemorrhage pattern

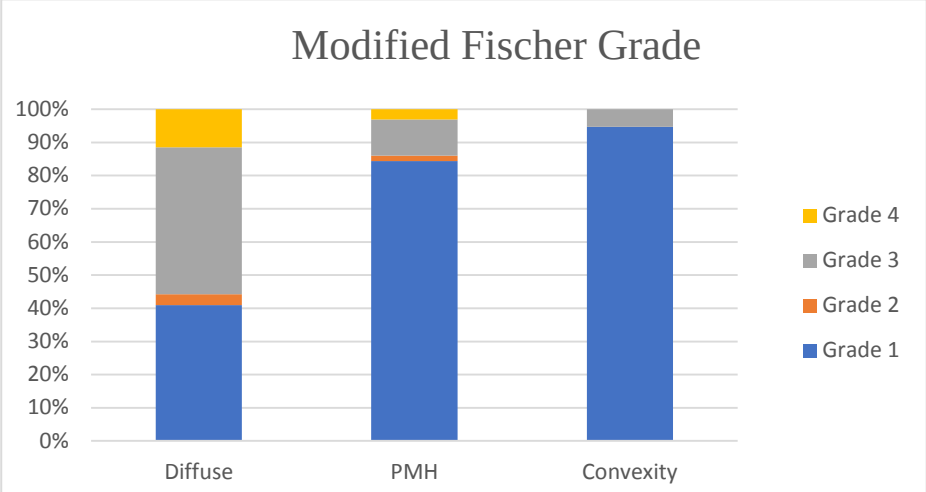

Figure 4: Graphical distribution of Modified Fischer grades in different bleed pattern

Table 7 Interval for initial CT, and DSA following SAH

		Areas of Haemorrhage						Total		p
		Diffuse		PMH		Convexity				
		N	%	N	%	N	%	N	%	
Interval for 1st CT Head	0	31	50.8	23	35.9	11	57.9	65	45.1	
	1-3	28	45.9	32	50	7	36.8	67	46.5	
	4-6	1	1.6	9	14.1	1	5.3	11	7.6	
	>6	1	1.6	0		0		1	0.7	0.098
Interval for Initial DSA	0	0	0.0	0	0.0	1	5.3	1	0.7	
	1-7	35	57.4	34	53.1	5	26.3	74	51.4	
	8-21	21	34.4	25	39.1	9	47.4	55	38.2	
	>21	5	8.2	5	7.8	4	21.1	14	9.7	0.044

Majority of patients were admitted within 7 days of SAH and more than 50% individual underwent initial angiogram within 7 days of ictus.

Complications related to SAH observed during hospitalization included vasospasm and hydrocephalus, which were more frequently found in group I diffuse SAH patients than in group II and III patients. Re-bleed was seen in only 2.8% of patient. Other complications like DVT, electrolyte disturbances, chest and urinary tract infection were significantly more with group III patient and overall was seen in 6.3% cases. No patient had delayed neurological deficits.

Table 8 Complications in different bleeding pattern during hospitalization

	Areas of Haemorrhage						Total		p
	Diffuse		PMH		Convexity				
	N	%	N	%	N	%	N	%	
Re-bleed	2	3.3	0		2	10.5	4	2.8	0.047
Hydrocephalus	14	23	7	10.9	1	5.3	22	15.3	0.075
Intraventricular Haemorrhage	11	18	6	9.4	1	5.3	18	12.5	0.203
Intra-parenchymal hematoma	4	6.6	0		2	10.5	6	4.2	0.061
Infarct	2	3.3	0		2	10.5	4	2.8	0.047
Vasospasm on DSA	21	34.4	10	15.6	6	31.6	37	25.7	0.046
Other Complications	5	8.2	0		4	21.1	9	6.3	0.003

Table 9 Hospital course and Discharge status of patient with angiogram negative SAH

		Areas of haemorrhage on initial CT						Total		p
		Diffuse		PMH		Convexity				
		N	%	N	%	N	%	N	%	
Hospital stay (days)	<4	47	77	60	93.8	9	47.4	116	80.6	
	5-7	10	16.4	2	3.1	7	36.8	19	13.2	
	>7	4	6.6	2	3.1	3	15.8	9	6.3	<0.001
Surgery following negative 1st DSA		2	3.3	0		0		2	1.4	0.252
deficits	No	57	93.4	63	98.4	15	78.9	135	93.8	
	Yes	4	6.6	1	1.6	4	21.1	9	6.3	0.009
mRS score	1	53	86.9	61	95.3	13	68.4	127	88.2	
	2	7	11.5	2	3.1	3	15.8	12	8.3	
	3	0		0		2	10.5	2	1.4	
	4	1	1.6	1	1.6	0		2	1.4	
	5	0		0		1	5.3	1	0.7	0.001
GOS score	2	1	1.6	1	1.6	1	5.3	3	2.1	
	3	0		0		1	5.3	1	0.7	
	4	3	4.9	1	1.6	2	10.5	6	4.2	
	5	57	93.4	62	96.9	15	78.9	134	93.1	0.085

Hospital stay was significantly more for convexity type SAH and was least for PMSAH type. Most patient admitted with deficits improved while in hospital care and persistent deficits were mostly seen in convexity type SAH. mRS at discharge was significantly lower in PMSAH group as compared to other two subgroups, however >93% patient had GOS scores of 5.

Follow-up data were analysed with the modified Rankin scale and Glasgow outcome scale. At 1st follow up, 98% of the patients in group II, and 95.9% of the patients in group I were found to have recovered to grade 0 or 1 while it was significantly higher for convexity type SAH, where 84% recovered to grade 0 or 1.

Mean interval for 1st follow up was 17 weeks. 34 patients lost to follow up after 1st follow up, and only 41 patients were available for long term follow up. However, almost all patients had a good prognosis on long-term follow-up, regardless of the

initial SAH pattern, and no statistically significant difference was found between these groups. Only 1 patient had new attack or re-bleed and this was before the 1st follow up imaging.

Table 10 Follow up outcomes of patients with angiogram negative SAH

		Areas of Haemorrhage						Total		p
		Diffuse		PMH		Convexity				
		N	%	N	%	N	%	N	%	
new deficits on follow up	No	48	98.0	50	100.0	19	100.0	117	99.2	
	Yes	1	2.0	0	0.0	0	0.0	1	0.8	0.492
new event /attack on f/u	No	48	98	50	100	19	100	117	99.2	
	Yes	1	2	0		0		1	0.8	0.492
mRS at 1st follow up	0	12	24.5	30	60.0	10	52.6	52	44.1	
	1	35	71.4	19	38.0	6	31.6	60	50.8	
	2	1	2.0	0	0.0	2	10.5	3	2.5	
	4	0	0.0	1	2.0	1	5.3	2	1.7	
	6	1	2.0	0	0.0	0	0.0	1	0.8	.002
GOS at 1st follow up	1	1	2.0	0	0.0	0	0.0	1	0.8	
	2	0	0.0	1	2.0	1	5.3	2	1.7	
	5	48	98.0	49	98.0	18	94.7	115	97.5	.447
Last follow up	<6 months	17	39.5	15	31.3	9	47.4	41	37.3	
	6-12 months	13	30.2	11	22.9	4	21.1	28	25.5	
	13-36 months	6	14.0	8	16.7	3	15.8	17	15.5	
	37-60 months	3	7.0	3	6.3	2	10.5	8	7.3	
	>60 months	4	9.3	11	22.9	1	5.3	16	14.5	0.602
Deficits at last follow up	No	42	100	47	97.9	17	89.5	106	97.2	
	Yes	0		1	2.1	2	10.5	3	2.8	0.062
mRS at last follow up	0	33	76.7	40	83.3	14	73.7	87	79.1	
	1	8	18.6	7	14.6	3	15.8	18	16.4	
	2	1	2.3	0	0.0	1	5.3	2	1.8	
	3	0	0.0	1	2.1	0	0.0	1	0.9	
	4	0	0.0	0	0.0	1	5.3	1	0.9	
	6	1	2.3	0	0.0	0	0.0	1	0.9	.419
GOS at last follow up	2	0		0		1	5.3	1	0.9	
	3	0		1	2.1	0		1	0.9	
	4	1	2.4	0		0		1	0.9	
	5	41	97.6	47	97.9	18	94.7	106	97.2	0.267

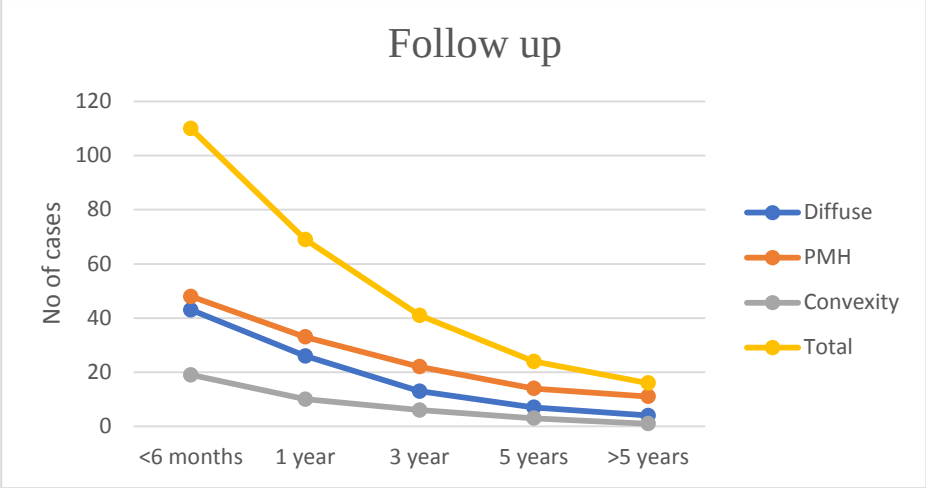

Figure 5: Line plot of all the patients who were on long term follow up

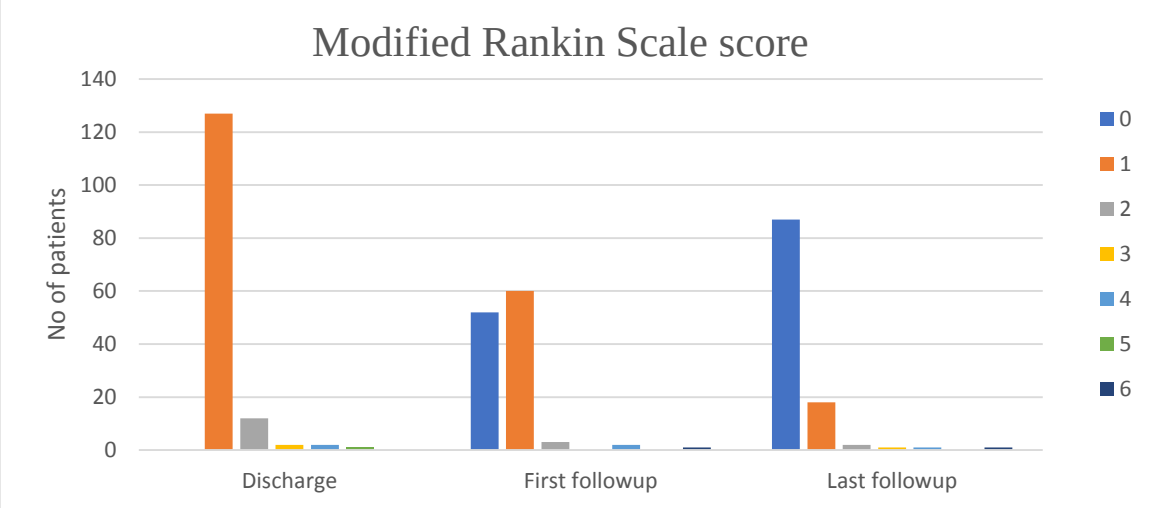

Figure 6: Graphical representation of mRS score of patient with angiogram negative SAH

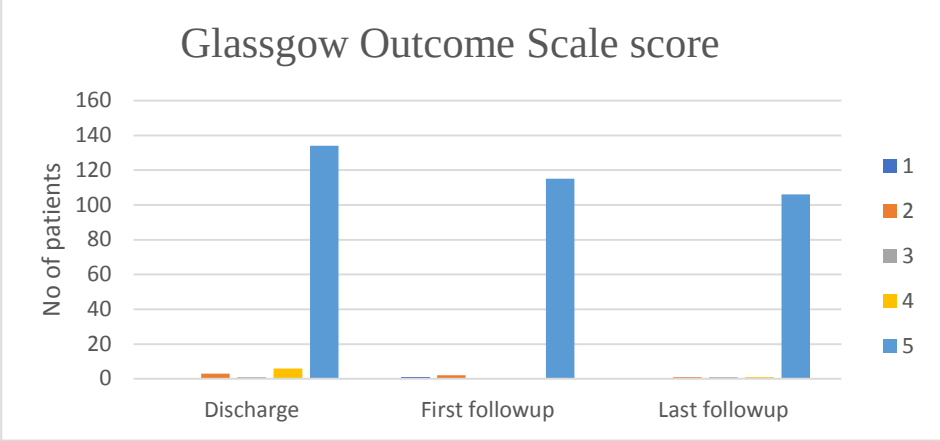

Figure 7: Graphical representation of Glasgow outcome scale score of patient with angiogram negative SAH

Table 11 Follow up imaging outcomes in different bleed patterns

		Areas of Haemorrhage						Total		p
		Diffuse		PMH		Convexity				
		N	%	N	%	N	%	N	%	
Imaging modality	DSA	18	36.7	15	30.6	5	26.3	38	32.5	
	CTA	30	61.2	33	67.3	7	36.8	70	59.8	
	MRI	1	2	1	2	7	36.8	9	7.7	<0.001
Findings	No	38	77.6	46	93.9	14	73.7	98	83.8	
	Yes	11	22.4	3	6.1	5	26.3	19	16.2	0.039
Surgery following 2nd imaging	No	48	94.1	64	100	19	100	131	97.8	
	Yes	3	5.9	0		0		3	2.2	0.082

Of the 117 patients who came for follow up imaging, 38 cases underwent repeat DSA, 70 patients underwent CTA and 9 patients underwent MRI.

in group 1, 18 patients received repeat four- vessel angiography, and cerebral aneurysm was found in 4 patients (22%), infundibulum in 1 patient and bleb in 2 patients.

In contrast, 15 patients in group II and 5 patients in group III had repeat four-vessel angiography, and cerebral aneurysms was not detected.

Of the 19 patients in whom some lesion was found on repeat imaging (Table 12), 11 were in group I.

Table 12 Summary of patients with lesion in follow up imaging

S no.	Haemorrhage pattern	follow up (weeks)	imaging	findings	new event/attack	Follow up GCS	Follow up mRS	Follow up GOS	surgery following 2nd imaging
1	diffuse	9	DSA	left MCA bleb	0	15	1	5	0
2	diffuse	14	CTA	left V4 seg infundibulum	0	15	1	5	0
3	diffuse	15	DSA	Pcom infundibulum	0	15	1	5	0
4	diffuse	28	CTA	Left TS- SS DAVF	0	15	1	5	0
5	diffuse	13	DSA	A1 dissection	0	15	1	5	0
6	diffuse	8	DSA	left Pcom aneurysm	0	15	1	5	1
7	diffuse	23	DSA	Left TS - SS thrombosis	0	15	1	5	0
8	diffuse	3	DSA	b/l supraclinoid ICA bleb	0	15	1	5	0
9	diffuse	140	DSA	MCA bifurcation aneurysm	0	15	1	5	1
10	diffuse	37	DSA	Pcom aneurysm	1	14	6	1	0
11	diffuse	11	DSA	Acom aneurysm	0	15	2	5	1
12	PMH	9	DSA	CVJ DAVF	0	15	1	5	0
13	PMH	3	DSA	bleb in cavernous ICA	0	15	1	5	0
14	PMH	12	CTA	Basilar tip bulbosity	0	15	1	5	0
15	convexity	12	MRI	right VA dissection	0	15	1	5	0
16	convexity	6	MRI	secondary deposit	0	15	4	2	0
17	convexity	5	DSA	conus AVM	0	15	1	5	0
18	convexity	24	MRI	cavernoma	0	15	1	5	0
19	convexity	8	MRI	tortous/beaded appearance	0	15	1	5	0

Table 13 Factors contributing to angiogram negative SAH

	Areas of Haemorrhage			
	diffuse	PMH	convexity	total
Aneurysm	4	0	0	4
Dissection	1	0	1	2
Cavernoma	0	0	1	1
Antiplatelet induced	1	3	1	5
Anticoagulant	0	1	1	2
Arteriovenous malformation	0	0	1	1
Reversible vasoconstriction syndrome	0	0	1	1
Intracranial hypotension	1	0	0	1
Spinal tumour	0	0	1	1
Dural arterio-venous fistula	1	1	0	2
Cortical venous thrombosis	1	0	1	2
Pregnancy	0	0	3	3

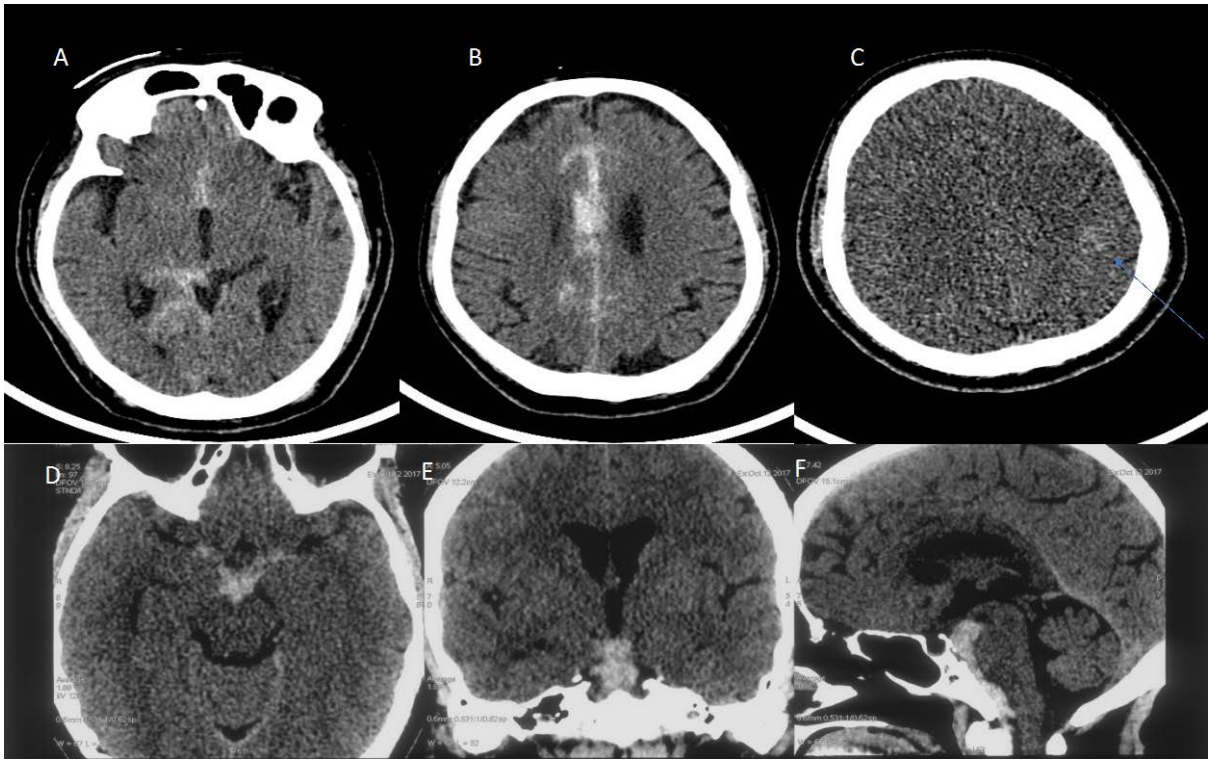

Image 1: A & B CT head images showing diffuse SAH, more in interhemispheric fissure; C shows left parietal convexity SAH (arrow)with diffuse cerebral oedema; D, E &F are axial, coronal and sagittal cuts showing PMH variant of SAH

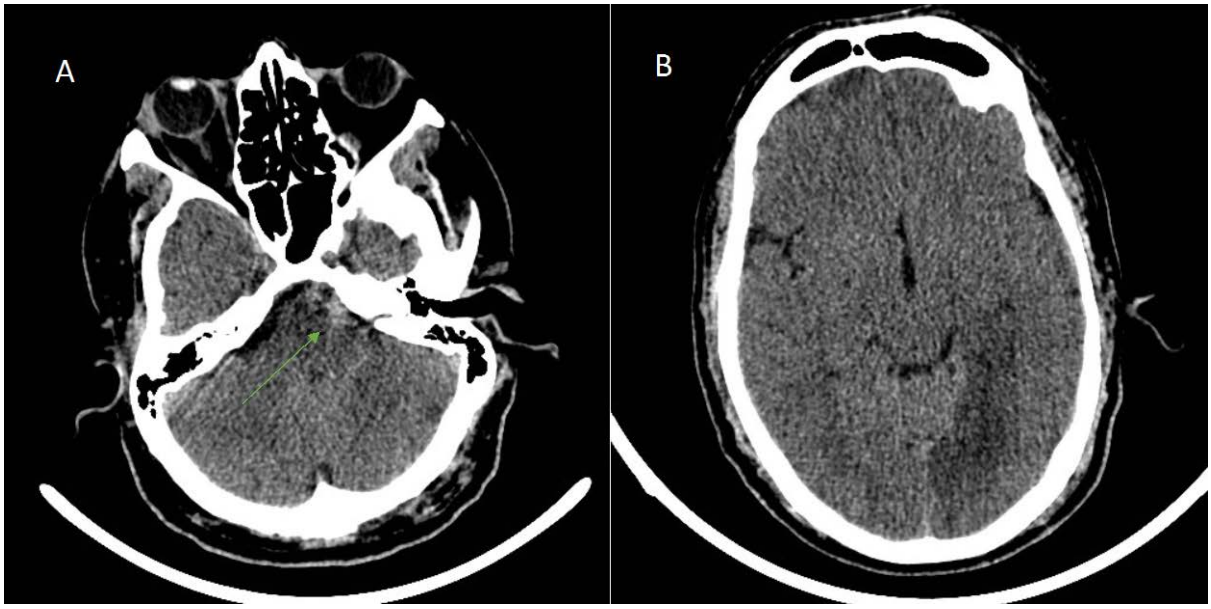

Image 2: Axial cuts of left cp angle SAH and left PCA territory infarct who underwent negative exploration with suspicion of aneurysm despite anSAH

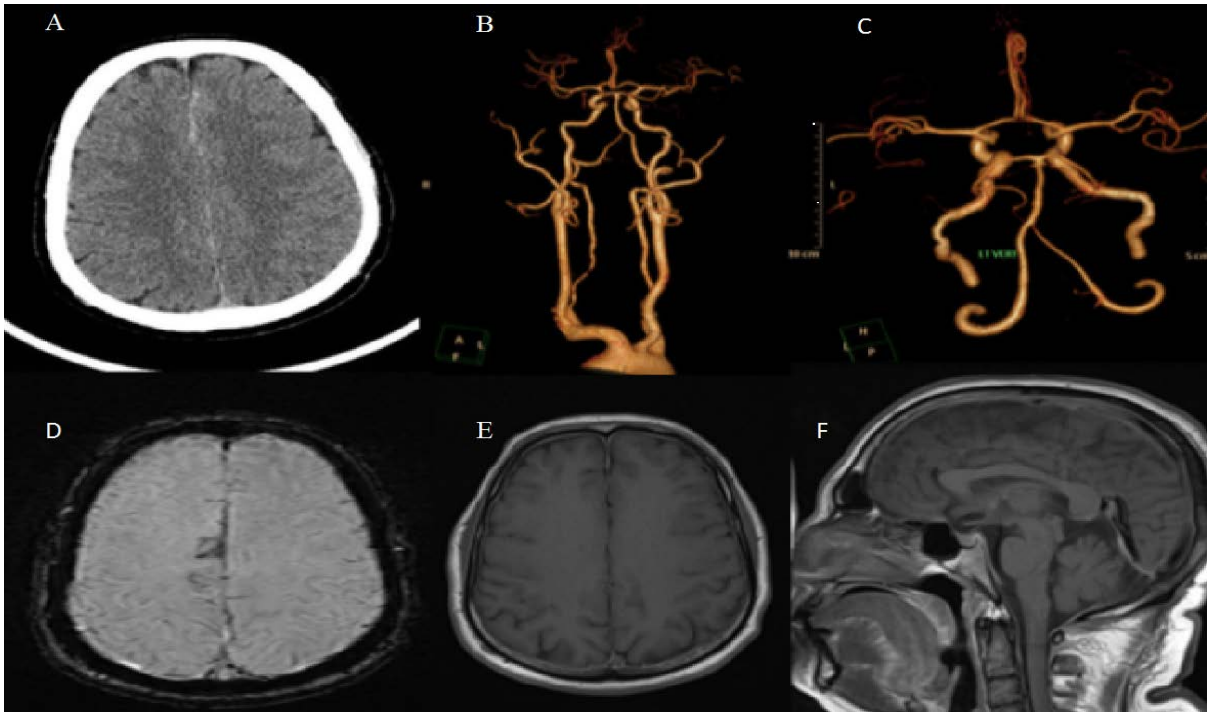

Image 3: A - axial cut of initial CT showing interhemispheric SAH, B and C showing normal circle of Willis without any vascular pathology; D, E and F shows follow up MRI, D showing blooming in interhemispheric region on SWI sequence, E & F shows diffuse meningeal enhancement with corpus callosal buckling and sagging of brainstem, suggestive of Intracranial hypotension.

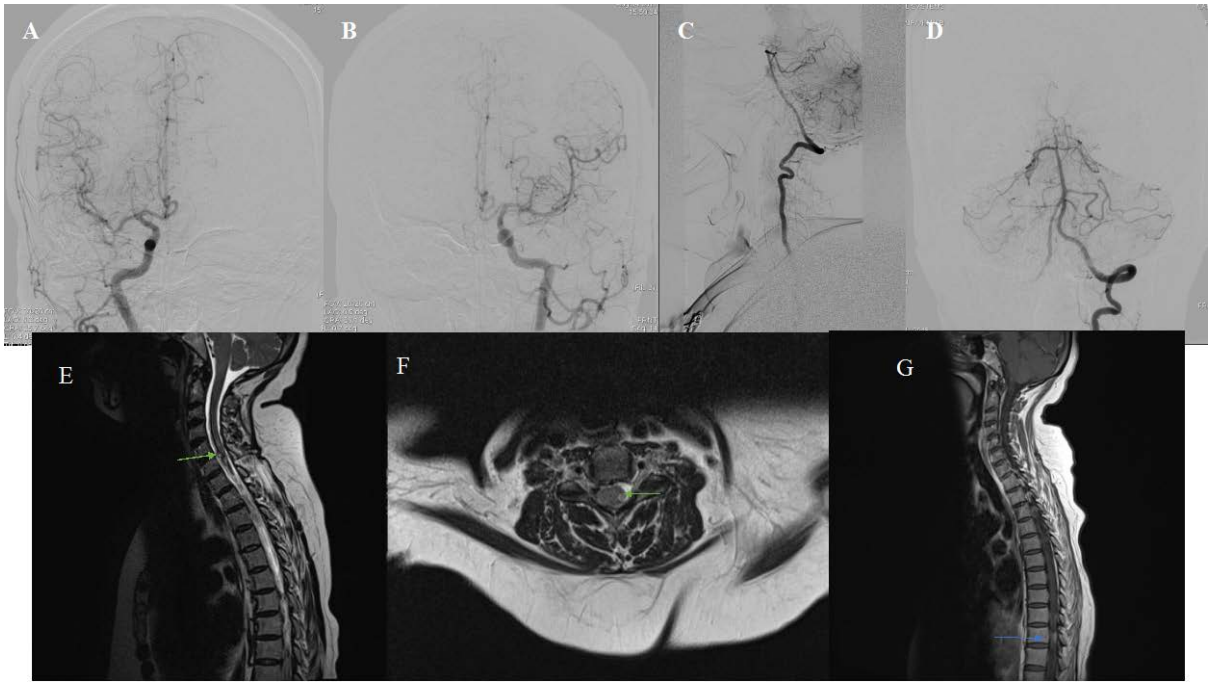

Image 4 A- D shows initial normal angiogram with follow up MRI spine showing small extramedullary lesion at C6 (green arrow) and D11 levels (blue arrow)

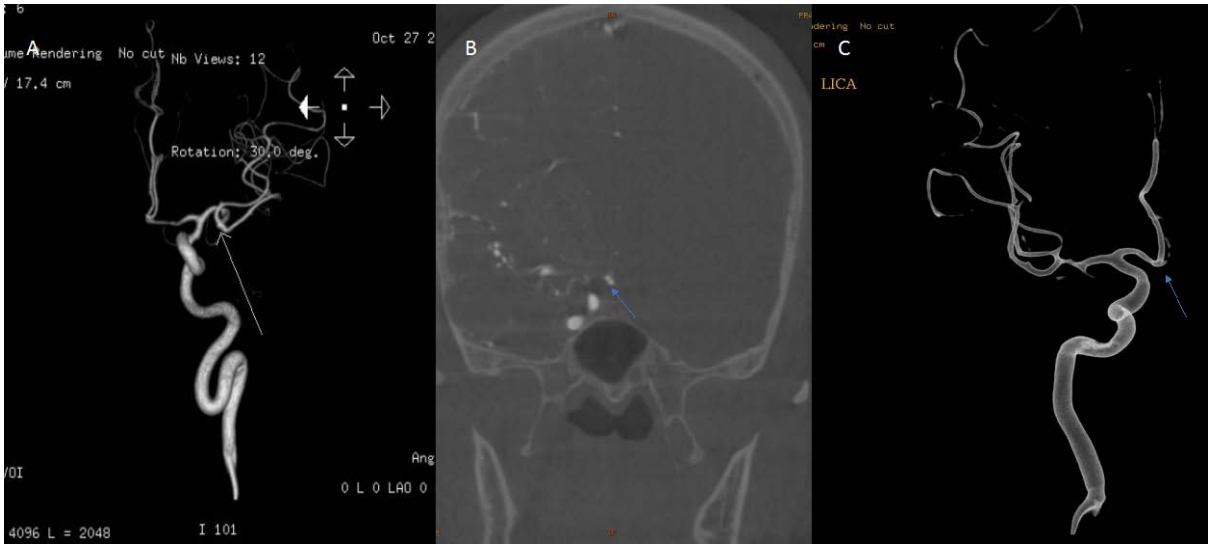

Image 5:3D rotational angiography reformatted images showing bleb at left MCA bifurcation (white arrow) (A) and left A1 ACA small dissection (blue arrow) (B&C)

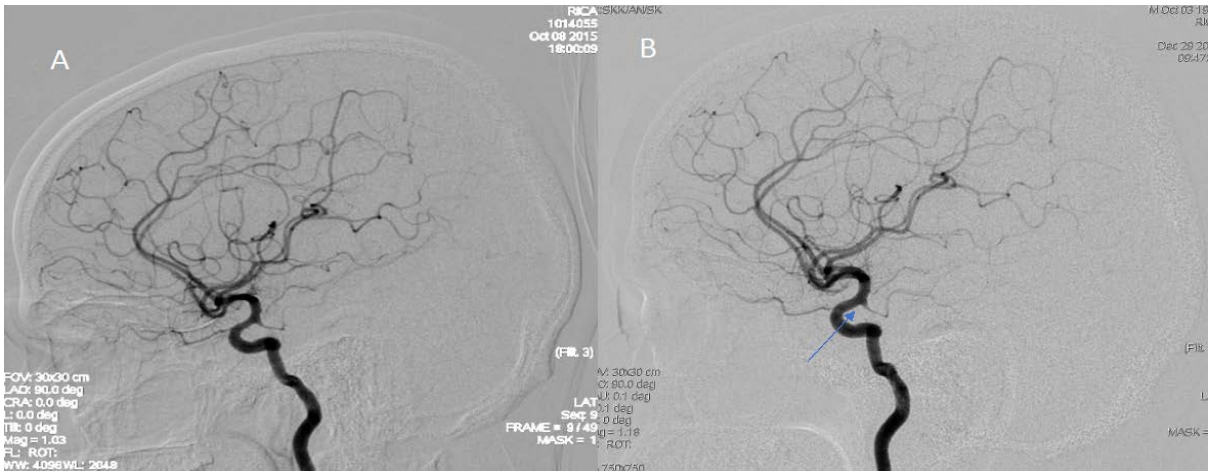

Image 6: Initial and follow up DSA images left ICA injection showing left Pcom infundibulum (arrow)

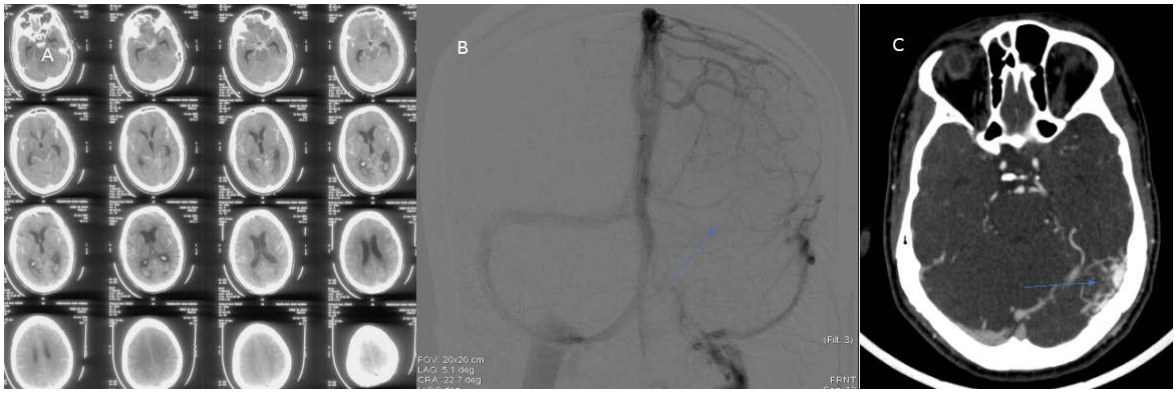

Image 7: A shows axial cuts of plain CT with diffuse SAH and hydrocephalus, B showing initial DSA venous phase showing left hypo plastic transverse and sigmoid sinuses; C shows follow up CT angiography axial cut showing dural AVF at left TS-SS junction (arrow)

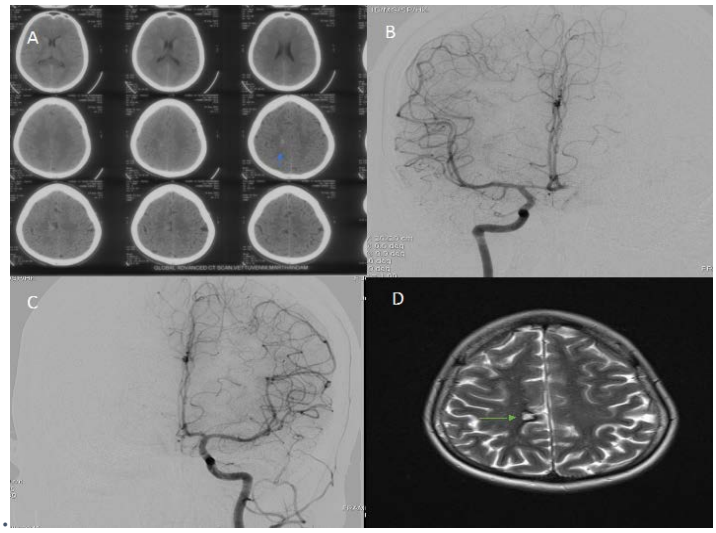

Image 8: A shows peripheral/ sulcal SAH in medial frontal region; B & C showing normal right and left ICA injection on DSA; follow up MRI T2 sequence shows well defined T2 hyperintense lesion with surrounding hypointense rim suggestive of cavernoma (arrow).

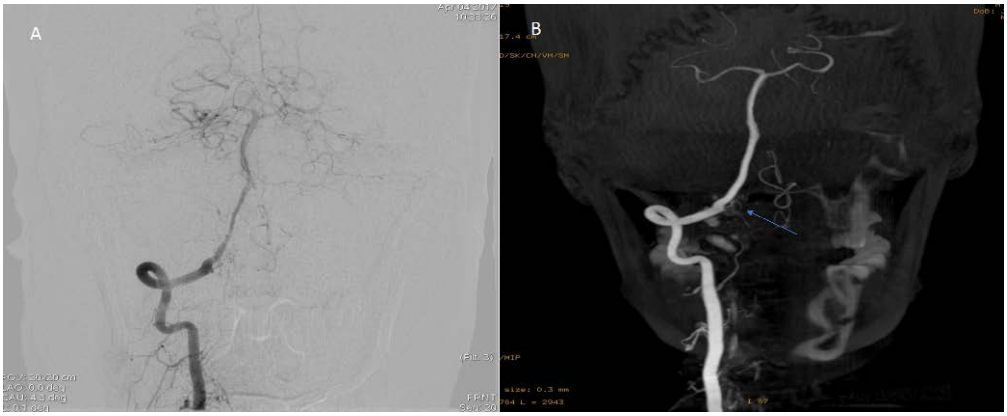

Image 9: Initial DSA with right VA injection (A) and follow up right VA injection showing dural AVF at CVJ region (B)(arrow).

DISCUSSION

Rupture of cerebral arterial aneurysm is the leading cause of spontaneous SAH, and the gold standard for evaluation is 4-vessel cerebral digital subtraction angiography. However, it has a false negative rate of 5 to 10%. The evaluation of such patients with negative angiogram is challenging as the likelihood of finding pathology requiring treatment is low and the consequences of a missed diagnosis are potentially severe and can result in substantial morbidity and mortality primarily from a re-bleed. Despite the incidence reported is from 2% to as high as 24%, the best diagnostic paradigm has been debatable for decades, and till now no definitive guidelines have been formulated for management of such patients.

Demographic data

The incidence of angiogram negative SAH has been variable ranging from 2% to 24% in various studies. Fontanella *et al*.(88) reported 2-24%, Khan et al (76) reported it to be 11% and Jung *et al* (82)reported 8-23% cases Coelho (118) found it to be 18.1% of total spontaneous SAH. Present study has the incidence of 13.25% similar to that mentioned in the literature.

The mean age of patients with angiogram negative SAH ranges from 45 - 55 years in various series. Rinkel et al(25) have reported mean age of 51years. Khan et al (76)have reported mean age of 52.5 years Coelho et al (118) had 54.76 ± 12.2 . Present study has mean age of 50.1years with range of 20-73 years, consistent with the literature. When compared with the international cooperative study for aneurysmal SAH(119), the mean age was 49.2±14.3 years, indicating similar ages for both aneurysmal as well as

non-aneurysmal SAH.

In the cooperative study of 464 patients with SAH of unknown origin, >50% of patients were males(120). Rinkel et al(25) have also reported male preponderance >56%. Little et al(5) have reported of female dominance similarly, Elhadi et al(121) have found female out numbering with female to male ratio of 2.3:1. The present study have slight female preponderance with 54.2% and female to male ratio of 1.18:1 similar to other series, though it was not statistically significant.

Different authors have described various patterns of bleed in SAH. Rinkel et al have divided into perimesencephalic and aneurysmal SAH(25), Little et al (5) and Agid *et al*. (9) have divided these patients into four groups as per the distribution of subarachnoid blood on plain CT head at the presentation: (i) perimesencephalic haemorrhage, (ii) diffuse or classical aneurysmal pattern, (iii) xanthochromic CSF on lumbar puncture with no blood demonstrated on CT, and (iv) peripheral sulcal pattern (with absence of basal cisternal blood). In the present, only CT- positive cases of SAH were included and were divided in 3 subsets as group 1- diffuse, group II- PMH and group III – convexity locations.

Table 14 Various studies evaluating anSAH with different bleeding patterns

Study	Year	Areas of Haemorrhage		
		Diffuse/classical	PMH	Convexity
Rinkel et al(25)	1991	36	77	-
Little et al (5)	2007	44	16	25
Agid et al (9)	2010	50	93	18
Fontanella et al(88)	2011	79	23	-
Khan et al (76)	2013	23	17	-
Dalyai et al (91)	2013	136	118	-
Boswell et al (122)	2013	16	14	-
Delgado et al (92)	2014	25	12	2
Elhadi et al (121)	2015	32	13	-
Zhong et al (123)	2016	34	49	-
Present study	2018	61	64	19

Mean age and sex in different haemorrhage groups were similar in above reported series.

Clinical Data

The clinical presentation of anSAH is similar to aneurysmal SAH with majority presenting with sudden severe headache and vomiting but with lesser severity. However, within the subgroups, convexity pattern less frequently presented with headache and vomiting when compared with other two patterns. Similarly, seizures, short term loss of consciousness and limb weakness was less frequently seen with PMH pattern. These findings were well supported by various studies in past. Zhong et al have reported that the initial neurological condition was much more serious in the diffuse group, and frequently noticed focal neurological deficits.(123) Similarly, Coelho et al found that decreased consciousness was more common in patients with non PMH pattern on SAH(118). Kapadia et al in their meta-analysis have found that patients with non-aneurysmal perimesencephalic SAH presented with milder symptoms than those with aneurysmal type of SAH with infrequent loss of consciousness at ictus (124). Kumar et al reported about convexity type of SAH and found Headache was the presenting symptom in 18 (62%) patients with severe in only 13 (45%). They also reported that elderly patients presented more frequent with temporary sensory or motor symptoms 54%)(33)

Hypertension was most common risk factor present in these patients more commonly seen in patient with diffuse and PMH pattern and was well supported by findings of Zhong et al (123) and Sarabia et al(106). Kapadia et al reported 35% (14%-39%) PMH type patient with pre-existing hypertension which is only slightly greater than the global prevalence of hypertension in adults (26%)(124). Family history was not

contributory in any pattern of SAH.

Rinkel et al have reported that 94 % patient with PMH type SAH presented with GCS 15 while only 64% patient with diffuse SAH had admission GCS of 15.(25) Similarly, Coelho reported 90% PMH patient and 54% patient with diffuse SAH patient with WFNS grade 1 and GCS of 15 (118). Khan et al reported 82% of PMSAH and 74% of diffuse SAH with WFNS grade 1(76). Present study had similar grades at presentation with 84% patient presenting with grade 1 while PMH subgroup patient were neurological intact at admission with GCS 15 and WFNS 1 in 95% patient.

Radiological findings

More than 90% of patients in this study had 1st CT done within 3 days. The sensitivity of CT for subarachnoid haemorrhage drops significantly as early as 2 days after SAH. Iwanaga et al showed the importance of early CT and concluded that if early CT scan shows no detectable blood or blood localized to perimesencephalic cistern than further angiographic studies were not required.(7)

Sarabia et al have compared 220 patients of idiopathic SAH with >900 patients of aneurysmal SAH and found that 42% patients of idiopathic SAH were Fischer grade 3 or 4 versus 79% of patient with aneurysm SAH.(106) Topcuoglu et al. reported 86 patients with negative angiogram and had 33/36 in PMH group with Fischer grade 2 while significant number of patient with non PMSAH had Fischer grade 3 (15/41).(11) Similarly, Little et al reported 56% PMSAH patients with Fischer grade 2 while 82% patient in classical type were grade 3.(5) Delgado et al have reported that most patient with diffuse/classical type had higher Fischer grade.(92)

Zhong et al have reported overall 66% patients with lower modified Fischer grade.

They reported all patients with PMSAH had a grade of 1-2 whereas 21.7% patients with diffuse SAH had a grade of 3-4.(123) Similarly, Coelho et al reported 44.8% patient with score of 2 versus 15.2% patients with non PMSAH while a score of 4 was calculated in 27.6% patient with PM-SAH (27.6%) versus 57.6% patients with Non PMSAH.(118) This study findings were similar to those reported in literature. Group III convexity SAH had significantly lower modified Fisher grade distributions (95%) followed by PMSAH subgroup (85%) compared with group I (44%) ($p < 0.001$).

Re-bleed is the most feared consequences of anSAH. Sarabia et al have reported it 3.6% as compared with 10% in aneurysmal SAH.(106) Rinkel et al reported 2/36 patient with diffuse SAH and 2/113 overall to have re-bled.(25) Boswell have reported 1/16 patient with diffuse SAH to rebleed.(122) Kapadia et al have found only 5 cases of early rebleeding among patients with PMSAH across 16 studies and 576 patients (0.9%).(124) Kumar et al have reported 4/29 convexity SAH patients with recurrent intracerebral haemorrhages in the follow-up period with 2 mortalities.(33) This study had 2 rebleed in diffuse group of patient and 2 in convexity group of patients without any re-bleed in PMSAH patients indicating good prognosis.

Hydrocephalus in SAH patients can be acute, mainly contributed by blood interfering with CSF flow through the aqueduct, fourth ventricle outlet, or subarachnoid space, and/or with reabsorption at the arachnoid granulations. Chronic hydrocephalus can be due to pia-arachnoid adhesions or permanent impairment of the arachnoid granulations. Rinkel et al have reported 25/113 patient had ventriculomegaly, however, 1 patient needed shunting.(25) Sarabia et al have reported 10% patients with idiopathic SAH to have temporary hydrocephalus and 3.2% to have permanent versus 27.4% case with aneurysmal SAH.(106) Little et al have reported hydrocephalus in 75% cases with

classical bleed while none in PMH or convexity type.(5) Kapadia et al have reported incidence of hydrocephalus within days of the haemorrhage around 9.3% (range 0%-17%) in PMSAH while Kumar et al reported none of the patients with hydrocephalus in convexity SAH.(33,124) Present study had overall 15.3% patients with hydrocephalus with most in diffuse type, however none of the patient required ventriculostomy or CSF diversion during haemorrhage period. 1 patient in diffuse subgroup who later developed feature of normal pressure hydrocephalus underwent ventriculoperitoneal shunting.

The occurrence of clinical deterioration associated with angiographic vasospasm is very low in patients with SAH of unknown origin, 0% -10 % in major series, as against 27 % in patients with aneurysmal SAH. On the other hand, angiographic vasospasm has been reported more frequently (20% to 45%). Sarabia et al reported 16 idiopathic SAH patients (7.3%) with radiological or clinical vasospasm, with no statistical differences among blood pattern subgroups.(106) Zhong et al reported only 6 % patient with clinical vasospasm.(123) Similarly Khan et al reported only 2 patient in diffuse group with vasospasm.(76) Andaluz et al reported 11% while Delgado in 2012 reported as high as 44.8%.(8,125) Boswell et al and Canovas et al reported 0% vasospasm in PMSAH group.(122,126) Kumar et al reported 4/29 patients with convexity SAH with vasospasm.(33) Present study found overall 25% patient with vasospasm which was significantly higher in diffuse and convexity type of SAH as compared to PMSAH.

Hospital course and discharge outcomes

Little et al reported mean hospital stay of 13 days for classical SAH while it was 9 days for PMH and 8 days for convexity type.(5) Boswell reported overall hospital stay of 12.9 days.(122) Delgado reported mean length of hospital stay as 13.2 days (median 12, range 2– 48 days) with a few patients with PMSAH and convexity SAH beyond 7

days.(92) Coelho et al had median inpatient period of 14 days in the PM-SAH group and 21 days in the non PMSAH group.(118) Kapadia et al in the literature review found hospitalization for PMSAH on average was shorter than for aneurysmal SAH with mean duration of stay in hospital of 10.5 days (4.3-19.6 days study means) among 195 patients with NAPSAH. This was also shorter than patients with a non PMH pattern of anSAH. (124)

Present study showed shorter hospital stay in PMH patients while it was significantly high with convexity type of SAH patients. This higher percentage for convexity group could be explained on basis that these patients were transferred to medical neurology side for further evaluation and management.

Zhong et al reported clinical complications such as pulmonary infections, new epilepsy and electrolyte disturbance only in diffuse SAH.(123) Similarly, Coelho et al reported overall complication rates higher in diffuse type, 84% as compared to 48% in PMH group.(118) Two patients of non PMSAH died during the hospital stay due to infectious complications (cerebral ventriculitis and pneumonia) with a mortality rate of 7.1%.

In this study, few overall non-neurological complications like deep venous thrombosis, and infections were seen, but were found to be significantly higher in group 3 as compared to other two groups, probably due to prolong hospital/ICU stay. 2 patients in diffuse subgroup underwent negative exploration despite negative angiogram with no positive findings.

Patients admitted with anSAH had some form of transient deficits but most improved over time. This was well supported by various studies in the literature. Rinkel et al reported 8 such patients who were drowsy or stuporous (GCS score 7-12) on admission, improved during the following days.(25) Permanent deficit in the present study was

mainly seen with convexity type of SAH, probably due to the vasospasm related infarct or other causes of SAH. Kumar et al reported similar findings with motor deficits especially with elderly patients.(33)

Sarabia et al reported significantly worse outcome in aneurysmal SAH patients ($p < 0,001$) with good outcome in only 57.8% and a mortality rate of 25.9%, when compared to idiopathic SAH patients.(106) Little et al have reported most patient in PMH and convexity type recovered at discharge with modified Rankin scale score of 1 or 0. However, more than 45% patient with classical haemorrhage had mRS score of 2 or more.(5) Similarly, Elhadi et al had overall favourable outcome at discharge. No deaths reported. 64% had a good recovery (GOS Score 5), 24% had moderate disability (GOS Score 4), and 11% had severe disability (GOS Score 3). 53% patients had an mRS score of 0 or 1 on discharge.(121) Kapadia et al in their meta-analysis reported 133/136 patients (97.8%) of PMSAH had good recovery or moderate disability on the GOS at discharge. mRS score of 108 patients, 97% of patients with PMSAH were able to live independently at the time of discharge.(124)

Present study reported no in-hospital death of any patient in any group. Modified Rankin score at discharge was significantly lower in PMSAH group and poorer in convexity type. However, overall outcome of patients with angiogram negative SAH was favourable with GOS % in over 93% patients.

Role of follow up imaging

Of 144, 117 patients were available for 2nd imaging. Imaging modality varied at the discretion of OPD consultant. 32% patient underwent DSA, 60% underwent CTA and 8 % underwent MRI. Mean interval for repeat imaging was 17 weeks. 18 patients with diffuse SAH received DSA, and cerebral aneurysm was found in 4 patients (22%),

infundibulum in 1 patient and bleb in 2 patients. In contrast, DSA failed to detect any aneurysm in group II and III. Our findings were slightly on higher side because infundibulum and blebs were also considered as lesion on follow up imaging. CTA and MRI on follow up did not detect any aneurysm in any pattern. However, they were useful in detecting causes other than aneurysm. This was contradictory to the findings of Wenz et al. In their long-term follow-up study, MRI did not show any de novo aneurysms or any other potential bleeding sources in anSAH patients and questioned on its routine use.(127) In the present study, MRI was particularly useful in convexity subgroup and could identify lesion in 4/7 patients, which included spontaneous intracranial hypotension, cortical sinus thrombosis, cavernoma and spinal metastatic lesion.

Table 15 Studies evaluating role of repeat angiography in identifying missed aneurysm

	Suzuki et al 1987(128)	Iwanaga et al, 1990(7)	Kaim et al, 1996(10)	Urbach et al 1998(80)	Rogg et al 1999(129)	Topcuoglu et al 2003 (11)	Jung et al 2006 (82)	Little et al 2007 (5)	Khan et al 2013 (76)	Delgado et al 2014 (92)	Kumar et al 2014(130)	Current study
No of patients	41	45	42	122	71	86	143	100		39	39	117
No of second angiogram	41	38	42	67	32	70	103	83	8	9	39	38
Yield												
Diffuse		31%			21%	8%	46%	10%	16.67%	8%	11.76%	33%
Pmh					0	0	1.5%	7%	0	0	0	0
Convexity												0
Overall	22%	21%	19%	6%	9%	4%	17.5%	7%	13%	5%	0	15.78%

Table 16 Studies evaluating role of MR imaging in identifying missed aneurysms

	Rogg et al 1999(129)	Topcuoglu et al 2003(11)	Little et al 2007(5)	Khan et al 2013(76)	Present study
No of patients	71	86	100	50	117
MRI brain/spine	57%	100%	85%	56%	7.70%
Yield					
Diffuse	8%	0	0	5.20%	0
PMH	0	0	0	11.11%	0
Convexity					0
Overall				10.71%	0

To support these findings, Spitzer et al. have reviewed patients of convexity haemorrhage and found the origin of haemorrhage in 10, including abscess, vasculitis, drug use, and posterior reversible encephalopathy syndrome.(34) However, they did not comment on the yield of repeat vascular studies with negative initial imaging. As few cases have been described in literature there is little guidance on the optimal evaluation of such patients.

This study could find various other causes of angiogram negative SAH like spontaneous intracranial hypotension, cortical venous thrombosis, dural arteriovenous fistula, cavernoma, spinal arteriovenous malformation, reversible vasoconstriction syndrome and spinal metastatic lesion.

Other factors contributing to SAH with a negative angiogram like use on antiplatelet drugs, anticoagulant drugs, pregnancy were also found. Little et al have reported 16 such cases in their series of 100 patients.(5)

Long-term follow up outcomes

Rinkle et al commented that angiogram negative SAH has favourable prognosis with PMH having the best prognosis and remote re-bleed most commonly associated with diffuse type SAH seen in 4/36 patients and 3 died of re-haemorrhage.(25)

Fontanella et al have reported long term follow up patient with angiogram negative SAH ranging from 7.9 to 16 years after SAH, with a mean follow-up period of 10.6 years with 63 in diffuse group and 23 in PMSAH group. They concluded PMSAH is a benign disease and deferred the need for second angiography. Similarly late follow-up of diffuse SAH was favourable and re-bleeding was very rare.(88) This study too

mirrored these findings.

Elhadi et al similarly reported overall favourable outcome among those who presented with no identifiable SAH source. Long-term outcome scores (GOS and mRS) were available in 44/56 patients. At the 3 year follow-up visit, the percentage of patients with good outcome (GOS Score 5) was 77% (34/44 Similarly, mRS score of 0 or 1 was 89% (39/44) at 3 years.(121)

In the present study, all the three groups had favourable long-term outcomes without any statistical difference. 41 patients had long term follow up of more than 1 year, and 16 patients had follow up more than 5 years with the longest of 12 years. 3/4 patient with diffuse SAH who were found to have aneurysm on follow up imaging underwent surgery. 1 patient re-bled on follow up, underwent DSA and was found to have aneurysm, but died before any intervention. However, missing aneurysm in initial DSA could not be explained. 1 patient in PMH subgroup developed malignant MCA stroke and underwent decompressive craniectomy. However, GOS score of 5 at last follow up was present in 97% patients and mRS of 0 to 1 in 95% patients. This indicates overall good prognosis in angiogram negative SAH with re-bleed very rare and mainly associated with diffuse pattern of SAH.

LIMITATION

The present series is a retrospective study and is limited by its inherent drawbacks. Most of the data retrieved was from medical records and imaging data could not be verified due to missing images in the PACS (imaging database at our institute).

Referral bias or selection bias may have influenced the results of this study as some patients included in this study were evaluated and managed by neuroradiology and medical neurology department of the hospital.

Third limitation is more than 50% cases were lost in follow up resulting in small sample size for long term follow up comparison which decreases the power of study.

Another drawback is the absence of definite management protocol for timing and type of follow up imaging to bring out the correct yield of each investigation.

CONCLUSIONS

Majority of patients with angiogram negative subarachnoid haemorrhage have good clinical grades with low incidence of vasospasm and other related complications.

Bleed pattern on initial CT helps in differentiating patient into groups to predict the prognosis, outcome and need for further evaluation.

This study underscores the need for a follow up imaging in patients with CT proven SAH, as an aneurysmal cause can be missed in the initial angiogram.

In those cases when the follow up imaging too is negative for cerebral aneurysms, the prognosis is excellent with good long-term outcome.

PMH type has excellent long-term prognosis with yield of finding a lesion very low on repeat imaging.

Diffuse type SAH tends to be benefited with repeat angiography; however, timings and number of follow up imaging needs to be further evaluated in prospective studies.

The convexity variant of haemorrhage necessitates MR imaging to complete the evaluation of angiogram negative SAH.

BIBLIOGRAPHY

1. Pinto AN, Ferro JM, Canhão P, Campos J. How often is a perimesencephalic subarachnoid haemorrhage CT pattern caused by ruptured aneurysms? Acta Neurochir (Wien). 1993;124(2–4):79–81.

2. Vermeer SE, Rinkel GJE, Algra A. Circadian Fluctuations in Onset of Subarachnoid Hemorrhage: New Data on Aneurysmal and Perimesencephalic Hemorrhage and a Systematic Review. Stroke. 1997 Apr 1;28(4):805–8.

3. Rinkel GJ, van Gijn J, Wijdicks EF. Subarachnoid hemorrhage without detectable aneurysm. A review of the causes. Stroke. 1993;24(9):1403–1409.

4. van Gijn J, Rinkel GJE. Subarachnoid haemorrhage: diagnosis, causes and management. Brain. 2001 Feb;124(2):249–78.

5. Little AS, Garrett M, Germain R, Farhataziz N, Albuquerque FC, McDougall CG, et al. Evaluation of patients with spontaneous subarachnoid hemorrhage and negative angiography. Neurosurgery. 2007;61(6):1139–1151.

6. Schievink WI, Wijdicks EFM, Spetzler RF. Diffuse Vasospasm after Pretruncal Nonaneurysmal Subarachnoid Hemorrhage. 2000;3.

7. Iwanaga H, Wakai S, Ochiai C, Narita J, Inoh S, Nagai M. Ruptured cerebral aneurysms missed by initial angiographic study. Neurosurgery. 1990 Jul;27(1):45–51.

8. Andaluz N. Yield of further diagnostic work-up of cryptogenic subarachnoid hemorrhage based on bleeding patterns on computed tomographic scans. Neurosurgery. 2008 May 1;

9. Agid R, Andersson T, Almqvist H, Willinsky RA, Lee SK, terBrugge KG, et al. Negative CT Angiography Findings in Patients with Spontaneous Subarachnoid Hemorrhage: When Is Digital Subtraction Angiography Still Needed? American Journal of Neuroradiology. 2010 Apr 1;31(4):696–705.

10. Kaim A, Proske M, Kirsch E, Weymarn A, Radü E-W, Steinbrich W. Value of repeat-angiography in cases of unexplained subarachnoid hemorrhage (SAH). Acta Neurologica Scandinavica. 1996;93(5):366–73.

11. Topcuoglu MA, Ogilvy CS, Carter BS, Buonanno FS, Koroshetz WJ, Singhal AB. Subarachnoid hemorrhage without evident cause on initial angiography studies: diagnostic yield of subsequent angiography and other neuroimaging tests. Journal of Neurosurgery. 2003 Jun;98(6):1235–40.

12. Maslehaty H, Barth H, Petridis AK, Doukas A, Maximilian Mehdorn H. Special features of subarachnoid hemorrhage of unknown origin: a review of a series of 179 cases. Neurological Research. 2012 Jan 1;34(1):91–7.

13. Cruz JP, Sarma D, Noel de Tilly L. Perimesencephalic subarachnoid hemorrhage: when to stop imaging? Emerg Radiol. 2011 Jun;18(3):197–202.

14. Taylor TN, Davis PH, Torner JC, Holmes J, Meyer JW, Jacobson MF. Lifetime Cost of Stroke in the United States. Stroke. 1996 Sep 1;27(9):1459–66.

15. European Registers of Stroke (EROS) Investigators, Heuschmann PU, Di Carlo A, Bejot Y, Rastenyte D, Ryglewicz D, et al. Incidence of stroke in Europe at the beginning of the 21st century. Stroke. 2009 May;40(5):1557–63.

16. Lovelock CE, Rinkel GJE, Rothwell PM. Time trends in outcome of subarachnoid hemorrhage: Population-based study and systematic review. Neurology. 2010 May 11;74(19):1494–501.

17. King JT. Epidemiology of aneurysmal subarachnoid hemorrhage. Neuroimaging Clin N Am. 1997 Nov;7(4):659–68.

18. Hijdra A, Braakman R, van Gijn J, Vermeulen M, van Crevel H. Aneurysmal subarachnoid hemorrhage. Complications and outcome in a hospital population. Stroke. 1987 Dec;18(6):1061–7.

19. Hijdra A, van Gijn J, Nagelkerke NJ, Vermeulen M, van Crevel H. Prediction of delayed cerebral ischemia, rebleeding, and outcome after aneurysmal subarachnoid hemorrhage. Stroke. 1988 Oct;19(10):1250–6.

20. Hop JW, Rinkel GJ, Algra A, van Gijn J. Changes in functional outcome and quality of life in patients and caregivers after aneurysmal subarachnoid hemorrhage. J Neurosurg. 2001 Dec;95(6):957–63.

21. van Gijn J, van Dongen KJ, Vermeulen M, Hijdra A. Perimesencephalic hemorrhage: a nonaneurysmal and benign form of subarachnoid hemorrhage. Neurology. 1985 Apr;35(4):493–7.

22. van der Schaaf IC, Velthuis BK, Gouw A, Rinkel GJE. Venous drainage in perimesencephalic hemorrhage. Stroke. 2004 Jul;35(7):1614–8.

23. Hayward RD. Subarachnoid haemorrhage of unknown aetiology. A clinical and radiological study of 51 cases. J Neurol Neurosurg Psychiatry. 1977 Sep;40(9):926–31.

24. McKissock W, Paine K, Walsh L. Further observations on subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry. 1958 Nov;21(4):239–48.

25. Rinkel GJ., Wijdicks EF., van Gijn J, Hasan D, Vermeulen M, Hageman L., et al. Outcome in patients with subarachnoid haemorrhage and negative angiography according to pattern of haemorrhage on computed tomography. The Lancet. 1991 Oct;338(8773):964–8.

26. Ferbert A, Hubo I, Biniek R. Non-traumatic subarachnoid hemorrhage with normal angiogram. Long-term follow-up and CT predictors of complications. J Neurol Sci. 1992 Jan;107(1):14–8.

27. Farrés MT, Ferraz-Leite H, Schindler E, Mühlbauer M. Spontaneous subarachnoid hemorrhage with negative angiography: CT findings. J Comput Assist Tomogr. 1992 Aug;16(4):534–7.

28. Velthuis BK, Rinkel GJ, Ramos LM, Witkamp TD, van Leeuwen MS. Perimesencephalic hemorrhage. Exclusion of vertebrobasilar aneurysms with CT angiography. Stroke. 1999 May;30(5):1103–9.

29. Lasjaunias P, Chiu M, ter Brugge K, Tolia A, Hurth M, Bernstein M. Neurological manifestations of intracranial dural arteriovenous malformations. J Neurosurg. 1986 May;64(5):724–30.

30. Kandel EI. Complete excision of arteriovenous malformations of the cervical cord. Surg Neurol. 1980 Feb;13(2):135–9.

31. Swann KW, Ropper AH, New PF, Poletti CE. Spontaneous spinal subarachnoid hemorrhage and subdural hematoma. Report of two cases. J Neurosurg. 1984 Nov;61(5):975–80.

32. Aminoff MJ, Logue V. Clinical features of spinal vascular malformations. Brain. 1974 Mar;97(1):197–210.

33. Kumar S, Goddeau RP, Selim MH, Thomas A, Schlaug G, Alhazzani A, et al. Atraumatic convexal subarachnoid hemorrhage: clinical presentation, imaging patterns, and etiologies. Neurology. 2010 Mar 16;74(11):893–9.

34. Spitzer C, Mull M, Rohde V, Kosinski CM. Non-traumatic cortical subarachnoid haemorrhage: diagnostic work-up and aetiological background. Neuroradiology. 2005 Jul;47(7):525–31.

35. Refai D, Botros JA, Strom RG, Derdeyn CP, Sharma A, Zipfel GJ. Spontaneous isolated convexity subarachnoid hemorrhage: presentation, radiological findings, differential diagnosis, and clinical course. J Neurosurg. 2008 Dec;109(6):1034–41.

36. Ziment I. Nervous system complications in bacterial endocarditis. Am J Med. 1969 Oct;47(4):593–607.

37. Lau AH, Takeshita M, Ishii N. Mycotic (Aspergillus) arteritis resulting in fatal subarachnoid hemorrhage: a case report. Angiology. 1991 Mar;42(3):251–5.

38. Steinberg GK, Guppy KH, Adler JR, Silverberg GD. Stereotactic, angiography-guided clipping of a distal, mycotic intracranial aneurysm using the Cosman-Roberts-Wells system: technical note. Neurosurgery. 1992 Mar;30(3):408–11.

39. Bjerre P, Videbaek H, Lindholm J. Subarachnoid hemorrhage with normal cerebral angiography: a prospective study on sellar abnormalities and pituitary function. Neurosurgery. 1986 Dec;19(6):1012–5.

40. Rinkel GJ, Wijdicks EF, Vermeulen M, Hasan D, Brouwers PJ, van Gijn J. The clinical course of perimesencephalic nonaneurysmal subarachnoid hemorrhage. Ann Neurol. 1991 May;29(5):463–8.

41. Schwartz TH, Mayer SA. Quadrigeminal variant of perimesencephalic nonaneurysmal subarachnoid hemorrhage. Neurosurgery. 2000 Mar;46(3):584–8.

42. Weyerbrock A, Woznica M, Rosahl S, Berlis A. Aneurysmal and Non-Aneurysmal SAH – Is Initial Computed Tomography Predictive? RöFo - Fortschritte auf dem Gebiet der Röntgenstrahlen und der bildgebenden Verfahren. 2009 Sep;181(09):881–7.

43. Nayak S, Kunz AB, Kieslinger K, Ladurner G, Killer M. Classification of Non-Aneurysmal Subarachnoid Haemorrhage: CT Correlation to the Clinical Outcome. The Neuroradiology Journal. 2011;11.

44. Wallace AN, Vyhmeister R, Dines JN, Chatterjee AR, Kansagra AP, Viets R, et al. Evaluation of an anatomic definition of non-aneurysmal perimesencephalic subarachnhoid hemorrhage. Journal of NeuroInterventional Surgery. 2016 Apr;8(4):378–85.

45. Lansberg MG. Concurrent presentation of perimesencephalic subarachnoid hemorrhage and ischemic stroke. J Stroke Cerebrovasc Dis. 2008 Aug;17(4):248–50.

46. Sangra MS, Teasdale E, Siddiqui MA, Lindsay KW. Perimesencephalic nonaneurysmal subarachnoid hemorrhage caused by jugular venous occlusion: case report. Neurosurgery. 2008 Dec;63(6):E1202-1203; discussion E1203.

47. Mathews MS, Brown D, Brant-Zawadzki M. Perimesencephalic nonaneurysmal hemorrhage associated with vein of Galen stenosis. Neurology. 2008 Jun 10;70(24 Pt 2):2410–1.

48. Rinkel GJ, Wijdicks EF, Vermeulen M, Ramos LM, Tanghe HL, Hasan D, et al. Nonaneurysmal perimesencephalic subarachnoid hemorrhage: CT and MR patterns that differ from aneurysmal rupture. AJNR Am J Neuroradiol. 1991 Oct;12(5):829–34.

49. Park SQ, Kwon O-K, Kim SH, Oh CW, Han MH. Pre-mesencephalic subarachnoid hemorrhage: rupture of tiny aneurysms of the basilar artery perforator. Acta Neurochirurgica. 2009 Dec;151(12):1639–46.

50. Alén JF, Lagares A, Campollo J, Ballenilla F, Kaen A, Núñez AP, et al. Idiopathic subarachnoid hemorrhage and venous drainage: are they related? Neurosurgery. 2008 Dec;63(6):1106–11; discussion 1111-1112.

51. Yamakawa H, Ohe N, Yano H, Yoshimura S, Iwama T. Venous drainage patterns in perimesencephalic nonaneurysmal subarachnoid hemorrhage. Clin Neurol Neurosurg. 2008 Jun;110(6):587–91.

52. Daenekindt T, Wilms G, Thijs V, Demaerel P, Van Calenbergh F. Variants of the basal vein of Rosenthal and perimesencephalic nonaneurysmal hemorrhage. Surg Neurol. 2008 May;69(5):526–9; discussion 529.

53. Shad A, Rourke TJ, Hamidian Jahromi A, Green AL. Straight sinus stenosis as a proposed cause of perimesencephalic non-aneurysmal haemorrhage. J Clin Neurosci. 2008 Jul;15(7):839–41.

54. Cánovas D, Gil A, Jato M, de Miquel M, Rubio F. Clinical outcome of spontaneous non-aneurysmal subarachnoid hemorrhage in 108 patients: Non-aneurysmal subarachnoid hemorrhage. European Journal of Neurology. 2012 Mar;19(3):457–61.

55. van Rooij WJ, Peluso JPP, Sluzewski M, Beute GN. Additional Value of 3D Rotational Angiography in Angiographically Negative Aneurysmal Subarachnoid Hemorrhage: How Negative Is Negative? American Journal of Neuroradiology. 2008 Feb 13;29(5):962–6.

56. Alexander MS, Dias PS, Uttley D. Spontaneous subarachnoid hemorrhage and negative cerebral panangiography: review of 140 cases. Journal of neurosurgery. 1986;64(4):537–542.

57. Mendelsohn DB, Moss ML, Chason DP, Muphree S, Casey S. Acute purulent leptomeningitis mimicking subarachnoid hemorrhage on CT. J Comput Assist Tomogr. 1994 Feb;18(1):126–8.

58. Melhem ER, Jara H, Eustace S. Fluid-attenuated inversion recovery MR imaging: identification of protein concentration thresholds for CSF hyperintensity. AJR Am J Roentgenol. 1997 Sep;169(3):859–62.

59. Maeda M, Yagishita A, Yamamoto T, Sakuma H, Takeda K. Abnormal hyperintensity within the subarachnoid space evaluated by fluid-attenuated inversion-recovery MR imaging: a spectrum of central nervous system diseases. Eur Radiol. 2003 Dec;13 Suppl 4:L192-201.

60. Tsuchiya K, Katase S, Yoshino A, Hachiya J. FLAIR MR imaging for diagnosing intracranial meningeal carcinomatosis. AJR Am J Roentgenol. 2001 Jun;176(6):1585–8.

61. al-Yamany M, Deck J, Bernstein M. Pseudo-subarachnoid hemorrhage: a rare neuroimaging pitfall. Can J Neurol Sci. 1999 Feb;26(1):57–9.

62. Given CA, Burdette JH, Elster AD, Williams DW. Pseudo-subarachnoid hemorrhage: a potential imaging pitfall associated with diffuse cerebral edema. AJNR Am J Neuroradiol. 2003 Feb;24(2):254–6.

63. Schievink WI, Maya MM, Tourje J, Moser FG. Pseudo-subarachnoid hemorrhage: a CT-finding in spontaneous intracranial hypotension. Neurology. 2005 Jul 12;65(1):135–7.

64. Ozturk A, Saatci I, Pamuk AG, Erdogan C, Akmangit I, Geyik S, et al. Focal increased cortical density in immediate postembolization CT scans of patients with intracranial aneurysms. AJNR Am J Neuroradiol. 2006 Oct;27(9):1866–75.

65. Kumar G, Soni CR, Sahota PK. Transient CT hyperattenuation after Merci clot retrieval and intraarterial thrombolysis in acute stroke mimicking subarachnoid hemorrhage. J Vasc Interv Radiol. 2010 Feb;21(2):281–4.

66. Deliganis AV, Fisher DJ, Lam AM, Maravilla KR. Cerebrospinal fluid signal intensity increase on FLAIR MR images in patients under general anesthesia: the role of supplemental O2. Radiology. 2001 Jan;218(1):152–6.

67. Braga FT, da Rocha AJ, Hernandez Filho G, Arikawa RK, Ribeiro IM, Fonseca RB. Relationship between the concentration of supplemental oxygen and signal intensity of CSF depicted by fluid-attenuated inversion recovery imaging. AJNR Am J Neuroradiol. 2003 Oct;24(9):1863–8.

68. Frigon C, Shaw DWW, Heckbert SR, Weinberger E, Jardine DS. Supplemental oxygen causes increased signal intensity in subarachnoid cerebrospinal fluid on brain FLAIR MR images obtained in children during general anesthesia. Radiology. 2004 Oct;233(1):51–5.

69. Lisanti C, Carlin C, Banks KP, Wang D. Normal MRI appearance and motion-related phenomena of CSF. AJR Am J Roentgenol. 2007 Mar;188(3):716–25.

70. Cianfoni A, Martin MGM, Du J, Hesselink JR, Imbesi SG, Bradley WG, et al. Artifact simulating subarachnoid and intraventricular hemorrhage on single-shot, fast spin-echo fluid-attenuated inversion recovery images caused by head movement: A trap for the unwary. AJNR Am J Neuroradiol. 2006 Apr;27(4):843–9.

71. Dechambre SD, Duprez T, Grandin CB, Lecouvet FE, Peeters A, Cosnard G. High signal in cerebrospinal fluid mimicking subarachnoid haemorrhage on FLAIR following acute stroke and intravenous contrast medium. Neuroradiology. 2000 Aug;42(8):608–11.

72. Martin AJ, Saloner DA, Roberts TPL, Roberts H, Weber OM, Dillon W, et al. Carotid stent delivery in an XMR suite: immediate assessment of the physiologic impact of extracranial revascularization. AJNR Am J Neuroradiol. 2005 Mar;26(3):531–7.

73. Michel E, Liu H, Remley KB, Martin AJ, Madison MT, Kucharczyk J, et al. Perfusion MR neuroimaging in patients undergoing balloon test occlusion of the internal carotid artery. AJNR Am J Neuroradiol. 2001 Sep;22(8):1590–6.

74. Köhrmann M, Struffert T, Frenzel T, Schwab S, Doerfler A. The hyperintense acute reperfusion marker on fluid-attenuated inversion recovery magnetic resonance imaging is caused by gadolinium in the cerebrospinal fluid. Stroke. 2012 Jan;43(1):259–61.

75. Morris JM, Miller GM. Increased signal in the subarachnoid space on fluid-attenuated inversion recovery imaging associated with the clearance dynamics of gadolinium chelate: a potential diagnostic pitfall. AJNR Am J Neuroradiol. 2007 Dec;28(10):1964–7.

76. Khan AA, Smith JDS, Kirkman MA, Robertson FJ, Wong K, Dott C, et al. Angiogram negative subarachnoid haemorrhage: Outcomes and the role of repeat angiography. Clinical Neurology and Neurosurgery. 2013 Aug;115(8):1470–5.

77. Perrett LV, Bull JW. Some aspects of subarachnoid haemorrhage: a symposium. III. The accuracy of radiology in demonstrating ruptured intracranial aneurysms. Br J Radiol. 1959 Feb;32(374):85–92.

78. Forster DM, Steiner L, Hakanson S, Bergvall U. The value of repeat pan-angiography in cases of unexplained subarachnoid hemorrhage. J Neurosurg. 1978 May;48(5):712–6.

79. Juul R, Fredriksen TA, Ringkjøb R. Prognosis in subarachnoid hemorrhage of unknown etiology. J Neurosurg. 1986 Mar;64(3):359–62.

80. Urbach H, Zentner J, Solymosi L. The need for repeat angiography in subarachnoid haemorrhage. Neuroradiology. 1998 Jan;40(1):6–10.

81. Inamasu J, Nakamura Y, Saito R, Horiguchi T, Kuroshima Y, Mayanagi K, et al. "Occult" ruptured cerebral aneurysms revealed by repeat angiography: result from a large retrospective study. Clin Neurol Neurosurg. 2003 Dec;106(1):33–7.

82. Jung JY, Kim YB, Lee JW, Huh SK, Lee KC. Spontaneous subarachnoid haemorrhage with negative initial angiography: A review of 143 cases. Journal of Clinical Neuroscience. 2006 Dec;13(10):1011–7.

83. Gilbert JW, Lee C, Young B. Repeat cerebral pan-angiography in subarachnoid hemorrhage of unknown etiology. Surg Neurol. 1990 Jan;33(1):19–21.

84. Pathirana N, Refsum SE, McKinstry CS, Bell KE. The value of repeat cerebral angiography in subarachnoid haemorrhage. Br J Neurosurg. 1994;8(2):141–6.

85. Bradac GB, Bergui M, Ferrio MF, Fontanella M, Stura G. False-negative angiograms in subarachnoid haemorrhage due to intracranial aneurysms. Neuroradiology. 1997 Nov;39(11):772–6.

86. Berdoz D, Uske A, de Tribolet N. Subarachnoid haemorrhage of unknown cause: Clinical, neuroradiological and evolutive aspects. J Clin Neurosci. 1998 Jul;5(3):274–82.

87. McMahon null, Dorsch null. Subarachnoid haemorrhage of unknown aetiology: what next? Crit Rev Neurosurg. 1999 May 25;9(3):147–55.

88. Fontanella M, Rainero I, Panciani PP, Schatlo B, Benevello C, Garbossa D, et al. Subarachnoid hemorrhage and negative angiography: clinical course and long-term follow-up. Neurosurgical Review. 2011 Oct;34(4):477–84.

89. Wang H, Li W, He H, Luo L, Chen C, Guo Y. 320-detector row CT angiography for detection and evaluation of intracranial aneurysms: comparison with conventional digital subtraction angiography. Clin Radiol. 2013 Jan;68(1):e15-20.

90. Ringelstein A, Mueller O, Timochenko O, Moenninghoff C, Sure U, Forsting M, et al. Reangiographie nach perimesenzephaler Subarachnoidalblutung. Nervenarzt. 2013 Jun 1;84(6):715–9.

91. Dalyai R, Chalouhi N, Theofanis T, Jabbour PM, Dumont AS, Gonzalez LF, et al. Subarachnoid hemorrhage with negative initial catheter angiography: a review of 254 cases evaluating patient clinical outcome and efficacy of short- and long-term repeat angiography. Neurosurgery. 2013 Apr;72(4):646–52; discussion 651-652.

92. Delgado Almandoz JE, Kadkhodayan Y, Crandall BM, Scholz JM, Fease JL, Anderson RE, et al. Diagnostic yield of delayed neurovascular imaging in patients with subarachnoid hemorrhage, negative initial CT and catheter angiograms, and a negative 7 day repeat catheter angiogram. Journal of NeuroInterventional Surgery. 2014 Oct;6(8):637–42.

93. Bakker NA, Groen RJM, Foumani M, Uyttenboogaart M, Eshghi OS, Metzemaekers JDM, et al. Repeat digital subtraction angiography after a negative baseline assessment in nonperimesencephalic subarachnoid hemorrhage: a pooled data meta-analysis: A systematic review. Journal of Neurosurgery. 2014 Jan;120(1):99–103.

94. Kershenovich A, Rappaport ZH, Maimon S. Brain computed tomography angiographic scans as the sole diagnostic examination for excluding aneurysms in patients with perimesencephalic subarachnoid hemorrhage. Neurosurgery. 2006 Oct;59(4):798–801; discussion 801-802.

95. McKinney AM, Palmer CS, Truwit CL, Karagulle A, Teksam M. Detection of Aneurysms by 64-Section Multidetector CT Angiography in Patients Acutely Suspected of Having an Intracranial Aneurysm and Comparison with Digital Subtraction and 3D Rotational Angiography. American Journal of Neuroradiology. 2008 Mar 1;29(3):594–602.

96. Hacein-Bey L, Provenzale JM. Current Imaging Assessment and Treatment of Intracranial Aneurysms. American Journal of Roentgenology. 2011 Jan;196(1):32–44.

97. Dupont SA, Lanzino G, Wijdicks EFM, Rabinstein AA. The use of clinical and routine imaging data to differentiate between aneurysmal and nonaneurysmal subarachnoid hemorrhage prior to angiography: Clinical article. Journal of Neurosurgery. 2010 Oct;113(4):790–4.

98. Kang D-H, Park J, Lee S-H, Park S-H, Kim Y-S, Hamm I-S. Does non-perimesencephalic type non-aneurysmal subarachnoid hemorrhage have a benign prognosis? J Clin Neurosci. 2009 Jul;16(7):904–8.

99. Jafar JJ, Weiner HL. Surgery for angiographically occult cerebral aneurysms. Journal of Neurosurgery. 1993 Nov;79(5):674–9.

100. Tatter SB, Crowell RM, Ogilvy CS. Aneurysmal and microaneurysmal "angiogram-negative" subarachnoid hemorrhage. Neurosurgery. 1995 Jul;37(1):48–55.

101. Woznica M, Rosahl SK, Berlis A, Weyerbrock A. Outcome correlates with blood distribution in subarachnoid hemorrhage of unknown origin. Acta Neurochirurgica. 2010 Mar;152(3):417–22.

102. Whiting J, Reavey-Cantwell J, Velat G, Fautheree G, Firment C, Lewis S, et al. Clinical course of nontraumatic, nonaneurysmal subarachnoid hemorrhage: a single-institution experience. Neurosurgical Focus. 2009 May;26(5):E21.

103. Gupta SK, Gupta R, Khosla VK, Mohindra S, Chhabra R, Khandelwal N, et al. Nonaneurysmal nonperimesencephalic subarachnoid hemorrhage: is it a benign entity? Surgical Neurology. 2009 May;71(5):566–71.

104. Hui FK, Tumialán LM, Tanaka T, Cawley CM, Zhang YJ. Clinical differences between angiographically negative, diffuse subarachnoid hemorrhage and perimesencephalic subarachnoid hemorrhage. Neurocrit Care. 2009;11(1):64–70.

105. Reynolds MR, Blackburn SL, Zipfel GJ. Recurrent idiopathic perimesencephalic subarachnoid hemorrhage. J Neurosurg. 2011 Sep;115(3):612–6.

106. Sarabia R, Lagares A, Fernández-Alén JA, Arikan F, Vilalta J, Ibáñez J, et al. Idiopathic subarachnoid hemorrhage: a multicentre series of 220 patients. 2010;11.

107. van der Worp HB, Fonville S, Ramos LMP, Rinkel GJE. Recurrent perimesencephalic subarachnoid hemorrhage during antithrombotic therapy. Neurocrit Care. 2009;10(2):209–12.

108. Hsu W, Pradilla G, Garonzik IM, Conway JE. Pretruncal nonaneurysmal subarachnoid hemorrhage causing basilar artery vasospasm. Neurocrit Care. 2010 Oct;13(2):256–60.

109. Mayor S, Erro ME, Zazpe I, Gállego J. [Pontine stroke due to vasospasm secondary to perimesencephalic subarachnoid hemorrhage]. Neurologia. 2008 May;23(4):256–8.

110. Canhão P, Ferro JM, Pinto AN, Melo TP, Campos JG. Perimesencephalic and nonperimesencephalic subarachnoid haemorrhages with negative angiograms. Acta Neurochir (Wien). 1995;132(1–3):14–9.

111. Samaniego EA, Dabus G, Fuentes K, Linfante I. Endovascular treatment of severe vasospasm in nonaneurysmal perimesencephalic subarachnoid hemorrhage. Neurocrit Care. 2011 Dec;15(3):537–41.

112. Ko S-B, Choi HA, Carpenter AM, Helbok R, Schmidt JM, Badjatia N, et al. Quantitative analysis of hemorrhage volume for predicting delayed cerebral ischemia after subarachnoid hemorrhage. Stroke. 2011 Mar;42(3):669–74.

113. Kostic A, Stojanov D, Stefanovic I, Novak V, Kostic E, Benedeto-Stojanov D, et al. Complications after angiogram-negative subarachnoid haemorrhage: Comparative study of pretruncal and nonpretruncal hemorrhage patients. Srpski arhiv za celokupno lekarstvo. 2012;140(1–2):8–13.

114. Rinkel GJE, Wijdicks EFM, Vermeulen M, Tans JTJ, Hasan D, Gijn J van. Acute hydrocephalus in nonaneurysmal Perimesencephalic hemorrhage. Neurology. 1992 Sep 1;42(9):1805.

115. Beseoglu K, Pannes S, Steiger HJ, Hänggi D. Long-term outcome and quality of life after nonaneurysmal subarachnoid hemorrhage. Acta Neurochir (Wien). 2010 Mar;152(3):409–16.

116. Alfieri A, Gazzeri R, Pircher M, Unterhuber V, Schwarz A. A prospective long-term study of return to work after nontraumatic nonaneurysmal subarachnoid hemorrhage. J Clin Neurosci. 2011 Nov;18(11):1478–80.

117. Vergouwen MDI, Vermeulen M, van Gijn J, Rinkel GJE, Wijdicks EF, Muizelaar JP, et al. Definition of Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage as an Outcome Event in Clinical Trials and Observational Studies: Proposal of a Multidisciplinary Research Group. Stroke. 2010 Oct 1;41(10):2391–5.

118. Coelho LGBSA, Costa JMD, Silva EIPA. Non-aneurysmal spontaneous subarachnoid hemorrhage: perimesencephalic versus non-perimesencephalic. Revista Brasileira de Terapia Intensiva. 2016;28(2).

119. Haley EC, Kassell NF, Torner JC. The International Cooperative Study on the Timing of Aneurysm Surgery. The North American experience. Stroke. 1992 Feb 1;23(2):205–14.

120. Nishioka H. Cooperative Study of Intracranial Aneurysms and Subarachnoid Hemorrhage: A Long-term Prognostic Study: III. Subarachnoid Hemorrhage of Undetermined Etiology. Archives of Neurology. 1984 Nov 1;41(11):1147.

121. Elhadi AM, Zabramski JM, Almefty KK, Mendes GAC, Nakaji P, McDougall CG, et al. Spontaneous subarachnoid hemorrhage of unknown origin: hospital course and long-term clinical and angiographic follow-up. Journal of Neurosurgery. 2015 Mar;122(3):663–70.

122. Boswell S, Thorell W, Gogela S, Lyden E, Surdell D. Angiogram-Negative Subarachnoid Hemorrhage: Outcomes Data and Review of the Literature. Journal of Stroke and Cerebrovascular Diseases. 2013 Aug;22(6):750–7.

123. Zhong W, Zhao P, Wang D, LI G, Sun H, Chen H, et al. Different Clinical Characteristics Between Perimesencephalic Subarachnoid Hemorrhage and Diffuse Subarachnoid Hemorrhage with Negative Initial Angiography. Turk Neurosurg. 2014;24(3):6.

124. Kapadia A, Schweizer TA, Spears J, Cusimano M, Macdonald RL. Nonaneurysmal Perimesencephalic Subarachnoid Hemorrhage: Diagnosis, Pathophysiology, Clinical Characteristics, and Long-Term Outcome. World Neurosurgery. 2014 Dec;82(6):1131–43.

125. Delgado Almandoz JE, Jagadeesan BD, Refai D, Moran CJ, Cross DT, Chicoine MR, et al. Diagnostic Yield of Repeat Catheter Angiography in Patients With

Catheter and Computed Tomography Angiography Negative Subarachnoid Hemorrhage: Neurosurgery. 2012 May;70(5):1135–42.

126. Cánovas D, Gil A, Jato M, de Miquel M, Rubio F. Clinical outcome of spontaneous non-aneurysmal subarachnoid hemorrhage in 108 patients. Eur J Neurol. 2012 Mar;19(3):457–61.

127. Wenz H, Ehrlich G, Wenz R, al Mahdi M-M, Scharf J, Groden C, et al. MR Angiography Follow-Up 10 Years after Cryptogenic Nonperimesencephalic Subarachnoid Hemorrhage. Ai J, editor. PLOS ONE. 2015 Feb 17;10(2):e0117925.

128. Suzuki S, Kayama T, Sakurai Y, Ogawa A, Suzuki J. Subarachnoid hemorrhage of unknown cause. Neurosurgery. 1987 Sep;21(3):310–3.

129. Rogg JM, Smeaton S, Doberstein C, Goldstein JH, Tung GA, Haas RA. Assessment of the value of MR imaging for examining patients with angiographically negative subarachnoid hemorrhage. American Journal of Roentgenology. 1999 Jan;172(1):201–6.

130. Kumar R, Das KK, Sahu RK, Sharma P, Mehrotra A, Srivastava AK, et al. Angio negative spontaneous subarachnoid hemorrhage: Is repeat angiogram required in all cases? Surg Neurol Int. 2014 Aug 7;5.

Annexure 1

WFNS grade:

WFNS Grade	GCS score*	Major focal deficits**
I	15	-
II	13-14	-
III	13-14	+
IV	7-12	+/-
V	3-6	+/-

* GCS - Glassgow Coma Scale.

**Aphasia, hemiparesis or hemiplegia (+ = present, - = absent)

Glasgow outcome scale score:

1. Death	Severe injury or death without recovery of consciousness
2. Persistent vegetative state	Severe damage with prolonged state of unresponsiveness and a lack of higher mental functions
3. Severe disability	Severe injury with permanent need for help with daily living
4. Moderate disability	No need for assistance in everyday life, employment is possible but may require special equipment.
5. Low disability	Light damage with minor neurological and psychological deficits.

Modified Rankin Scale score:

– 0: No symptoms.

– 1: No significant disabling symptom.

– 2: Slight disability.

– 3: Moderate disability.

– 4: Moderate/severe disability.

– 5: Severe Disability.

– 6: Dead.

Modified Fischer scale:

Grade	Blood on CT*
0	No SAH or IVH
1	Focal or diffuse thin SAH, no IVH
2	Focal or diffuse thin SAH, with IVH
3	Focal or diffuse thick SAH, no IVH
4	Focal or diffuse thick SAH, with IVH

* measurements made in the greatest longitudinal & transverse dimension,

Annexure II

ABBREVIATIONS

SAH – Subarachnoid haemorrhage

AnSAH – Angiogram negative subarachnoid haemorrhage

CT – Computed tomography

DSA -- Digital subtraction angiogram

PMSAH – Perimesencephalic non-aneurysmal subarachnoid haemorrhage

AVM -- Arteriovenous malformations

PMH – Perimesencephalic haemorrhage

MRI -- Magnetic resonance imaging

CTA -- CT angiography

CSF -- Cerebrospinal fluid

WFNS – World Federation of Neurosurgical Surgeons grade

GOS -- Glasgow Outcome score

MFG – modified Fischer Grade

mRS – Modified Rankin scale score

DAVF – Dural arteriovenous fistula

GCS – Glasgow Coma scale

MRA -- Magnetic Resonance Angiography

TOF -- 3 dimensional time-of-flight MRI

Annexure III

PROFORMA

A. GENERAL INFORMATION

Anonymized Patient ID:

Age,

Gender,

B. CLINICAL DETAILS

Clinical Presentation- headache, vomiting, seizures, LOC, limb weakness, cranial nerve palsy, memory disturbances, speech disturbances, visual disturbances, neck stiffness/pain, papilloedema, others

Co-morbidities – Diabetes, Hypertension, others

Family history of SAH

GCS on admission

WFNS Grade

Duration of hospital stay

Complication of SAH – neurological and non-neurological

Surgical exploration

Discharge status – deficits, GCS, mRS score and GOS score

C. IMAGING DETAILS

Interval between ictus and initial CT (days)

Pattern of SAH- diffuse, PMH, convexity

CT grade of bleed

Intra-parenchymal/ intra-ventricular bleed

Hydrocephalus

Infarct

Interval between ictus and initial angiogram (days)

Suspicious lesion on initial angiogram

Vasospasm

Complication of angiogram

D. FOLLOW UP

Interval between ictus and 1st follow up

Status at 1st follow up – GCS, mRS, GOS, Deficits

Interval between ictus and last follow up

Status at last follow up – GCS, mRS, GOS, Deficits

New attack/event of follow up

Surgery/intervention on follow up

E. FOLLOW UP IMAGING

Interval between ictus and follow up imaging

Imaging modality – DSA, CTA, MRI

Findings on follow up imaging

Complication of any modality

Annexure IV

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

Institutional Ethics Committee
(IEC Regn No. ECR/189/Inst/KL/2013)

SCT/IEC/1037/APRIL-2017 17.05.2017

Dr. Palak Jaiswal
Senior Resident
Department of Neurosurgery
SCTIMST, Thiruvananthapuram

Dear Dr. Palak Jaiswal,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "A RETROSPECTIVE STUDY OF ANGIOGRAM-NEGATIVE SUBARACHNOID HAEMORRHAGE: ASSESSMENT OF CLINICAL PROFILE, BLEEDING PATTERN AND LONG-TERM OUTCOMES (IEC/1037)" on 15th April, 2017.

The following documents were reviewed:

Original submission

1. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 04.04.2017 with check list*
2. *Forwarding letter from HOD dated 04.04.2017*
3. *TAC Approval Letter*
4. *IEC Application Form*
5. *Project Proposal*
6. *Proforma*
7. *Declaration Form*
8. *CV of Principal Investigator and Co-Principal Investigators*

Revised submission

1. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 07.05.2017 with check list*
2. *TAC Approval Letter*
3. *Revised IEC Application Form*
4. *Copy of forwarding letter from HOD dated 04.04.2017*
5. *Project Proposal*
6. *Proforma*
7. *Copy of Declaration Form*
8. *CV of Principal Investigator and Co-Principal Investigators*

The following members of the Ethics Committee were present at the meeting held on 15th April, 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. Kala Kesavan. P	MBBS, MD	Female	Basic Medical Scientist	No
3.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
4.	Dr. S S Giri Sankar	LL.M. Ph.D.	Male	Legal Expert	No
5.	Dr. Aneesh V Pillai	BA. LLB (Hons.), LLM, Ph. D, SET (Law)	Male	Legal Expert	No
6.	Mr. Satheesh Chandran	MSW, PGDPM	Male	Lay person/ NGO/ Social Scientist	No
7.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
8.	Dr. P. Manickam	BSMS, MSc (Epid)., PhD.,	Male	Health Science Expert/ Social Scientist	No
9.	Dr. V. Raman Kutty	M D, M Phil, M P H	Male	Health Sciences Expert/Clinician	Yes
10.	Dr. K R S Krishnan	M.E., Ph.D.	Male	Medical Technology	Yes
11	Dr.Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
12.	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

Annexure V

Plagiarism Checker X Originality Report

"A RETROSPECTIVE STUDY OF ANGIOGRAM -NEGATIVE SUBARACHNOID HAEMORRHAGE: ASSESSMENT OF CLINICAL PROFILE, BLEEDING PATTERN AND LONG-TERM OUTCOMES"

Similarity Found: 7%

Date: Saturday, July 28, 2018
Statistics: 345 words Plagiarized / 4928 Total words
Remarks: Low Plagiarism Detected

INTERNET SOURCES:

0% - http://www.ajnr.org/content/37/2/297
0% - https://www.sciencedirect.com/science/ar
1% - https://www.researchgate.net/publication
0% - http://www.iosrjournals.org/iosr-jdms/pa
0% - https://www.researchgate.net/profile/Yuo
1% - http://thejns.org/doi/10.3171/2014.10.JN
1% - http://thejns.org/doi/10.3171/2014.10.JN
1% - http://thejns.org/doi/10.3171/2014.10.JN
0% - https://www.scribd.com/doc/307392713/Dia
0% - https://www.sciencedirect.com/science/ar
0% - http://thejns.org/doi/pdf/10.3171/2013.9
0% - http://dspace.sctimst.ac.in/jspui/bitstr
1% - https://www.sciencedirect.com/science/ar
1% - https://www.sciencedirect.com/science/ar
1% - https://www.sciencedirect.com/science/ar
1% - http://europepmc.org/articles/PMC4135542
1% - https://www.researchgate.net/publication
0% - http://scielo.isciii.es/scielo.php?scrip
0% - http://www.rbti.org.br/artigo/detalhes/0
0% - http://scielo.isciii.es/scielo.php?scrip
0% - https://link.springer.com/article/10.100
1% - http://thejns.org/doi/10.3171/2014.10.JN

Annexure VI

Key to master chart

Sex

1= Male

2= Female

Clinical features

0 = absent

1 = present

Family history

0 = absent

1 = present

Other comorbidities

1 = Migraine

2 = Dyslipidaemia

3 = Cerebrovascular disease

4 = Heart disease

5 = Hypothyroid

Addictions

1 = Alcohol

2 = Smoking

3 = Both

Areas of haemorrhage

1 = Diffuse

2 = PMH

3 = Convexity

Radiological parameters (rebleed, hydrocephalus, intraventricular haemorrhage, intraparenchymal haemorrhage, and vasospasm)

0 = absent

1 = present

Complications during hospitalization

0 = absent

1 = present

Surgical exploration

0 = absent

1 = present

Follow up imaging modality

1 = DSA

2 = CTA

3 =MRI

Findings on repeat imaging

0 = absent

1 = present

Complication of imaging modality

0 = absent

1 = present

Deficits, new event/deficits

0 = absent

1 = present

Sr no	Age	Sex	Headache	Vomiting	Seizure	LOC	Altered sensorium	Limb weakness	Cranial nerve palsy	Visual disturbances	Speech disturbances	Memory disturbances	Neck pain/stiffness	Papilloedema	Warning symptoms	Diabetes	Hypertension	Other comorbidities	Addictions	Family History	GCS on admission	WFNS on admission	Interval for 1st CT	Areas of haemorrhage	MFG	Rebleed	Hydrocephalus	Intraventricular hemorrhage	Intraparenchymal hemorrhage	Infarct	Interval for DSA	Suspicious lesion	Vasospasm	Complication during hospitalization	Surgery following negative dsa	Duration of hospitalization	GCS at discharge	Deficit at discharge	mRS at discharge	GOS at discharge	Interval for 1ST F/U & imaging(WEEKS)	F/u imaging modality	Findings	Surgery following repeat imaging	complications of modality	f/u GCS	New deficits on f/u	New event/attack f/u	F/u mRS	F/u GOS	interval for last f/u (months)	last f/u GCS	Deficits at last f/u	mRS at last f/u	GOS at last f/u
1	63	1	1	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	15	1	0	1	3	0	0	0	0	0	0	2	0	0	0	0	3	15	1	2	4	10	1	0	0	0	15	0	0	1	5	12	15	0	0	5
2	30	1	1	1	0	0	0	0	1	1	0	0	0	0	1	0	0	2	3	0	15	1	0	3	1	1	0	0	0	1	8	1	1	0	0	8	15	1	2	4	12	3	1	0	0	15	0	0	2	5	3	15	1	2	5
3	46	1	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	15	1	0	1	3	0	0	0	0	0	2	0	0	0	0	4	15	1	2	4				0	0										
4	48	2	1	1	0	0	0	0	0	0	0	0	1	0	0	0	1	5	0	0	15	1	1	1	3	0	0	0	0	0	17	1	0	0	0	3	15	0	1	5	9	1	1	0	0	15	0	0	1	5	6	15	0	0	5
5	54	2	1	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	15	1	5	2	3	0	0	0	0	0	13	0	1	0	0	4	15	0	1	5				0	0										
6	58	2	1	1	0	0	0	1	0	1	0	0	0	0	0	1	1	2	0	0	15	1	2	2	3	0	0	0	0	0	54	0	1	0	0	3	15	1	2	4	9	2	0	0	0	15	0	0	1	5	6	15	0	1	5
7	35	2	1	1	1	0	0	1	0	0	0	0	0	0	1	0	0	1	0	0	15	1	1	3	1	0	0	0	0	1	0	7	0	1	1	0	3	15	0	1	5	13	3	0	0	0	15	0	0	1	5	6	15	0	0	5
8	49	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	0	1	3	0	0	0	0	1	8	1	1	0	1	7	15	0	2	4	6	2	0	0	0	15	0	0	1	5	6	15	0	0	5
9	43	2	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	15	1	0	3	1	0	0	0	0	0	37	0	0	0	0	3	15	0	1	5	6	3	0	0	0	15	0	0	0	5	6	15	0	0	5
10	51	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	15	1	0	3	1	0	0	0	0	0	2	0	0	0	0	5	15	0	2	5	6	2	0	0	0	15	0	0	1	5	6	15	0	0	5
11	52	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	0	2	1	0	0	0	0	0	7	0	0	0	0	6	15	0	2	5	9	1	0	0	0	15	0	0	0	5	6	15	0	0	5
12	77	1	1	1	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	13	2	0	1	3	0	0	0	0	0	25	0	1	1	0	7	15	0	1	5	25	1	0	0	0	15	0	0	1	5	6	15	0	1	5
13	58	2	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	15	3	0	3	1	0	0	0	0	0	17	0	0	1	0	8	15	1	5	2	6	3	1	0	0	15	0	0	4	2	3	15	1	4	2
14	20	1	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	15	1	0	3	1	0	0	0	0	0	0	0	0	0	0	3	15	0	1	5	5	1	1	0	0	15	0	0	1	5	6	15	0	1	5
15	69	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	1	4	0	0	15	1	0	3	1	0	0	0	0	0	2	0	0	0	0	3	15	0	1	5	6	2	0	0	0	15	0	0	0	5	2	15	0	0	5
16	57	1	1	1	0	0	1	0	0	0	0	0	1	0	0	1	0	0	0	0	15	1	0	2	1	0	0	0	0	0	6	0	0	0	0	3	15	0	1	5	6	1	0	0	0	15	0	0	0	5	6	15	0	0	5
17	37	2	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	1	3	1	0	0	0	0	0	18	0	0	0	0	3	15	0	1	5	24	3	1	0	0	15	0	0	1	5	12	15	0	1	5
18	48	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	15	1	1	2	1	0	0	0	0	0	21	0	0	0	0	4	15	0	1	5				0	0										
19	48	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	15	1	0	2	1	0	0	0	0	0	13	0	0	0	0	2	15	0	1	5	13	1	0	0	0	15	0	0	0	5	6	15	0	0	5
20	34	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	0	2	3	0	0	0	0	0	5	0	1	0	0	4	15	0	1	5	9	1	1	0	0	15	0	0	1	5	9	15	0	1	5
21	16	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	0	3	1	0	0	0	0	0	40	0	0	0	0	7	15	0	1	5	6	2	0	0	0	15	0	0	0	5	6	15	0	0	5
22	46	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	1	2	1	0	0	0	0	0	13	1	0	0	0	2	15	0	1	5	3	1	1	0	0	15	0	0	0	5	6	15	0	0	5
23	41	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	4	2	1	0	0	0	0	0	6	0	0	0	0	2	15	0	1	5	17	1	0	0	0	15	0	0	0	5	7	15	0	0	5
24	57	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	1	2	1	0	0	0	0	0	19	0	0	0	0	4	15	0	1	5	40	2	0	0	0	15	0	0	0	5	11	15	0	0	5
25	53	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	2	2	3	0	0	0	0	0	34	0	0	0	0	3	15	0	1	5	20	2	0	0	0	15	0	0	1	5	12	15	0	1	5
26	19	1	0	0	0	0	0	1	1	0	1	0	0	1	0	0	0	0	0	0	11	3	0	3	3	0	0	0	1	0	4	1	1	0	0	7	15	1	3	3	8	1	0	0	0	15	0	0	1	5	18	15	0	0	5
27	52	1	1	1	0	1	0	1	1	0	0	0	0	1	0	0	1	0	3	0	14	2	1	1	3	0	0	0	0	0	11	0	1	1	0	5	15	1	4	2				0	0										
28	22	2	1	1	0	0	1	1	1	1	0	0	1	0	1	0	0	0	0	0	13	3	0	3	1	0	0	0	1	0	1	8	1	1	1	0	3	15	1	3	4	14	3	0	0	0	15	0	0	2	5	12	15	0	1	5
29	67	1	0	0	1	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	15	1	0	1	3	0	0	0	0	0	6	0	0	0	0	7	15	0	1	5	8	2	0	0	0	15	0	0	1	5	7	15	0	0	5
30	30	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	0	2	3	0	0	0	0	0	2	0	0	0	0	2	15	0	1	5	15	2	0	0	0	15	0	0	0	5	9	15	0	0	5
31	34	1	0	0	1	1	0	0	0	0	0	0	0	0	1	0	1	0	1	0	15	1	6	3	1	0	0	0	0	0	12	0	0	0	0	3	15	0	1	5	10	1	0	0	0	15	0	0	0	5	9	15	0	0	5
32	44	2	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	5	0	0	15	1	0	1	3	0	0	0	1	0	23	0	0	0	0	3	15	0	1	5	15	1	0	0	0	15	0	0	1	5	8	15	0	0	5
33	59	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	3	3	1	0	1	0	0	0	9	0	0	0	0	5	15	0	1	5	4	2	0	0	0	15	0	0	0	5	8	15	0	0	5
34	56	2	1	1	0	1	0	1	0	0	0	0	0	1	0	1	1	0	0	0	13	2	0	1	4	0	1	1	0	0	3	0	1	0	0	3	15	0	1	5	6	2	0	0	0	15	0	0	1	5	6	15	0	1	5
35	32	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	5	2	3	0	0	0	0	0	9	1	0	0	0	3	15	0	1	5	8	2	0	0	0	15	0	0	1	5	6	15	0	0	5
36	57	2	1	1	0	1	1	1	0	0	0	0	0	0	0	1	0	0	0	0	13	3	0	1	4	0	0	1	0	0	2	0	1	0	0	2	15	0	1	5	13	2	0	0	0	15	0	0	1	5	7	15	0	1	5

37	62	1	1	1	0	0	0	0	0	0	0	0	1	0	0	0	1	2	0	0	15	1	1	2	1	0	0	0	0	0	4	0	0	0	0	4	15	0	1	5	4	1	0	0	0	15	0	0	0	5	13	15	0	0	5
38	23	1	1	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	15	1	2	1	3	0	0	0	0	0	11	0	1	0	0	3	15	0	1	5	5	1	0	0	0	15	0	0	1	5	14	15	0	0	5
39	67	2	1	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	15	1	0	2	1	0	0	0	0	0	20	0	0	0	0	2	15	0	1	5	32	2	0	0	0	15	0	0	0	5	8	15	0	0	5
40	68	2	1	1	0	0	1	1	0	0	0	1	0	0	0	0	1	3	0	0	13	3	3	1	3	0	0	0	0	0	8	0	1	0	0	2	15	0	1	5	14	2	1	0	0	15	0	0	1	5	24	15	0	0	5
41	60	2	1	1	0	1	0	0	1	0	0	0	0	0	0	0	1	0	0	0	15	1	0	1	1	0	0	0	0	0	19	0	0	0	0	3	15	0	1	5	17	1	0	0	0	15	0	0	0	5	5	15	0	0	5
42	58	2	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	15	1	0	1	1	0	0	0	0	0	11	0	0	0	0	4	15	0	1	5	8	1	0	0	0	15	0	0	0	5	5	15	0	0	5
43	40	1	1	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	15	1	0	1	3	0	0	0	0	0	21	0	0	0	0	4	15	0	1	5	15	1	1	0	0	15	0	0	1	5	5	15	0	0	5
44	54	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14	1	3	3	1	0	0	0	0	0	24	0	0	0	0	3	15	0	1	5	13	1	0	0	0	15	0	0	0	5	3	15	0	0	5
45	42	1	1	1	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	14	2	1	1	4	0	1	1	0	0	3	0	1	1	0	10	15	0	1	5	28	2	1	0	0	15	0	0	1	5	7	15	0	1	5
46	53	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	14	2	0	1	3	0	0	0	0	0	21	0	0	0	0	5	15	0	1	5	13	2	0	0	0	15	0	0	1	5	9	15	0	1	5
47	45	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	0	2	1	0	0	0	0	0	1	0	0	0	0	3	15	0	1	5				0	0										
48	50	1	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	15	1	0	1	2	0	0	1	0	0	9	0	1	0	0	2	15	0	1	5	13	1	1	0	0	15	0	0	0	5	30	15	0	0	5
49	52	2	0	0	0	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	15	1	0	1	3	0	0	0	0	0	5	0	1	0	0	7	15	1	2	5	8	1	1	1	0	15	0	0	1	5	6	15	0	0	5
50	48	2	1	1	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0	15	1	1	3	1	0	0	0	0	0	9	0	1	0	0	6	15	0	1	5	10	2	0	0	0	15	0	0	0	5	18	15	0	0	5
51	69	1	1	1	0	0	0	1	0	0	0	0	0	0	1	1	1	0	0	0	15	1	1	1	1	0	0	0	0	0	28	0	0	0	0	4	15	0	1	5	23	1	1	0	0	15	0	0	0	5	6	15	0	0	5
52	58	1	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	15	1	1	2	1	0	0	0	0	0	9	0	1	0	0	2	15	0	1	5				0	0										
53	55	2	1	1	0	0	0	0	0	0	0	0	1	1	0	1	0	0	0	0	15	1	3	2	4	0	0	1	0	0	8	0	1	0	0	4	15	0	1	5	24	2	0	0	0	15	0	0	1	5	20	15	0	1	5
54	35	1	1	1	0	0	0	0	0	1	0	0	1	1	1	0	1	0	0	0	15	1	0	1	3	1	1	0	0	0	10	0	0	0	0	6	15	0	2	5	32	1	0	0	0	15	0	0	1	5	8	15	0	0	5
55	50	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	15	1	0	2	1	0	0	0	0	0	4	0	0	0	0	3	15	0	1	5	11	1	0	0	0	15	0	0	1	5					
56	43	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	15	1	0	2	1	0	0	0	0	0	9	1	1	0	0	2	15	0	1	5	11	2	0	0	0	15	0	0	1	5	24	15	0	0	5
57	60	2	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	15	1	0	3	1	1	0	0	0	0	15	0	1	0	0	5	15	0	2	5	50	2	0	0	0	15	0	0	1	5	24	15	0	0	5
58	57	1	1	1	0	0	0	0	0	1	0	0	1	1	0	0	1	4	0	0	15	1	0	2	1	0	0	0	0	0	4	0	0	0	0	2	15	0	4	2	9	2	0	0	0	15	1	0	4	2	30	15	1	3	3
59	59	2	1	1	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	15	1	0	1	1	0	0	1	0	0	7	0	0	0	0	3	15	0	1	5	8	2	0	0	0	15	0	0	1	5					
60	60	1	1	1	0	0	0	0	0	0	0	0	1	1	0	0	1	0	0	0	15	1	1	1	1	0	0	0	0	0	12	0	1	0	0	2	15	0	1	5	9	2	0	0	0	15	0	0	1	5					
61	55	1	1	1	0	1	0	1	0	0	0	0	0	0	0	0	1	0	0	0	15	1	1	1	1	0	0	0	0	0	93	0	0	0	0	19	15	0	1	5	100	1	0	0	0	15	0	0	0	5	32	15	0	0	5
62	34	1	1	1	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	15	1	1	1	1	0	0	0	0	0	2	0	1	0	0	3	15	0	1	5															
63	48	2	1	1	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	15	1	2	2	1	0	0	0	0	0	12	0	0	0	0	3	15	0	1	5	8	2	0	0	0	15	0	0	1	5	26	15	0	1	5
64	44	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	1	1	1	0	0	0	0	0	7	0	0	0	0	2	15	0	1	5	10	2	0	0	0	15	0	0	0	5	66	15	0	0	5
65	56	1	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	3	0	15	1	4	2	1	0	0	1	0	0	11	0	0	0	0	2	15	0	1	5	24	2	0	0	0	15	0	0	0	5	7	15	0	0	5
66	49	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	1	1	1	0	0	0	0	0	25	1	0	0	0	2	15	0	1	5															
67	65	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	0	2	1	0	0	1	0	0	14	0	0	0	0	4	15	0	1	5				0	0										
68	47	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	1	2	1	0	0	0	0	0	1	0	0	0	0	3	15	0	1	5	4	1	0	0	0	15	0	0	0	5	12	15	0	0	5
69	36	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	15	1	1	1	1	0	0	0	0	0	17	1	0	0	0	4	15	0	1	5	82	2	0	0	0	15	0	0	0	5	48	15	0	0	5
70	60	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	2	2	1	0	0	0	0	0	4	0	0	0	0	2	15	0	1	5	24	2	0	0	0	15	0	0	1	5	14	15	0	0	5
71	52	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	1	2	1	0	0	0	0	0	8	0	0	0	0	2	15	0	1	5	8	2	0	0	0	15	0	0	0	5	64	15	0	0	5
72	50	2	1	1	0	1	1	0	0	0	0	0	0	0	0	0	1	4	0	0	14	2	0	1	1	0	1	1	0	0	7	1	0	0	0	4	15	0	1	5	3	1	1	0	0	15	0	0	1	5					
73	44	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	6	2	1	0	0	0	0	0	55	0	0	0	0	3	15	0	1	5	19	1	0	0	0	15	0	0	0	5	4	15	0	0	5
74	42	2	1	1	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	15	1	2	2	1	0	1	0	0	0	6	0	1	0	0	3	15	0	1	5	8	2	0	0	0	15	0	0	0	5	12	15	0	0	5
75	59	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	1	1	1	0	0	0	0	0	6	0	0	0	0	2	15	0	1	5															
76	43	2	1	1	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	15	1	1	1	2	0	0	0	0	0	2	0	0	0	0	2	15	0	1	5	9	2	0	0	0	15	0	0	0	5	3	15	0	0	5
77	44	1	0	0	1	0	0	1	0	0	0	0	0	0	1	1	1	0	0	0	15	1	0	1	1	0	0	0	0	0	1	0	0	0	0	6	15	0	1	5	6	1	0	0	0	15	0	0	0	5	6	15	0	0	5
78	65	2	1	1	0	1	0	0	0	0	0	0	1	0	0	1	1	0	0	0	15	1	1	1	1	0	0	0	0	0	2	0	1	0	0	2	15	0	1	5															
79	40	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	4	2	1	0	0	0	0	0	7	0	1	0	0	2	15	0	1	5				0	0										
80	54	2	1	1	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	15	1	0	2	1	0	0	0	0	0	7	0	0	0	0	4	15	0	1	5	24	2	0	0	0	15	0	0	1	5	31	15	0	1	5
81	47	2	1	1	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	15	1	1	3	1	0	0	0	0	0	48	0	0	0	0	6	15	0	1	5	8	3	1	0	0	15	0	0	0	5	54	15	0	0	5
82	60	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	2	2	1	0	0	0	0	0	15	0	0	0	0	2	15	0	1	5	9	2	0	0	0	15	0	0	0	5	5	15	0	0	5
83	52	1	1	1	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	14	2	1	2	1	0	0	0	0	0	11	0	1	0	0	10	15	0	1	5	9	1	0	0	0	15	0	0	0	5	5	15	0	0	5
84	49	2	1	0	0	0	0	1	0	0	0	0	1	0	1	0	0	0	0	0	15	1	3	1	3	0	0	0	0	0	8	0	1	0	0	2	15	0	1	5	17	2	0	0	0	15	0	0	1	5	6	15	0	0	5
85	60	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	0	2	1	0	0	0	0	0	5	0	0	0	0	2	15	0	1	5	12	2	0	0	0	15	0	0	0	5	12	15	0	0	5
86	40	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	15	1	6	2	1	0	0	0	0	0	15	0	0	0	0	2	15	0	1	5				0	0										
87	47	1	1	1	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	15	1	0	2	1	0	0	0	0	0	2	0	0	0	0	2	15	0	1	5				0	0										
88	55	2	1	1	0	0	0	0	0	0	0	0	0	1	0	1	1	0	0	0	15	1	5	2	1	0	0	0	0	0	15	0	0	0	0	2	15	0	1	5				0	0										
89	58	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	14	2	0	1	3	0	0	0	1	0	2	0	1	0	0	2	15	0	1	5	9	2	0	0	0	15	0	0	1	5	8	15	0	1	5
90	52	2	1	1	0	1	0	0	0	0	0	0	1	1	0	0	1	0	0	0	15	1	0	2	1	0	0	0	0	0	2	0	0	0	0	2	15	0	1	5	12	2	1	0	0	15	0	0	1	5	56	15	0	0	5

91	55	2	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	15	1	1	2	2	0	0	1	0	0	7	0	0	0	0	2	15	0	1	5	8	1	0	0	0	15	0	0	0	5	3	15	0	0	5
92	64	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	15	1	3	2	1	0	0	0	0	0	30	0	0	0	0	2	15	0	1	5				0	0										
93	60	2	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	15	1	1	1	1	0	0	0	0	0	4	1	0	0	0	2	15	0	1	5															
94	48	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	15	1	3	1	3	0	0	0	0	0	5	0	0	0	0	2	15	0	1	5	6	2	0	0	0	15	0	0	1	5	63	15	0	0	5
95	40	2	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	15	1	0	1	1	0	0	0	0	0	3	0	0	0	0	2	15	0	1	5															
96	49	2	1	0	0	0	0	1	0	0	0	0	1	0	1	0	1	0	0	0	15	1	3	1	3	0	0	0	0	0	6	0	1	0	0	2	15	0	1	5	18	2	0	0	0	15	0	0	1	5	12	15	0	0	5
97	49	2	1	1	0	1	0	0	0	0	0	0	1	0	0	0	1	0	0	0	15	1	0	1	4	0	1	1	0	0	10	0	0	0	0	4	15	0	1	5	140	1	1	1	0	15	0	0	1	5	48	15	0	0	5
98	50	1	1	1	0	0	0	1	0	1	0	0	1	0	0	0	1	0	1	0	15	1	1	2	3	0	1	0	0	0	4	0	0	0	0	2	15	0	1	5	7	2	0	0	0	15	0	0	1	5	5	15	0	0	5
99	67	1	1	0	0	0	0	0	0	0	0	0	1	0	1	0	1	0	0	0	14	2	2	2	4	0	1	1	0	0	10	0	0	0	0	3	15	0	1	5				0	0		0	0	1	5	116	15	0	1	5
100	56	2	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	15	1	2	1	1	0	1	0	0	0	5	0	1	0	0	2	15	0	1	5	7	2	0	0	0	15	0	0	0	5	98	15	0	0	5
101	58	2	1	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	0	13	2	0	1	1	0	1	0	0	1	7	0	1	0	0	2	15	0	1	5	7	2	0	0	0	15	0	0	1	5	69	15	0	0	5
102	57	1	1	1	0	0	0	0	0	0	0	0	1	0	0	1	1	0	0	0	15	1	0	1	3	0	1	0	0	0	4	0	0	0	0	2	15	0	1	5	7	2	0	0	0	15	0	0	1	5	6	15	0	0	5
103	32	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	2	1	1	0	0	0	0	0	14	0	0	0	0	3	15	0	1	5	21	2	0	0	0	15	0	0	0	5	60	15	0	0	5
104	40	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	0	1	3	1	0	0	1	0	3	0	0	0	0	7	15	0	2	5	10	2	0	0	0	15	0	0	1	5	6	15	0	0	5
105	61	1	1	1	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	15	1	1	2	1	0	0	0	0	0	2	0	0	0	0	3	15	0	1	5	5	2	0	0	0	15	0	0	0	5	6	15	0	0	5
106	67	2	1	1	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	15	1	3	2	1	0	1	0	0	0	4	0	0	0	0	2	15	0	1	5	5	3	0	0	0	15	0	0	0	5	3	15	0	0	5
107	57	2	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	15	1	1	1	3	0	0	0	1	0	7	0	0	0	0	2	15	0	1	5	14	2	0	0	0	15	0	0	1	5	17	15	0	0	5
108	45	2	1	1	0	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	14	2	0	1	3	0	1	1	0	0	13	1	0	1	1	10	15	0	2	5	14	3	0	0	0	15	0	0	1	5	3	15	0	1	5
109	42	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	0	2	1	0	0	0	0	0	6	0	1	0	0	3	15	0	1	5	28	2	0	0	0	15	0	0	0	5	60	15	0	0	5
110	23	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	0	3	1	0	0	0	0	0	4	1	0	1	0	15	15	0	1	5	9	1	0	0	0	15	0	0	0	5	60	15	0	0	5
111	41	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	1	2	1	0	0	0	0	0	5	0	0	0	0	2	15	0	1	5	10	2	0	0	0	15	0	0	1	5	144	15	0	0	5
112	37	2	1	1	0	1	0	0	0	0	0	0	1	0	1	0	0	0	0	0	15	1	1	1	1	0	0	0	0	0	17	0	0	1	0	2	15	0	1	5															
113	65	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	0	2	1	0	0	0	0	0	16	0	0	0	0	2	15	0	1	5	38	2	0	0	0	15	0	0	0	5	69	15	0	0	5
114	58	2	1	1	0	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	14	2	1	2	1	0	1	0	0	0	6	0	0	0	0	3	15	0	1	5	31	2	0	0	0	15	0	0	0	5	118	15	0	0	5
115	53	2	1	1	0	1	0	0	0	0	0	0	1	0	0	1	0	0	0	0	15	1	1	1	1	0	0	0	0	0	4	0	1	0	0	3	15	0	1	5															
116	53	1	1	1	0	0	0	0	1	0	0	0	0	1	0	1	1	0	0	0	15	1	1	2	1	0	0	0	0	0	8	0	0	0	0	4	15	0	1	5	29	2	0	0	0	15	0	0	0	5	72	15	0	0	5
117	65	2	1	1	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	15	1	0	2	1	0	0	0	0	0	25	0	0	0	0	4	15	0	1	5	6	2	0	0	0	15	0	0	1	5					
118	35	1	1	1	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	15	1	1	2	1	0	0	0	0	0	16	1	0	0	0	10	15	0	1	5	6	1	0	0	0	15	0	0	1	5	43	15	0	0	5
119	53	2	1	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	15	1	1	2	1	0	0	0	0	0	21	0	0	0	0	3	15	0	1	5	28	1	0	0	0	15	0	0	0	5	68	15	0	0	5
120	28	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	1	1	1	0	0	0	0	0	6	0	1	0	0	10	15	0	1	5	12	2	0	0	0	15	0	0	0	5	6	15	0	0	5
121	60	1	1	1	0	0	0	0	0	0	0	0	1	0	0	1	1	4	0	0	15	2	1	2	1	0	0	0	0	0	7	0	0	0	0	7	15	0	1	5				0	0										
122	27	1	1	1	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	15	1	0	1	3	0	0	0	0	0	4	0	0	0	0	4	15	0	1	5	13	2	0	0	0	15	0	0	1	5	14	15	0	0	5
123	55	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	15	1	1	2	1	0	0	0	0	0	13	0	0	0	0	4	15	0	1	5	24	1	0	0	0	15	0	0	0	5	12	15	0	0	5
124	52	1	1	1	0	0	1	0	0	0	0	0	1	0	0	1	1	0	0	0	14	2	4	1	3	0	0	0	0	0	10	0	0	0	0	2	15	0	1	5	6	2	0	0	0	15	0	0	1	5	7	15	0	1	5
125	55	1	1	1	0	1	0	0	1	1	0	0	0	1	0	0	1	0	0	0	15	1	1	2	2	0	1	1	0	0	5	0	0	0	0	2	15	0	1	5	22	2	0	0	0	15	0	0	1	5	72	15	0	0	5
126	63	1	1	0	0	1	1	0	0	0	0	0	0	0	0	1	1	0	0	0	14	2	1	1	1	0	0	0	0	0	5	0	0	0	0	3	15	0	1	5	12	2	0	0	0	15	0	0	1	5					
127	14	2	1	1	1	1	1	0	1	0	0	0	1	0	0	0	0	0	0	0	14	2	0	1	3	0	1	0	0	0	2	0	0	0	0	3	15	0	1	5	37	1	1	0	0	14	1	1	6	1	9	14	1	6	1
128	55	2	1	1	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	15	1	0	1	4	0	1	1	0	0	4	0	0	0	0	3	15	0	1	5	4	2	0	0	0	15	0	0	1	5					
129	60	2	1	1	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	15	1	3	2	1	0	0	0	0	0	7	0	0	0	0	4	15	0	1	5	59	2	0	0	0	15	0	0	0	5	82	15	0	0	5
130	52	2	1	1	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	15	1	3	2	1	0	0	0	0	0	7	0	0	0	0	4	15	0	1	5	59	2	0	0	0	15	0	0	1	5	82	15	0	0	5
131	55	2	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	13	2	0	1	3	0	1	0	0	0	2	0	0	0	0	5	15	0	1	5															
132	53	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	15	1	1	3	1	0	0	0	0	0	11	0	0	0	0	2	15	0	1	5	72	2	0	0	0	15	0	0	0	5	74	15	0	0	5
133	60	1	0	0	0	0	0	1	0	0	0	0	0	0	0	1	1	0	0	0	15	1	0	2	1	0	0	0	0	0	3	0	0	0	0	2	15	0	1	5				0	0										
134	68	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	0	1	3	0	1	0	0	0	4	0	0	0	0	3	15	0	1	5	20	2	0	0	0	15	0	0	1	5	5	15	0	0	5
135	62	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	15	1	4	2	1	0	0	0	0	0	5	0	0	0	0	2	15	0	1	5				0	0										
136	59	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	0	2	1	0	0	0	0	0	16	0	0	0	0	2	15	0	1	5	31	2	0	0	0	15	0	0	0	5	5	15	0	0	5
137	50	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	0	2	1	0	0	0	0	0	3	0	0	0	0	2	15	0	1	5				0	0										
138	54	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	7	1	4	0	1	1	0	0	10	0	1	0	0	3	15	0	1	5	10	2	0	0	0	15	0	0	1	5	10	15	0	0	5
139	48	2	1	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	15	1	1	1	1	0	0	0	0	0	6	1	0	0	0	3	15	0	1	5	5	2	0	0	0	15	0	0	1	5					
140	68	2	1	1	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	14	2	0	1	4	0	0	1	0	0	13	0	0	0	0	3	15	0	1	5	11	1	1	1	0	15	0	0	2	5	12	15	0	2	4
141	60	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	15	1	0	2	1	0	1	0	0	0	2	0	0	0	0	2	15	0	1	5	7	2	0	0	0	15	0	0	1	5	18	15	0	0	5
142	62	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	15	1	0	2	1	0	0	0	0	0	5	0	0	0	0	3	15	0	1	5	10	2	0	0	0	15	0	0	0	5	3	15	0	0	5
143	52	1	1	1	0	1	0	0	0	1	0	0	1	1	0	0	1	0	0	0	15	1	1	2	1	0	0	0	0	0	7	0	0	0	0	2	15	0	1	5	14	2	0	0	0	15	0	0	0	5	141	15	0	0	5
144	53	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	1	2	1	1	0	0	0	0	0	4	0	0	0	0	2	15	0	1	5															