From the department of Neurosurgery

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University of Regensburg

Cerebral aneurysms - Facts and Conflicts:

State-of-the-Art-Outcome (New Scoring System)

Inaugural Dissertation

Submitted in fulfillment of the requirements for the doctor degree

In Human Medicine

by

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MB Bch, M.Sc. Neurosurgery

Regensburg

2019

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Tag der mündlichen prüfung: May 6th, 2019

Statutory declaration

I hereby declare that I have written this PhD thesis independently in my own unaided work, that I have not used other than the sources indicated, and that all direct and indirect sources are acknowledged as references. I have carried out my scientific work according to the principles of good scientific practice in accordance with the current rules of Regensburg University. This PhD thesis has not been submitted for conferral of degree elsewhere.

Regensburg 2018
Bahaa Hassanin

To my parents, my wife Rahma and my doughter Farida

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Abbreviations

2D	= Two-dimensional
3D	= Three-dimensional
ACA	= Anterior cerebral artery
AChoA	= Anterior choroidal artery.
AcomA	= Anterior communicating artery
AHA	= American heart association
ASDH	= Acute subdural hemorrhage
AVM	= Arteriovenous malformation
CNS	=Central nervous system
CSF	= Cerebrospinal fluid
CT	= Computerized tomography
CTA	= Computerized tomography angiography
DCI	= Delayed cerebral ischemia
DSA	= Digital subtraction angiography
EEL	= External elastic lamina
EEG	=Electroencephalogram
IA	= Intracranial aneurysm
ICA	= Internal carotid artery
ICH	= Intracerebral hematoma
IEL	= Internal elastic lamina
ISAT	= International Subarachnoid Aneurysm Trial Study
ISUIA	= International Study of Unruptured Intracranial Aneurysms
IV	=Intra venous
MCA	= Middle cerebral artery
MRA	= Magnetic resonance angiography
MRI	= Magnetic resonance imaging
NF	=Neurofibromatosis
NMR	=Nuclear magnetic resonance
OphA	=Ophthalmic artery
PcomA	= Posterior communicating artery
PET	=Postion emission tomography
PICA	=Posterior inferior cerebellar artery
SAH	= Subarachnoid hemorrhage
SMC	= Smooth muscle cells
TCD	=Trans cranial doplar
US	= Ultrasonography

Zusammenfassung

Hintergrund:

Der am häufigsten benutzte Ergebniswert für die Bewertung der Behandlung cerebraler Aneurysmata ist der Glasgow Outcome Score (GOS). Dieser Score zeigt jedoch lediglich die Sicherheit der Behandlung an, wobei dessen Effizienz außer Acht gelassen wird. Ein unvollständig okkludiertes Aneurysma ist jedoch eine der Hauptursachen für eine verminderte Lebensqualität der Patienten (lebenslange Kontrolle oder erneute Behandlung, gesteigertes Blutungsrisiko). Daher schlagen wir ein neues Ergebnis-Scoring-System (BRS) vor, das auf dem konventionellen GOS basiert und nun zusätzlich den Grad der Okklusion des Aneurysma enthält.

Zielsetzungen:

1- Das Grundwissen über die zerebralen Aneurysmen mit einer kurzen zusammenfassendenden Betrachtung von Konfliktbereichen zu überprüfen um den aktuellen Forschungsstand bezüglich cerebraler Aneurysmen zu kennen um die zukünftigen Forschungstrends abzuleiten.

2- Wissenschaftliche Evaluation durchzuführen, um einen dieser Konflikte zu lösen und um eine neue Skala zu entwickeln welche das Ergebnis der Behandlung cerebraler Aneurysmen bewertet.

Material und Methoden:

Wir haben unsere institutionelle Datenbank konsultiert und 532 Patienten (mit 622 Aneurysmen) identifiziert, bei denen mindestens ein cerebrales Aneurysma mit Clip oder Coil behandelt wurde. Wir haben alle für die neue Beurteilung erforderlichen spezifischen Daten (BRS - kombinierter Score: GOS + Okklusionsgrad) extrahiert: die neurologische Leistung und den Grad der Okklusion des Aneurysma (basierend auf der postoperativen Rotationsangiographie (Okklusionsgrad: vollständig = A; kleiner Rest ≤ 3 mm = B; großer Rest> 3 mm = C)).

Ergebnisse:

- <u>Bei innozenten Aneurysmen:</u>

GOS, Clipping Gruppe: 5=98.8% (n=166), 4=1.2% (n=2). GOS, Coiling Gruppe: 5=95.9% (n=139), 4=4.1% (n=6). BRS score, Clipping Gruppe: 5A=79.2% (n=133), 4A=1.2% (n=2), 5B=15.5% (n=26), 5C=4.2% (n=7). BRS score, Coiling Gruppe: 5A=64.8% (n=94), 4A=0.7% (n=1), 5B=14.5% (n=21), 4B=2.1% (n=3), 5C=17.9% (n=26).

- <u>Bei rupturierten Aneurysmen:</u>

GOS, Clipping Gruppe: 5=61.5% (n=80), beeinträchtigtes Patientenergebnis=24.7% (n=32), Coiling Gruppe: 5=62% (n=111), beeinträchtigtes Patientenergebnis=17.3% (n=31).

BRS score, Clipping Gruppe: 5A=56.2% (n=73), 5B=2.3% (n=3), 5C=3.1% (n=4). 4A=4.6% (n=6), 4B=0.8% (n=1), 3A=13.8% (n=18), 3B=0.8% (n=1), 2A (n=4.6%).

Coiling Gruppe: 5A=33% (n=59), 5B=18.4% (n=33), 5C=10.6% (N=19), 4A=3.4% (n=6), 4B=3.4% (n=6), 4C=1.1% (n=2), 3A=5% (n=9), 3B=3.4% (n=6), 2A=0.6% (n=1), 2C=0.6% (n=1) .

Im Vergleich mit dem GOS hatte der BRS eine signifikant höhere Sensitivität und Spezifität, um die Effizienz der Behandlung vorherzusagen. Nach dem BRS erreichten signifikant mehr

Patienten nach dem Clipping den höchsten Grad (5A) als nach dem Coiling ($p < 0,05$).

Fazit:

Unsere neuen Scores (BRS- und Extended BRS), die die neurologische Leistung und die radiographisch bestätigte Okklusion kombinieren, sind einfach anzuwendende Graduierungen um das Ergebnis nach der Behandlung cerebraler Aneurysmata präzise vorherzusagen.

Aims of the study:

1- Review basic knowledge about the cerebral aneurysms, with brief telescopic view on areas of conflicts, to know the current state of research regarding the cerebral aneurysms to conclude what the future research trends should be.

2- Conduct scientific research to solve one of these conflicts to evolve a new scale to evaluate the outcome of cerebral aneurysms treatments.

1. Introduction

Cerebral aneurysms are focal dilatations of the intracranial arteries, which usually occur at their branching points. Most cerebral aneurysms remain asymptomatic and never rupture. When an IA ruptures, it may bleed into the brain parenchyma resulting in a parenchymal hemorrhage, or more often it will bleed into the subarachnoid space, resulting in a subarachnoid hemorrhage (SAH). [25]

Aneurysms are not a disease unique to modern society. Both ancient literature and bony artifacts dating back to ancient Egypt indicate occurrences of aneurysms and at least some extracranial aneurysms were treated. Despite occasional reports, cerebral aneurysms were not well-recognized as a cause of human illness until the end of the 19th century. [19]

Intracranial aneurysms are relatively common, with a prevalence of approximately 6%. There are four main types of intracranial aneurysms: saccular, fusiform, dissecting, and mycotic type. The saccular type accounts for 90% of intracranial aneurysms, 85% of which arises from the arteries of the anterior cerebral circulation. [24, 32]

A SAH is a catastrophic medical event with a mortality rate of 25% to 50%. Permanent disability occurs in nearly 50% of the survivors, thus, only approximately one-third of patients who suffer from a SAH have a positive outcome. [25, 30, 43] The clinical manifestations of unruptured aneurysms are much more subtle, with the majority being identified incidentally during evaluation for other conditions. [38, 148]

Symptoms related to unruptured aneurysms mainly occur due to a mass effect, but the real danger is when an aneurysm ruptures, leading to a subarachnoid hemorrhage. Although most cerebral aneurysms are asymptomatic and will not rupture, they grow unpredictably and even small aneurysms carry a risk of rupture. [111,112]

There is a great conflict and controversy surrounding the natural history of unruptured aneurysms. It is such a hot topic because knowing the likely course of aneurysms will play a pivotal role in determining the appropriate management. Prior to 1998, the estimated rate of rupture for aneurysms was 1 to 2.5% per year. This value indicates that over many years, the risk of rupture is very significant, and therefore, surgical or endovascular treatment is appropriate in patients with incidental aneurysms [135]. Treatment options include observation, endovascular coiling, and surgical clipping; microsurgical clipping has been used for the treatment of intracranial aneurysms for longer than 40 years and endovascular coiling devolped a lot in the past 20 years. Both neurosurgeon and neurointerventioists appreciate their methods of treating cerebral aneurysms, with all reports comparing both modality outcomes to be good. [75, 79, 86]

2. Review of literteur:

2.1 Pathophysiology;

2.1.1 Epidemiology;

Studies have shown that IAs are common and the overall incidence ranges from 0.4% to 10%, e.g. in the German population approximately 1.5–2 million people are assumed to harbour a cerebral aneurysms. Frequency increases with age beyond the third decade; incidence is rare in the pediatric population and is approximately 1.6 times more common in women. The risk of harbouring IAs is 2-4 times higher in families with two or more members with a history of IAs. Most IAs occurrences are sporadic and only less than 10% of patients have a family history of aneurysms. About one-third of all patients with IAs have multiple aneurysms. (72, 95)

Although the incidence of IAs is comparable worldwide, their rupture rates are different. The incidence of aneurysmal SAH in most populations is 6–10 cases per 100,000 person/year; in united state about 30,000 people suffer a brain aneurysm rupture every year. In other words, there is a brain aneurysm rupturing every 18 minutes. The rupture rate increases in Finland, Japan and Northern Sweden, the incidence is 10–16 cases per 100,000 person/year. This higher incidence may be due to environmental or genetic factors, but reason still remains unknown. (116,122)

2.1.2 Hypothesis for intracranial aneurysms formation:

The majorities of intracranial aneurysms are not considered to be congenital as it has been assumed in the past, but it is generally accepted that IAs are acquired lesions, the actual mechanism of their formation is unknown. (115)The popular theory of a congenital defect in the tunica media of the muscle layer as a weak spot through which the inner layer of the arterial wall would bulge has had doubt cast upon it due to a number of contradictory observations: Gaps in the muscle layer are equally present in patients with and without aneurysms. If an aneurysm has formed, defect in the muscle layer is not located at the neck, but somewhere in the aneurysmal wall of the sac. (6,115)

The most plausible pathogenetic theory is that they are acquired due to hemodynamic stress on the relatively unsupported bifurcations of cerebral arteries. This is supported by the clinical observation that many patients with an anterior communicating artery (Acom) aneurysm do have one hypoplastic or absent Al segment and thus an increased hemodynamic stress on the AcomA occurs. Other factors than hemodynamics and structural alterations of the vessel wall contributing to the development of saccular aneurysms may be genetic, infection, vascular trauma, neoplasms, radiation or idiopathic. (6, 83,120)

The role of acquired changes in the arterial wall, in adults, is more likely to happen because there are general risk factors for both subarachnoid hemorrhage (SAH) and development of the aneurysms like hypertension, smoking and alcohol abuse. These factors might contribute to general thickening of the intimal layer in the arterial wall, distal and proximal to branching sites. These “intimal pads” are probably the earliest stages of aneurysm formation. Within these pads, the intimal layer is inelastic and therefore causes increased strain of the more elastic portions of the vessel wall. Abnormalities in structural proteins of the extracellular matrix additionally contribute to aneurysm formation. However, it is not

known why only some adults develop aneurysms at arterial bifurcations and most do not. (115,120,126,157)

Inflammation has been found to have a principal role in the process of IA formation and subsequent rupture. Aspirin with its anti-inflammatory effects was found to be effective in decreasing the risk of aneurysm formation and subsequent SAH without increasing the risk of intracerebral hemorrhage. Aspirin might be a promising prophylactic drug against IA growth and rupture. (28,134)

Many hereditary connective tissue diseases have been associated with formation of aneurysms, most likely as a result of the weakening of the vessel wall. Cerebral aneurysms may develop in 10%–15% of patients with polycystic kidney disease, an autosomal dominant disorder. Although Marfan syndrome was previously identified as a risk factor for aneurysms, recent studies do not identify any significant correlation. Coarctation of the aorta, fibromuscular dysplasia and pheochromocytoma are associated with intracranial aneurysms, most likely because of the elevated blood pressure that occurs under such conditions. There are some presumptions on neurofibromatosis type 1 (NFl) and intracranial aneurysms. In a recent study, an association between NFl and intracranial aneurysms has never been identified in large clinical studies and that there is no evidence for any association between NFl and intracranial aneurysms. (21, 96,117)

Also, it is suggested that the formation of an intracranial aneurysm is a consequence of a systemic vascular pathology, which is associated with pleomorphism in different candidate genes. Understanding of the mechanisms behind the formation of IAs can provide an opportunity for the development of pharmacological therapy for IAs. (83,115,157)

2.1.3 Genetics of intracranial aneurysms;

Many genetic studies have aimed to determine if some genetic variants predispose individuals to the development of IAs. Multinational genome-wide association studies have defined five loci with strong statistical evidence and another 14 loci with suggestive evidence of an association with IAs. 5q26 is one suggestive risk locus for IAs which was also found to be associated with a risk of high systolic blood pressure. Besides, 9p21, which is a general cardiovascular risk locus, was found to be a strong risk locus for IAs. This overlapping genetic background suggests that the formation of IAs might be a part of generalized vasculopathy rather than a separate disease. (41,155)

Prevalence of intracranial aneurysms among first-degree relatives of patients with cerebral aneurysms or a SAH is higher than in the general population, with the risk of harbouring an aneurysm is about three to four times higher than the general population. (115)

Familial aneurysms are generally larger at time of rupture and more likely to be multiple than sporadic aneurysms. Cerebral aneurysms in patients with a positive family history might result from a mesenchymal defect affecting the cerebral vessel wall produced by a lesion of chromosome 16. (41)

2.1.4 Histology of intracranial aneurysms:

The wall of cerebral arteries is composed of three histologic layers: tunica intima, tunica media and tunica adventitia. The internal elastic lamina (IEL) separates the tunica intima and

tunica media. The wall of cerebral arteries differs from that of extracranial arteries in that it lacks the external elastic lamina (EEL) normally present in extracranial arteries between the tunica media and the tunica adventitia. Additionally, the cerebral arteries have a paucity of supportive perivascular tissues and fewer smooth muscle cells (SMC) in the tunica media and in IEL than extracranial arteries. Moreover, at the bifurcation of cerebral arteries which is the typical location for the formation of IAs, the tunica media consists mainly of collagen arranged in such a way that it increases resistance to mechanical stress. So the internal elastic lamina is an important layer of the arterial wall in the cerebral vessels. Thus, disruption of this layer due to alterations in hemodynamic and histological characteristics, would promote the formation of aneurysms especially at the regions around the bifurcations. In Helsinki, Frosen et al., four histological wall types for IAs are identified: type A, an endothelialized wall with linearly organized SMC; type B, a thickened wall with disorganized SMC; type C, a hypocellular wall; and type D, an extremely thin thrombosis- lined hypocellular wall. These types probably reflect consecutive stages (A through D) of degeneration suggesting a dynamic nature to the IA wall. [39, 75,134]

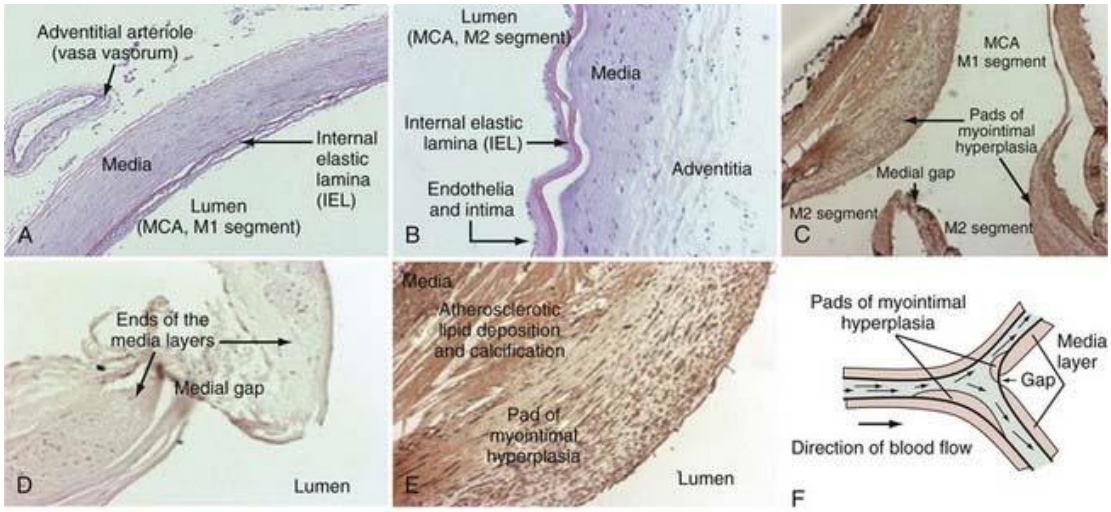


Figure (1) Histology of the intracranial arteries depicting three layers of the intracranial wall (A and B) and the presence of medial gaps and pads of myointimal hyperplasia (C-E). F, drawing showing the relative locations of medial gaps and pads of myointimal hyperplasia at a vessel bifurcation.MCA, middle cerebral artery. (From Frosen J. The Pathobiology of Saccular Cerebral Artery Aneurysm Rupture and Repair: University of Helsinki; 2006).

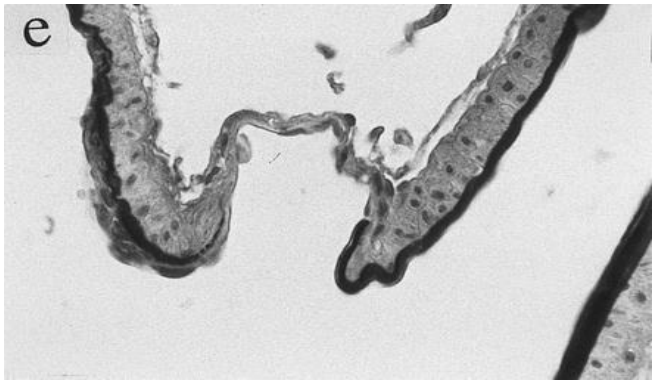


Figure (2) Saccular aneurysm, the thinning or the disappearance of the medial smooth muscle layer and the fragmentation or the absence of the internal elastic lamina are observed (elastica van Gieson stain, magnification ×100).

2.1.5 Morphology and classification of intracranial aneurysms:

Classification of intracranial aneurysms can be based on morphology, size, location and etiology. Usually, intracranial aneurysms are divided into three basic types: saccular aneurysms when the protrusion is pouch-like or fusiform aneurysms when circumferential involvement of the parent artery occurs without a definite base or neck and dissecting aneurysms with unknown true prevalence. Traumatic, infectious or tumor-associated aneurysms are rare. (25, 26)

2.1.5.1 Saccular aneurysms:

Most cerebral aneurysms (66%–98%) are saccular and arise at arterial branching sites**.** They can arise as solitary (70%–75%) or multiple (25%–30%) vascular lesions. The majority of cerebral aneurysms (85%) are located in the anterior and only 15% are located in the posterior circulation. (25,156)

Size:

Saccular aneurysms may be divided into three, i.e. small, medium and large, four, five and even six groups. The most applicable is the five groups classification adapted by Yasargil: (153,154)

1) Baby aneurysms (<2mm) (discovered during operative dissections)
2) Small size (2- 6mm).
3) Medium size (6-15 mm).
4) Large size (15-25 mm).
5) Giant aneurysms (25-60 mm). (7,154)

Appearance:

The neck of the saccular aneurysm may be small (1-3 mm) or large (4-10 mm) and well defined or not defined at all.(154) The variable Uni, bi or multilobular configurations with and without single or multiple thin or thick walled and even with well-defined secondary aneurysms are seen. Although small aneurysms are generally thought to have thin walls and the larger aneurysms increasingly thicker walls, it is not infrequently found unusual varieties. Usually the neck of an aneurysm has a thicker wall than the fundus and dome, but here again variations are also occurred. Each aneurysm appears to have its own "structural dynamics" or "natural history of development**".** (94,129)

2.1.5.2 Aneurysms Associated with Arteriovenous Malformations:

There is an increased incidence, or better, an increased amount of visible aneurysms associated with arteriovenous malformations. The incidence of these aneurysms in AVMs is up to 25%. Approximately 50% of these aneurysms are located on a feeding artery, 25% within the nidus. (14,123)

Flow related aneurysms probably develop due to hemodynamic stress caused by increased flow and pressure, with subsequent dilatation and pathologic changes in feeding arteries. AVM-associated aneurysms contribute to an increased risk of hemorrhage. A 7% risk of hemorrhage for these combined lesions is estimated compared to a 1.7%–3% risk for AVMs without associated aneurysms. (90)

In case of rupture, the hemorrhage is more often located intraparenchymally than subarachnoidally. Management of these combined lesions is still debatable. In fact,

hemodynamics change after elimination of the AVM might place the aneurysm at risk. On the other hand, proximal asymptomatic aneurysms may regress after removal of the AVM. However, aneurysms located in the posterior circulation associated with an AVM are at higher risk of rupture and therefore should be treated as soon as possible even if they had not ruptured before. (14, 90,130)

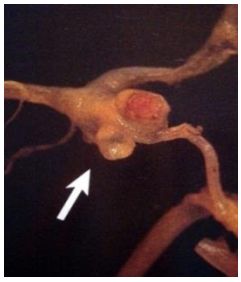


Figure (3) Gross pathology specimen demonstrating saccular aneurysm (arrow), that arises at ICA- PComA Junction. Osborn et al., 1994

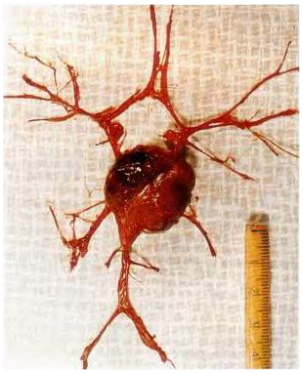


Figure (4) Autopsy of unrecognized basilar bifurcation aneurysm in 2years child, Yasargil 1984

2.1.6 Rupture of intracranial aneurysms:

Most cerebral aneurysms remain clinically silent until they rupture. The International study of unruptured intracranial aneurysms (ISUIA) has been the most comprehensive clinical study of its kind to date, sseveral factors related to the patient and aneurysm-specific characteristics have been examined as possible predisposing factors for the rupture of IAs. In phase II of ISUIA, a higher rupture rate was reported to be associated with larger aneurysms, location in the posterior circulation, and previous history of SAH. (106)

2.1.6.1 Patient-related risk factors:

Prevalence of aneurysms and rupture risks were shown to increase in both studies due to the factors such as age of the patient; this risk increases accumulatively with age to peak between 40–65 years of age, pre-existing familial conditions, in patients with a family history of SAH, IAs rupture at a younger age. (33, 58) hypertension is the most frequently reported health condition associated with the formation of IAs and their subsequent rupture and was also found to be a risk factor for multiple IAs and for the rupture of small sized IAs. Smoking has been also associated with higher prevalence aneurysms and its rate of rupture. High alcohol consumption, cocaine use has been found to be significantly associated with aneurysmal SAH. (67,106)

IAs are more commonly diagnosed in women than in men. Furthermore, aneurysmal SAH is more common in women. IAs, in women, carry a higher risk of rupture especially after menopause, which is probably related to the hormonal effects of estrogen on the vascular wall. (28, 50)

2.1.6.2 Aneurysm-related risk factor:

Although aneurysm size has traditionally been considered a risk factor for the rupture of IAs, a single threshold value for an increased rupture risk has not been defined. Many studies have reported a significantly higher risk of rupture for saccular IAs larger than 10 mm compared to smaller aneurysms. The ISUIA reports that the rupture rate for aneurysms smaller than 7 mm was significantly lower than for those larger than 7 mm. However, in clinical experience, it is obvious that many small aneurysms do rupture and about 1/3 of all ruptured aneurysms were smaller than 7 mm in size. (102,148)

Location of the aneurysms has been considered a risk factor for rupture, where posterior circulation aneurysms and aneurysms arising from the posterior communicating artery (PcomA) have a higher risk of rupture relative to anterior circulation aneurysms. Among anterior circulation aneurysms, Acom aneurysms have been reported to have the highest rupture rate, while MCA aneurysms had the lowest rupture rate. (13, 148)

More recent studies focus on morphological characteristics of aneurysms to predict rupture risks. Several geometric indices, measured by using three-dimensional rotational angiography or digital subtraction angiography correlate with increased rupture rates. (119) The two highest indicators were the aspect ratio (the ratio of the aneurysm's height to its neck) and the volume to neck ratio.(148) other noted two factors include presence of daughter sacs and the non-sphericity index, were strong predictors of aneurysm rupture as well. (102)

2.1.6.3. Mechanism of rupture of intracranial aneurysms;

It can be concluded that the growth potential of an individual aneurysm is unpredictable and as a result, no aneurysm regardless of size can be considered safe from enlargement and rupture over any period of time. IAs increase in size through real growth rather than stretching which attenuates the wall. Thus, aneurysm size might depict only the degree of wall growth, but not its strength. Wall morphology, on the other hand, correlates more strongly with the quality of wall growth and its resistance to rupture. (22,136)

It is generally accepted that rupture occurs when the intra-aneurysmal hemodynamic stress surpasses its wall resistance. (67,119,148) other factors, such as complement activation and protein kinases are involved in IA growth and rupture. Although several hypotheses have been postulated to explain this association, the underlying mechanism is still unproven. Histological, genetic, immunological and molecular biologic studies are still needed to explain the relationship between the morphological characteristics of IAs and their rupture. Besides, large-scale clinical studies are needed to evaluate the predictive value of other morphological variables related to the risk of rupture. (87)

2.1.7 Spontaneous Thrombosis of Cerebral Aneurysms:

Although not frequently, various degrees of thrombosis may occur within aneurysms of any size, but thrombosis within larger lesions is more common. The histopathological series clearly demonstrate that thrombus formation on luminal surface of the aneurysm wall is part of the wall degeneration with the first degenerative change is the loss of intact endothelial layer, which leads to the formation of the fibrin network and thrombus on the exposed collagen surface. Thrombosis within an aneurysm is important with regard to both the

increased difficulty of management and the possible treatment of aneurysms without intracranial procedures by the initiation of thrombosis within the lesion. Luminal thrombus formation induction in the aneurysm fundus can prevent later rupture if the thrombus becomes stable and organized into fibrous tissue. However, up to 20% of embolized aneurysms, recanalization occurs on follow up, and may regrow and rupture due to thrombus organization failure. (34,154)

There is no evidence that an aneurysm found at angiography or computerized tomography to contain some thrombus will go on to complete thrombosis and the degree of protection against rupture or rerupture afforded by thrombosis unfortunately, cannot at present be stated with certainty. (34,154)

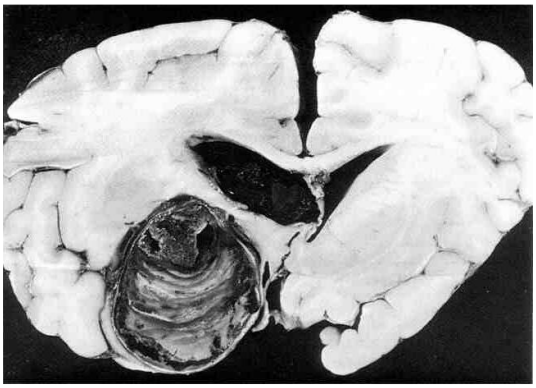


Figure (5) Intraventricular hemorrhage and death was caused by the rupture of this almost completely thrombosed right internal carotid bifurcation aneurysm in a 48 year old man, yasargil 1984

2.2 Clinical Presentation:

The clinical presentation of an intracranial aneurysms depends on several factors, mainly the location of the aneurysm, its size, whether it ruptures or not and if it does, the amount of bleeding resulting from its rupture, the site of bleeding, the presence or absence of additional complications.(76, 92) Accordingly, patients with cerebral aneurysms may experience the following:

1) Warning premonitory signs and symptoms
2) Rupture of the aneurysms.
3) Unruptured symptomatic aneurysm.
4) Unruptured asymptomatic aneurysms. (87)

2.2.1 Aneurysmal SAH:

Most intracranial aneurysms remain silent till the time of rupture. SAH, a medical neurologic emergency, is by far the most common initial clinical presentation. A history of abrupt onset of a severe headache of atypical quality (“the worst headache in my life”) is typical of SAH. Headache onset may or may not be associated with brief loss of consciousness, nausea and vomiting, focal neurologic deficits or meningism.(76,98,146) the rupture of an IA is the main cause of nontraumatic SAH, accounting for around 80% of all cases, and responsible for 2–5% of all new strokes. The mean age at presentation is 55 years with an increasing incidence with age. Women are at a 1.6 times higher risk of experiencing aneurysmal SAH than men. (37,139)

There may be a small number of SAH that functions as a “warning leak” or sentinel hemorrhage, usually associated with milder symptoms, which is only a sudden severe headache. In general, there is a correlation between the extent of SAH and the clinical grade, incidence of vasospasm, and other complications such as cerebral ischemia, increased intracranial pressure, and hydrocephalus. With increased severity of SAH there are increasing changes in physiologic parameters such as reduced cerebral blood flow (due to reduced cerebral autoregulation), hypovolemia, hyponatremia, hypermetabolism and cardiac arrhythmia. Stopping of a SAH is caused by a combination of tamponade due to reduced transmural pressure gradient across the arterial wall and coagulation. (59, 76, 92,136)

2.2.1.1 Rebleeding after SAH:

Rebleeding is a frequent and sometimes devastating neurologic complication of SAH which clinically coexist with new neurologic deficits, increasing headache, vomiting and a decreased level of consciousness. It is postulated to be due to breakdown of perianeurysmal clots as clot formation and tissue damage stimulate fibrinolytic activity in the CSF. The efficacy of antifibrinolytic therapy such as aminocaproic acid and tranexamic acid to prevent rebleeding showed a significantly decreased incidence of rebleeding, however, mortality was not altered, but this therapeutic approach was associated with an increased risk of delayed cerebral ischemia, embolism, and deep venous thrombosis. (86,114)

The peak incidence of rebleeding is during the first day, a secondary peak occurs a week after SAH. Early rebleeding in the first hours after admission for the initial hemorrhage with clinical deterioration occurs in up to 18% of patients. (40) Since these early rebleedings commonly occur before the first CT scan is obtained, the true frequency of early rebleeding is definitely underestimated. As many as 20% of patients may rebleed within the first 2 weeks, one third in the first month, and 50% will rebleed within 6 months, if the aneurysm is not treated and the mortality of recurrent SAH is 50%. (86,143,156)

Women have a 2.2 times higher recurrence rate of hemorrhage than men. The worse the clinical grade on admission, the more likely rebleeding occurs. Hypertension increased the likelihood of rebleeding among patients. Of patients with a diastolic blood pressure below 90 mm Hg, 25% rebleed, whereas of those with a diastolic pressure above 109, 75% rebleed. Older patients are more prone to rebleeding. Aneurysms pointing down are less likely to rebleed than those pointing up in the direction of the jet stream of the blood. Short broad aneurysms rebleed more frequently than long narrow aneurysms. Posterior communicating artery aneurysms rebleed at a higher rate than do anterior communicating artery and vertebrobasilar aneurysms. (114,132)

2.2.1.2 Vasospasm related to SAH:

Vasospasm is a major cause of morbidity and mortality in patients after SAH and is often associated with delayed cerebral ischemia. However, many patients are asymptomatic despite various degrees of angiographically visible vasospasms. Although vasospasm is noted angiographically in 70% of patients after SAH, it becomes symptomatic only in about half of those patients. This difference probably suggests additional factors determining whether and where secondary cerebral ischemia occurs like the degree of arterial narrowing,

its location and the adequacy of collateral blood flow, as well as other factors such as increased intracranial pressure or the presence of cerebral oedema. [69]

Unlike rebleeding, the clinical presentation of vasospasm develops slowly over hours up to days. The onset being rare before the third post-ictal day, with a peak incidence at about the seventh day, between day 4 and 12, it rarely persists for longer than 3 weeks after SAH. [49, 78]

Vasospasm is best detected on angiograms. However, transcranial Doppler ultrasound is the method of choice to monitor blood flow velocities in patients after SAH. CTA and MRA role has not been determined in this subgroup of patients. A CT perfusion is feasible in detecting vasospasm and might even predict outcome. [55, 56]

Despite intensive research, the pathogenesis of vasospasm has not been entirely elucidated. Releases of yet unidentified factors into the subarachnoid space are considered to induce vasospasm and subsequent cerebral ischemia. There is a widespread postulation of a close relationship between the amount of subarachnoid blood clots and the degree of vasospasm and delayed cerebral ischemia. However, there are several arguments against these assumptions; subarachnoid blood is not a predictor of vasospasm perse, since vasospasm and delayed cerebral ischemia rarely occur in patients with SAH after rupture of an AVM or perimesencephalic SAH, one would expect a lower incidence of vasospasm after clipping compared to coiling, since there is no way to remove a subarachnoidal clot during coiling. But this effect has not been observed. Furthermore, the site of delayed cerebral ischemia does not always correspond with the distribution of subarachnoid blood. [55, 57]

2.2.2 Interparynchymal Hematoma:

Intracerebral hematoma (ICH) occurs in up to 30% of patients with aneurysmal rupture. The outcomes for those patients were found to be worse than SAH alone. It was reported in one cooperative study that ICH was present in 90% of patients who died within 72 hours of the aneurysmal SAH ictus. Acute subdural hematoma (SDH) is usually associated with recurrent aneurysmal rupture. However, SDH can also occur with the initial SAH or can be the only extravascular space involved after aneurysmal rupture. [128,140]

2.2.3 Unruptured Aneurysms:

Asymptomatic aneurysms may be defined as additional aneurysms found in patients with another symptomatic aneurysm, which are not responsible for the clinical symptoms or those aneurysms found in patients investigated because they are at risk of harbouring an aneurysm and those found unexpectedly in patients undergoing investigation for any other suspected pathology or unrelated clinical symptoms. [74]

Depending on the location of an unruptured aneurysm it can be completely asymptomatic. On the other hand, unruptured aneurysms can cause neurologic symptoms while touching or transmitting pulsation to cranial nerves or other cerebral structures. Symptoms can be pain, cranial nerve palsies, visual disturbances, dysesthesia, vertigo and seizures. Thromboembolism ischemic events can occur distal to both small and large unruptured intracranial aneurysms (predominantly in the anterior circulation) were observed in 3.3%. [101]

Symptomatic unruptured aneurysms are usually larger than incidental aneurysms and are often discovered near to the skull base where they are more likely to affect cranial nerves. The most frequent affected cranial nerves are the ocuoculomotor nerve and the optic nerve. (74,100)

Given the high mortality and morbidity associated with an aneurysm rupture, it is crucial to determine the likelihood of rupture to decide whether to treat an aneurysm or not. The findings of the ISUA have a lot of criticism and failed to solve these issues. (74,148)

2.3 Diagnostic Studies of intracranial aneurysms:

Cerebral angiography was introduced in 1927 (Moniz), and has been the mainstay of diagnosis in cerebral aneurysms ever since. In the past, the purpose of angiography has been two folds: to define the aneurysm and the anatomical and physiological state of the blood vessels associated with it, and to detect hematoma, hydrocephalus and brain shifts associated with rupture of the aneurysm. (2, 53, 80) with the coming of computerized tomography, there has necessarily been a change in the application of angiography to patients with ruptured cerebral aneurysm. While angiography remains the most accurate method of delineating an aneurysm, determining the presence of multiple aneurysms, and of assessing the cerebral circulation, CT has proved more useful in defining the real size of an aneurysm in determining the degree of thrombosis, and in evaluating associated hydrocephalus, infarction, and intracerebral hematomas. (2, 153, 154)

2.3.1 Computed Tomography.

Currently, the diagnosis of intracranial aneurysms on the CT scan is only approximate, as only angiography gives in most of the cases a clear picture. However, the CT diagnosis of aneurysms down to 6 mm in size has been possible and also Thrombus within an aneurysm is usually well shown by CT. (2, 53)

By good discrimination between relatively similar densities within the cranial vault, CT is the initial diagnostic imaging modality of choice and clearly the gold standard to identify, localize and quantify subarachnoid hemorrhage and to portray many of the pathogenetic sequelae of ruptured cerebral aneurysm i.e. hydrocephalous, ischemia. (80,154)

CT sensitivity for detecting SAH depends on the volume of the extravasated blood, the hematocrit, and the time elapsed after the acute event. With modern CT scanners, within the 24 h after the ictus CT detects SAH in up to 95%. However, due to dilution by CSF the density of the hemorrhage decreases rapidly over time, thus after only a few days it may be impossible to demonstrate subarachnoid blood on CT. (102) Sensitivity of CT decreases to 80% at day 3, to 70% at day 5, to 50% at 1 week, and to 30% at 2 weeks. (109)

The pattern of SAH can suggest the location of the underlying aneurysm i.e. sylvian SAH suggest MCA aneurysms, interhemispheric for Acom. (62,154) and in cases of multiple aneurysms the presence of localized hematoma or infarction may suggest which of the lesions has bled. (154)

Fisher et al. (1980) provided a description for a correlation between the amount and distribution of subarachnoid blood after aneurysmal rupture on the initial CT, with subsequent occurrence of vasospasm demonstrated by angiography. Since then, the CT-

based Fisher classification of quantifying local amounts of subarachnoid blood as a powerful predictor for the occurrence of vasospasms and delayed cerebral ischemia has been confirmed by several clinical and experimental studies.[89, 124] However, the predictive value of the Fisher grading system is not perfect. Never assume that a patient will not develop vasospasm just because he has a low Fisher score. [82]

Score	Description
0	Unruptured.
1	No blood detected.
2	Diffuse or vertical layers <1 mm thick.
3	Localized clot and/or vertical layer >1 mm thick.
4	Intracerebral or intraventricular clot with diffuse or no subarachnoid haemorrhage.

Table (1) Fischer grading score, Mayfrank 2001

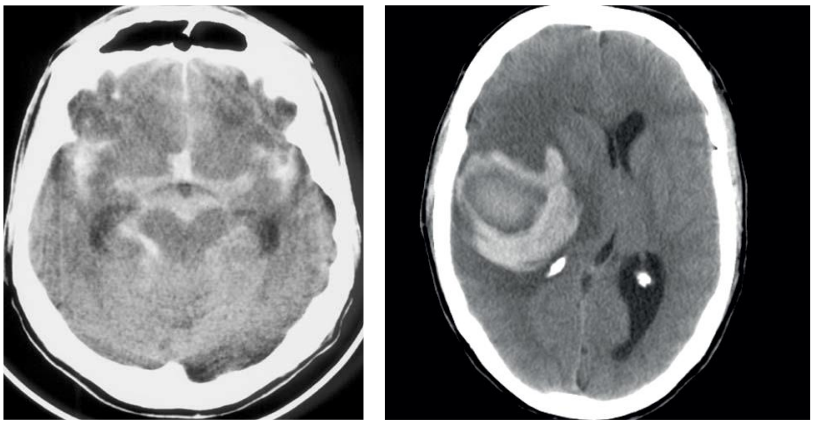


Figure (6) Plain axial CT brain; RT SAH, LT MCA Intracerebral hemorrhage.Elshargawy2014

2.3.2 CT Angiography (3D CTA):

Angiography via CT scanning has a potentially important role in the acute investigation of spontaneous SAH. Such a tool is particularly attractive even to the endovascular therapist since once the cause of aneurysmal SAH has been identified, treatment can be planned and DSA performed under general anaesthesia, immediately prior to embolization. As a tool to identify patients with unruptured aneurysms among those with thunderclap headache, an accurate noninvasive vascular imaging technique would be of considerable interest. [80]

Sensitivity of single-slice CT angiography in the investigation of intracranial aneurysms has been reported after the improvement of image quality and spatial resolution. Wintermark et al. (2003) concludes that sensitivity, specificity and accuracy values of multi-row CTA of 99%, 95.2% and 98.3%, respectively. [144] Nevertheless, this technique has demonstrated a limited sensitivity for aneurysms smaller than 3 mm (25%–64%). Multi-row CT technology will make life clearly easier at emergency departments; patients with a first-time headache and a negative unenhanced CT scan will get a quick and reliable CTA, to optimize treatment planning and work-flow CTA may also be used to stratify patients into endovascular and surgical treatment groups. [45,144]

CTA requires an iodine contrast agent and is associated with radiation exposure, which is a significant drawback in using CTA for community screening, particularly if this needs to be performed several times during an individual patient's lifetime. However, CTA clearly plays a

role in the pre-therapeutic phase in large, giant, partially calcified and thrombosed aneurysms, as it visualize the exact anatomy of the neck, the relationship to adjacent bony structures and to determine the best treatment modality. (45,151)

CTA is more likely to be useful in patients after aneurysm clipping, as there are reconstruction algorithms available that allow for the reduction of clip-related artifacts to a minimum and thus enables decision-making whether the aneurysm is completely clipped or not. (45,151)

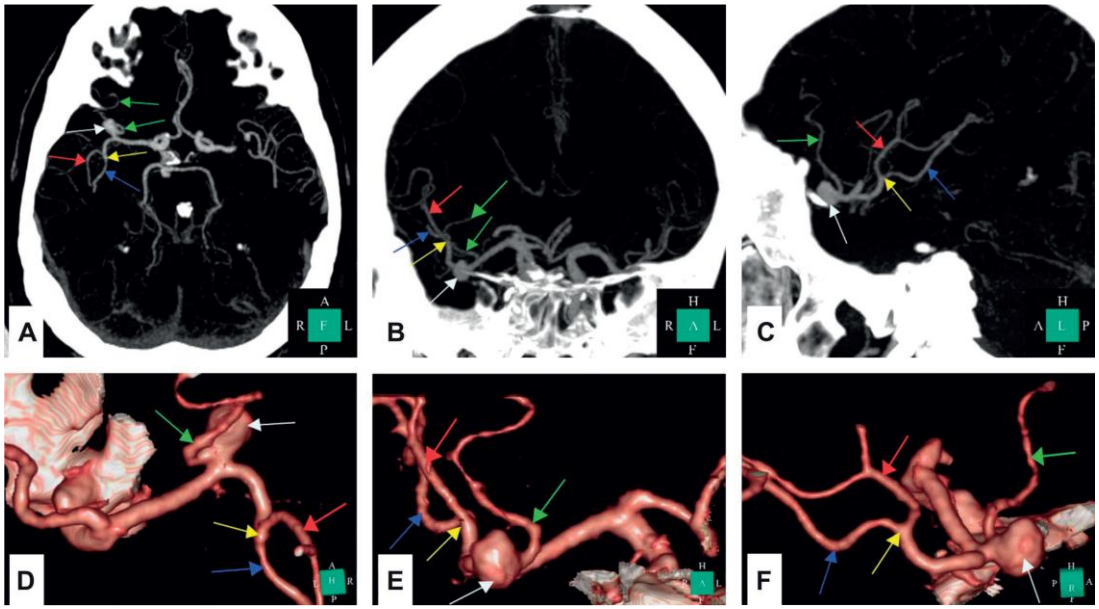


Figure (7) CTA images (A: axial, B: coronal, C: sagittal and the corresponding 3D reconstruction views (D, E and F, respectively) illustrating MCA aneurysm (white arrows) arising at the origin of a large early frontal cortical branch (green arrow) just proximal to the right MCA genu.Elshargawy2014.

2.3.3 Magnetic Resonance Imaging (MRI):

Magnetic resonance imaging and MRA are increasingly used in the diagnostic work-up of patients with cerebral aneurysms. However, MRI is less suitable than CT in patients with acute SAH because they are often restless and need extensive monitoring. (118) Subtle amounts of subarachnoid blood can be detected by MRI when using FLAIR or proton-density weighted MR sequences, even before it can be detected by CT. (118,149) MRI is also superior to CT in demonstrating SAH in patients presenting late after aneurysm rupture and may be positive for SAH when CT is normal. (118)

MRI is more useful in detection of other causes of subarachnoid haemorrhage in patients with a negative angiogram, such as a thrombosed aneurysm or spinal vascular malformation and it will increasingly be used in screening programs and as a follow-up tool after endovascular therapy. Diffusion weighted MR imaging is a potentially useful tool for monitoring patients after endovascular treatment, in order to permit early detection of ischemic complications, as it is more sensitive than CT leading to their early treatment. (118,149)

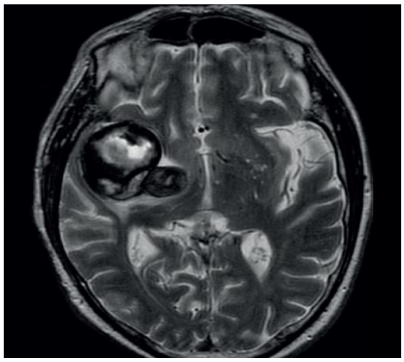


Figure (8) Axial T2 MRI brain scan, showing a partially thrombosed giant MCA aneurysm on the RT side. Osborn2003

2.3.4 **Magnetic Resonance Angiography:**

MR angiography provides a fast, accurate and non-invasive evaluation of intracranial aneurysms without the risk of conventional angiography; however, MRA has not yet replaced catheter angiography. [2, 12] Aneurysm size is a crucial factor for sensitivity. MRA studies consistently indicate sensitivity rates of more than 95% for aneurysms larger than 6 mm, but much less for aneurysms smaller than 5 mm, which constitute as many as a third of aneurysms in asymptomatic patients, detection rates of 56% and less have been reported. [2,113]

Present indications for MRA in the evaluation of cerebral aneurysms in general include: Incidental findings on CT or MRI suspicious for an aneurysm. Evaluation of specific clinical symptoms (i.e. third cranial nerve palsy) or non-specific symptoms in whom an aneurysm might explain the clinical presentation, screening in “high risk” patients (first-degree relatives of patients with SAH, multiple aneurysms, polycystic kidney or connective tissue diseases). [12]

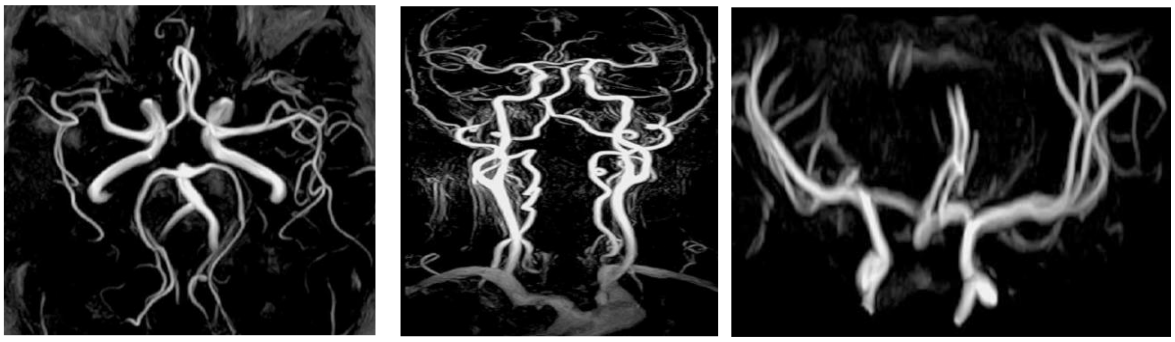


Figure (9) (a) Time of flight MR angiography of normal intracranial vessels(b) Contrast-enhanced MRA technique with a large field-of-view covering all vessels from the aortic arch to the circle of Willis(c) small A COMM aneurysm. Atlas of neurovascular anatomy and pathology2007.

2.3.5 Intra-arterial Digital subtiaction Augiography (IA-DSA):

Owing to its excellent spatial resolution, conventional cerebral angiography is still the gold standard for detecting a cerebral aneurysm. Currently, this is performed during the first available moment after presentation of the patient at the hospital after SAH, as the risk of rehemorrhage is highest in the first 24h. [8] Compared to the non-invasive methods (CTA

and MRA), DSA is the gold stander method to evaluate all components of the circle of Willis, identify the aneurysm site, anatomical assessment of its vascular geometry (in particular delineating the size, shape, number of lobules, direction of fundus projection, presence of irregularities or loculations in the aneurysm wall, and relationship of the aneurysm neck to the parent arteries and adjacent arteries, distinguish aneurysm from vascular loops and infundibula and appreciate the cross filling from one side to the other and from the vertebrobasilar circulation and elongation, tortuosity, and atherosclerotic narrowing of cerebral vessels.[35,154] It is also helpful in screening for aneurysms, to follow the status of untreated or partially treated aneurysms, to ensure proper aneurysm obliteration postoperatively, and to sequentially evaluate the status of vasospasm. [8, 35, 97]

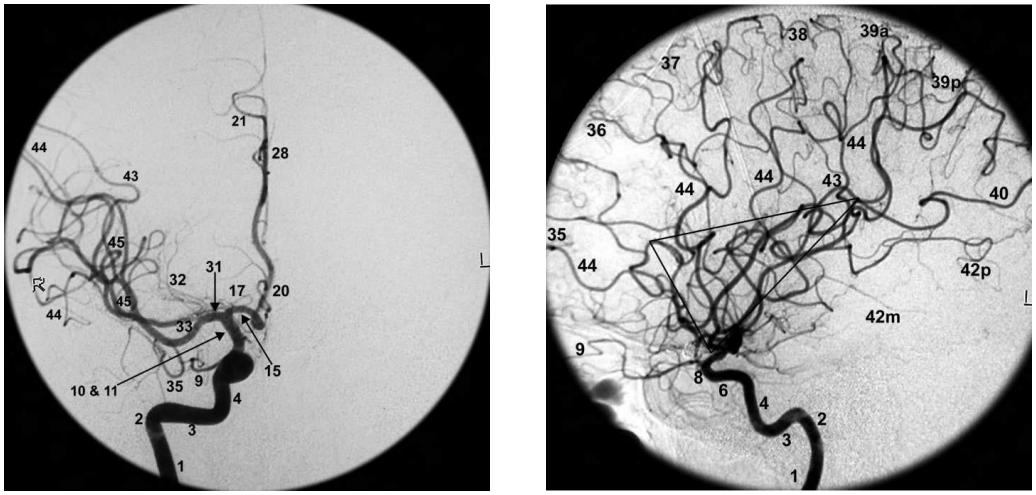


Figure (10) RT internal carotid artery angiography. The normal carotid circulation; 1 internal carotid artery – cervical segment 2 internal carotid artery – vertical petrous segment 3 internal carotid artery – horizontal petrous segment 4 presellar (Fischer C5) segment internal carotid artery 6 horizontal (Fischer C4) intracavernous internal carotid artery 9 ophthalmic artery 10 & 11 proximal and distal supraclinoid segment internal carotid artery 12 posterior communicating artery 13 anterior choroidal artery 14 internal carotid artery bifurcation 15 A1 segment of anterior cerebral artery 17 recurrent artery of Heubner 20 proximal A2 segment anterior cerebral artery 21 callosomarginal branch of anterior cerebral artery 28 pericallosal branch of anterior cerebral artery 31 M1 segment of middle cerebral artery 32 lateral lenticulostriate arteries 33 bifurcation/trifurcation of middle cerebral artery 34 anterior temporal lobe branches of middle cerebral artery 35 orbitofrontal branch of middle cerebral artery 43 sylvian point 44 opercular branches of middle cerebral artery 45 sylvian (insular) branches of middle cerebral artery,3D Angiography atlas of neurovascular anatomy and pathology2007.

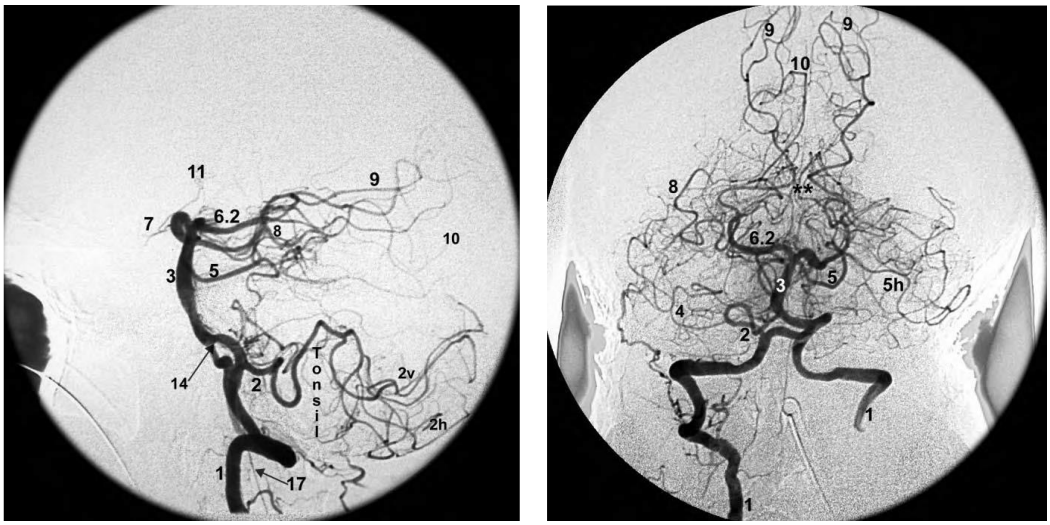


*Figure (11) Vertebrobasilar angiography, frontal & lateral , The normal intracranial vertebral basilar circulation.1 vertebral artery 2 posterior inferior cerebellar artery (PICA) 2v vermian branch of PICA 2h hemispheric branch of PICA 3 basilar artery 4 anterior inferior cerebellar artery (AICA) 5 superior cerebellar artery (SCA) 5h hemispheric branch of SCA 6 posterior cerebral artery (PCA) 6.2 P2 segment of posterior cerebral artery 7 posterior communicating artery 8 posterior temporal branch of PCA 9 parieto-occipital branch of PCA 10 calcarine branch of PCA 11 anterior thalamoperforators 12 posterior thalamoperforators 13m medial posterior choroidal arteries 13L lateral posterior choroidal arteries 14 vertebral-basilar junction 15 splenial branch (posterior pericallosal artery) of PCA 17 anterior spinal artery ** region of quadrigeminal plate cistern, 3D Angiography atlas of neurovascular anatomy and pathology2007.*

2.3.6 Plain Skull Radiography:

Although not used nowadays, it is reported that, small intracranial aneurysms cause no abnormalities on plain radiography of the skull but large aneurysms may show erosion of the base of the skull, particularly in the sphenoid bone and sella turcica, or the lesion itself may be partially calcified. (154)

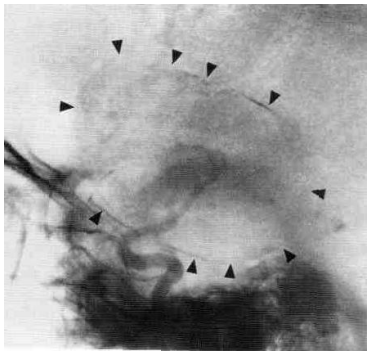


Figure (12) lat view plain X ray the calcified wall of the aneurysm is outlined (arrow heads), Yasargil V2 1984.

2.3.7 Transcranial Ultrasound:

Although the technique is quick, safe, inexpensive and non-invasive, it is highly dependent on the skills of the operator. At the moment, TCD for the detection of cerebral aneurysms is only of scientific interest and cannot be recommended for routine use. In fact, it does not play any role in diagnostic work-up of SAH patients or in screening. (46,147) TCD is used to

study changes in cerebral arterial flow velocity after subarachnoid hemorrhage and after surgery of cerebral aneurysms. A steep early increase in flow velocity seems to predict future ischemia. Velocities over 200 cm per second almost always occur in patients with severe vasospasm. Flow velocitie is only a rough guide to vasospasm and must take in account the clinical conditions and available radiological imaging. (147)

2.3.8 Electroencephalography (EEG):

While EEG has little use in the diagnosis and localization of ruptured cerebral aneurysm, it nevertheless finds some application in the evaluation of brain function in patients who are obtunded or comatose following subarachnoid hemorrhage. (154)

Van der Drift (1961) summarized the findings on EEG in patients with ruptured cerebral aneurysm and noted that EEG findings basically paralleled the disturbances in cerebral blood flow, but noted that the EEG tracing tended to normalize within 6 weeks of hemorrhage while blood flow alterations could persist. (138)

In an interesting recent case, in the author's series, a 45-year-old woman presented with subarachnoid hemorrhage and angiography revealed bilateral MCA aneurysms. Computerized tomography was not helpful in determining which of the lesions had bled. An EEG, however, showed dysfunction on the left cerebral hemisphere. Because the right-sided aneurysm was significantly larger than the left, operation was carried out on the right side and an unruptured aneurysm was found. Subsequent left sided exploration revealed the aneurysm which had bled. In this case EEG proved more helpful than angiography for localization of hemorrhage. (62) Techniques such as this might find application in the prognosis of comatose patients and in determining case selection for operation. (138,154)

2.3.9 Positron Emission Tomography:

Positron Emission Tomography or PET scanning is an in vivo autoradiographic technique for measuring cerebral blood flow and metabolism. A variety of radioactive short half-life materials are injected intra-arterial necessitating the immediate availability of a cyclotron. This drastically limits the widespread use of PET scanning, currently confined to research purposes. With its ability to quantitate cerebral blood flow and metabolism, PET scanning is being applied to aneurysm patients with associated vasospasm. Efforts are underway to demonstrate that symptomatic patients with vasospasm have an uncoupling of cerebral blood flow and metabolism. Future work with this new investigative device will certainly shed light on the pathophysiology of subarachnoid hemorrhage induced vasospasm. (80,147,154)

2.3.10 Nuclear Magnetic Resonance:

Nuclear Magnetic Resonance or NMR scanning allows a tomographic picture of tissue based on its electron density. At present, the application of imaging and metabolic NMR to cerebral aneurysms awaits further development. (46, 80,147)

2.4 Treatment of intracranial aneurysms:

2.4.1 Management of aneurysmal SAH:

In addition to the prevention of rebleeding, the main goal of treatment for patients with ruptured IAs is to manage the complications associated with SAH, in particular, vasospasm. For vasospasm prophylaxis, oral Nimodipine is traditionally administered and prescribed to

patients for three weeks once aneurysmal SAH is diagnosed. Nimpodipine was associated with a 40% reduction in poor outcomes after an aneurysmal SAH. Other drugs, such as magnesium sulphate and statins, are occasionally used, but with fewer reported benefits. The use of triple-H therapy (hypervolemia, hemodilution and hypertension) is more controversial and is usually reserved for symptomatic patients. Endovascular mechanical and/or pharmacological angioplasty is increasingly being used to treat cerebral vasospasms. (23, 29, 31, 44, 152)

2.4.1.1 Anesthetic consideration for aneurysmal SAH:

Hypertension, which may be the precipitating event that leads to the rupture of the aneurysm, is often a long-standing issue for patients with SAH. Thus, blood pressure control may be relative to a patient's baseline blood pressure. To avoid lowering blood pressure excessively, cerebral perfusion pressure (CPP) must be maintained at adequate levels. The American Heart Association (AHA) 2012 Guidelines for the management of aneurysmal SAH do not give any specific blood pressure recommendation. However, general recommendations call for systolic blood pressure <160 mmHg because of the risk of rebleeding. (29, 84)

Nimodipine is recommended by AHA for all patients with SAH for vasospasm prophylaxis. Although it has not been shown to improve cerebral vasospasm by angiogram, Nimodipine has decreased delayed ischemia and improved neurologic outcomes. Verapamil has been shown to improve neurologic outcomes without increasing ICP. Erythropoietin has shown some promise in lowering the incidence of vasospasm and DCI, it also has shown improved outcomes, but further studies are needed to confirm this result. (133,141)

Up to 26% of patients with SAH experience seizure-like episodes. Some small, nonrandomized studies have shown that prophylactic use of anticonvulsant therapy in the immediate posthemorrhage period may be beneficial, but definitive research suggests its efficacy is lacking. If such therapy is used, only a short course (3-7days) is recommended. (62,108)

Anemia is common in SAH patients. The average drop in hemoglobin concentration in SAH patients is 3 g/dL. Higher hemoglobin levels have been associated with positive functional outcome. Blood transfusions, however, carry associated risks, such as an impaired immune system and increased incidence of infection. The Neurocritical Care Society recommends maintaining hemoglobin between 8-10 g/dL and maintaining higher levels (up to 12 g/dL) for patients at risk for DCI. (9,108, 127)

When aneurysm obliteration is delayed, antifibrinolytic drugs such as aminocaproic acid or tranexamic acid have been shown to reduce the incidence of rebleeding, although neither of these drugs is approved by the United States FDA for this use. (29,86,90) Data suggest that treatment with statins may help reduce the size and growth progression of cerebral aneurysms, but more investigation is necessary to determine dosing, as conflicting data show that statins may increase aneurysm size at higher doses. (9, 54)

2.4.1.2 Time of Aneurysm Treatment after Subarachnoid Hemorrhage:

Over many years, the most suitable timing of ruptured aneurysm surgery has been debatable. In the 1960s and 1970s, most patients were operated on in the late phase 2 or 3

weeks after the hemorrhage as surgery in the initial 2 weeks was considered too dangerous, because operating on swollen and vulnerable brain tissues led to high rates of perioperative complications. This was particularly true during the period of maximum vasospasm between days 4 and 10 which was considered a particularly dangerous period to operate, because of the risk of delayed cerebral ischemia (DCI). Extensive evidence is available demonstrating that early surgery within 72 hours after the onset of SAH is associated with improved outcome among patients with ruptured cerebral aneurysms in the anterior circulation. The ideal timing of surgery for cerebral aneurysms in the posterior circulation is still controversial. A Cohrane review in 2001 identifies only 1 randomized clinical trial on timing of surgery after aneurysmal SAH. In this trial, patients undergoing early surgeries (days 0–3) tended to have the best outcome, and patients undergoing intermediate surgeries (days 4–7) the worst. A systematic review that included not only this trial, but also 10 observational studies in 2012, concludes that both early (days 0–3) and intermediate (days 4–7) surgical treatments resulted in better outcomes than did late surgery. In conclusion, it is evident that aneurysm treatment after day 10 is associated with worse outcome, regardless of treatment modality and advocates treatment of the aneurysm as early as possible after SAH. [159]
Interestingly, microsurgical clipping between days 5 to 10 did not lead to a higher chance of DCI, whereas coiling between days 5 to 10 did increase the chance of DCI, but not poor outcome. Based on these results, it is not recommend to postpone clipping until day 10 or later in patients who are candidates for aneurysm treatment earlier. [159]

2.4.2 Management of ruptured IAs with ICH:

There is still some controversy regarding the adequate management of patients with a massive ICH caused by the rupture of an IA. It has been reported that the surgical evacuation of ICH without the clipping of the ruptured IA was associated with a 75% mortality rate, while combining aneurysm obliteration with ICH evacuation resulted in a 29% mortality rate. While some advocate for the coiling of the ruptured aneurysm first and, then, evacuating the ICH, the combination of endovascular and surgical treatments would expose the patient to the risks associated with both treatment modalities. Early surgical removal of massive ICH is believed to improve the outcome of ruptured aneurysms and avoid time delays with an increased intracranial pressure. [1, 93,129]

2.4.3 Treatment of Unruptured cerebral Aneurysms:

This is still a controversial topic and no solid indications up till now have been in agreement about. The management of asymptomatic unruptured aneurysms remains controversial and depends on a full understanding of their natural history balanced against the risks of treatment and long-term protection afforded. [65,148] unfortunately, unruptured aneurysms are a heterogeneous entity, both in terms of morphology and behaviour, e.g. tendency to rupture. Aneurysm size, certain locations with an increased risk of rupture perse: posterior circulation aneurysms and those aneurysms arising from the pcomm, hypertension, aneurysm multiplicity, multilobular aneurysm, female sex, heavy alcohol consumption,

smoking, and ruptured aneurysm in another location being specific risk factors for a higher probability of rupture and therefore treatment is indicated. [65, 142, 146]

Surgical and endovascular treatment of unruptured aneurysms demonstrated that the costs treating an unruptured aneurysm are significantly lower than treating patients with SAH regarding length of hospital stay and sequelae of morbidity and mortality. [65]

Currently, healthcare is undergoing a major reorganization to meet growing economic pressure and the aspect of preventive therapy becomes more and more important. Therefore, indication for treatment of an unruptured aneurysm has to be considered in several respects: what is the risk of aneurysm rupture and what are the costs to treat a subarachnoid hemorrhage? What are the costs of treating an unruptured aneurysm either neurosurgically or via an endovascular approach to avoid SAH with possibly fatal complications? Rising costs of treating an aneurysmal hemorrhage have to be weighted against the risk of rupture of an incidentally detected aneurysm [65, 146]

2.4.4 Different modalities of aneurysm treatment:

Medical therapy is usually only an option for the treatment of unruptured intracranial aneurysms. Strategies include smoking cessation and blood pressure control; the only factors that have been shown to have a significant effect on aneurysm formation, growth, and/or rupture. Periodic radiographic imaging (either MRA, CT scan or conventional angiography) may be recommended at intervals to monitor the size and/or growth of the aneurysm. Because the mechanisms of aneurysm rupture are incompletely understood, and because even aneurysms of very small size may rupture, the role of serial imaging for cerebral aneurysm is undefined. [11, 33,110]

Microsurgical clipping is still the preferred treatment modality in most centers due to the relatively straight forward surgical approach to most of the aneurysms. In addition to the major advantage of surgery which provides effective and durable exclusion of the aneurysms, surgery also allows for the management of the increased intracranial pressure through evacuation of ICH, the release of cerebrospinal fluid (CSF) and/or hemicraniectomy. [11, 36, 48, 110]

In the last decade after tremendous advances in endovascular techniques and devices, several relatively large studies of the endovascular management were published, due to the concept that. In spite of the advances, surgical clipping remains an invasive and technically challenging procedure. [33]

2.4.4.1 Endovascular treatment:

Induce thrombosis of aneurysms by introducing foreign bodies or application of electrical or thermic injury through arterial catheterization date back to the first half of the nineteenth century. With subsequent improvements in endovascular devices and techniques, led to the opening of a new era in the endovascular cerebral aneurysm treatment. [66,86,131,148] Filling techniques to induce aneurysm thrombosis and subsequent closure, the “coiling” technique represent a “gold standard” in endovascular aneurysm treatment, which has showed much progress with development of new coil designs or other endovascular devices like ballon or stent to assist embolization. Then the endovascular therapy progressed and replaced the

simply filling techniques with materials that promote real endothelialization of the aneurysm neck. (47, 91,137)

Endovascular therapy was restricted to surgical difficult or inaccessible lesions, mostly in the posterior circulation, but the increasing experience and development of devices have improved the potential, and endovascular therapy has become an alternative to surgical treatment. Some limitations are still such as the anatomic situation of the aneurysm, aneurysm size or unfavourable or invisible geometry (neck/fundus ratio). The decision to treat an aneurysm endovascularly rather than surgically is not easy and requires a multidisciplinary input that requires both the neurosurgeon and the interventionalist to be extremely honest about what they think they can achieve with each approach. Neurosurgery and interventional neuroradiology are not competitive facilities, but the complementary nature of techniques offers the best chance for reducing treatment morbidity and improving long-term outcome in difficult aneurysms. (47, 52, 66, 86)

Flow diverter is among the newest technologies for aneurysm embolization, where only in 2008 several models were approved in Europe for the treatment of cerebral aneurysms. (68, 88,145) The aim of this vascular support is to reconstruct the carrier vessel of the aneurysm. This functional principle is based on the one hand on the diversion of the blood flow away from the aneurysm, which subsequently leads to the thrombosis, followed by fibrotic remodelling, Secondly, the vessel wall is restored by covering the stent at the neck of the aneurysm with a neointima consisting of smooth muscle and connective tissue cells.(18,68)

Figure (13) Dendrone electric detachable coils different varieties: A, standard. B, Cage coil, C, Multidiameter coil (Donauer et al., 2002).

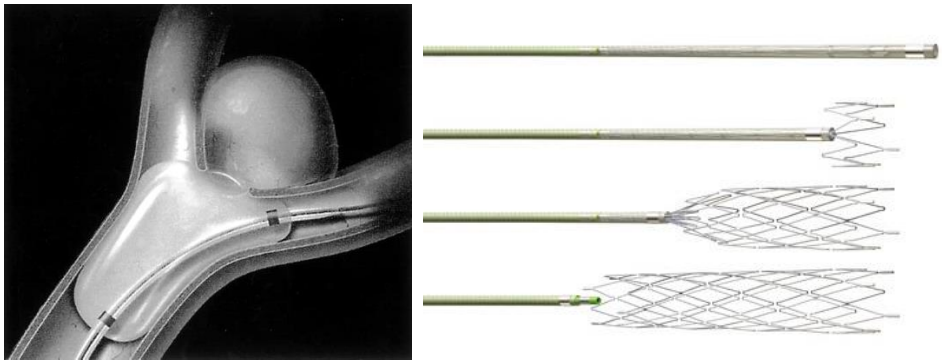


Figure (14) Rt, Diagram of the Hyperform balloon microcatheter, Lt, self-expanding Neuroform microstent (Baldi et al., 2003).

2.4.4.2 Microsurgical clipping:

Microsurgical clipping has been used for treating intracranial aneurysms, for more than 40 years. This procedure involves placing a surgical clip at the junction of the healthy artery and the neck of the aneurysm, to ensure the exclusion of the aneurysm from the cerebral

circulation, reducing the mass effects on adjacent structures and preserving the parent vessel, while eliminating any aneurysmal rests that may subsequently redevelop. [75, 79]

The application of microsurgical techniques, have provided a better understanding of the aneurysm. The greatest improvements have been in the surgeons' ability to carry out fine manipulations through a tiny gap under high magnification and the availability of precision instruments of adequate lengths, parallel to excellent microanatomy orientation through the surgical field that can be viewed at great depth, in sharp focus and stereoscopically. Thus, with increased experience there has been less need for an alternative method to clipping. Nevertheless, there do remain a few cases where clipping is not possible. [4, 81, 125, 154]

2.4.4.2.1 Strategy for aneurysmal clipping:

The General strategy an aneurysms surgery is very similar irrespective of the aneurysm location or size, with a much less difference between rupture and unuptured aneurysms. Giant, partially thrombosed, calcified, and fusiform aneurysms are special subgroups, which often need a customized strategy with options for bypassing procedures, endovascular balloon occlusions, and intraoperative DSA angiography. Fortunately, these cases represent only about 5% of all known aneurysms. [81,154]

The actual surgical strategy for treating aneurysms includes the following procedures: craniotomy; brain relaxation via releasing CSF and possible partial removal of space occupying ICH; establishing proximal and distal control of the parent arteries; aneurysm neck dissection under temporary clipping of the arteries; insertion of the pilot clip; further dissection of the aneurysm dome from the surrounding structures and possible remodeling of the dome; final clipping and checking the patency of the surrounding arteries; removal of the remaining ICH if present; application of Surgicel with papaverine locally to prevent vasospasm; and wound closure. [81,154]

In ruptured aneurysms, the greater differences are the more oedematous the brain becomes and a constant fear of aneurysm re-ruptures. Thus, in ruptured aneurysms, more time is initially spent on obtaining a slack brain and more CSF needs to be released. Unruptured aneurysms, in general, are easier to approach than ruptured ones. Aneurysm can be approached more freely with only good neuroanesthesia or just releasing CSF from the actual cistern where the aneurysm is located. All anatomical structures can be better identified and the dissection plane is easier to maintain. A smaller opening of the arachnoid is often sufficient and less surrounding structures need to be exposed. [81, 85]

2.4.4.3 Surgical vs Endovascular management:

For some aneurysms, endovascular treatment may be preferred, whereas for others microsurgery is still superior in both cost and outcomes. [17]The choice of open surgery vs. endovascular techniques to treat cerebral aneurysms remains an individualized decision. Many factors play a role in treatment decision making: age, past medical history, and medical/neurological conditions help to determine the patient's ability to tolerate a specific treatment. For example, an old patient with a ruptured aneurysm in poor neurological and general condition, coil embolization may be superior to surgery in this setting. On the other hand, a young patient with an unruptured aneurysm may be a good candidate for open

surgery in anticipation of achieving a durable result. Aneurysm characteristics such as location (suitability for surgical access), morphology, and size i.e. MCA aneurysms tend to have complex morphologies with wide necks and important arterial branches may be incorporated into the aneurysm, these aneurysms tend to be more suitable for open surgery. Also, a ruptured aneurysm with a large intracerebral hematoma and mass effect may be better suited for surgery. Patient preference also plays a role in which treatment is chosen in some instances. Operator preferences are often understated but equally important, this includes the operator's bias toward a certain treatment because of experience and familiarity. Some complex aneurysms may require a combination of open and endovascular surgeries. [86,158]

The International subarachnoid aneurysms trial (ISAT), a randomized, multicenter study that compared clinical outcomes of patients presenting with ruptured aneurysms, whose treated either by clipping or by coiling. Initial clinical outcomes from ISAT indicated little difference between endovascular and surgical treatment. However, outcome results at 1 year follow up were convincing enough to lead to an early termination of the study, because those treated with endovascular coiling had a 6.9% absolute risk reduction and 22% relative risk reduction in poor outcome compared with surgical clipping. [86]

The microsurgical clipping procedure was significantly superior regarding the occlusion of ruptured aneurysms. Initial subtotal occlusion is stated in 1.6% of the microsurgical cases versus 19.1% of the endovascular cases, in ISAT the complete occlusion rate in the endovascular group (discharge until over 2 years) was 66% of the treated aneurysms. Retreatment was performed on 17.4% of the patients who underwent endovascular therapy and in 3.8% of patients who underwent surgical clipping. Long term follow ups indicated endovascular coiling had a higher risk of rebleeding than clipping (6.1% versus 0.4%), but the risk was low and remained similar to risk of SAH from another aneurysm. [17, 86,158]

Van Rooij et al noticed that, the significantly lower absolute rate of symptomatic ischemic stroke is (endovascular treatment 19.7% versus microsurgical clipping 5.3%). Also, the safety and efficacy profile of flow diversion should discourage the use of these devices in aneurysms that can be treated with other techniques. Direct mortality was not significantly different between the two groups (endovascular group: 0.9%microsurgical clipping group: 0.7%). [86,158]

Although the ISAT study indicated that endovascular treatment was a safe and effective alternative to surgical treatment for certain ruptured aneurysms, the results were not sufficient to determine that endovascular treatment is superior to surgical treatment in all patients with ruptured aneurysms and cannot be applied to unruptured aneurysms. [86]

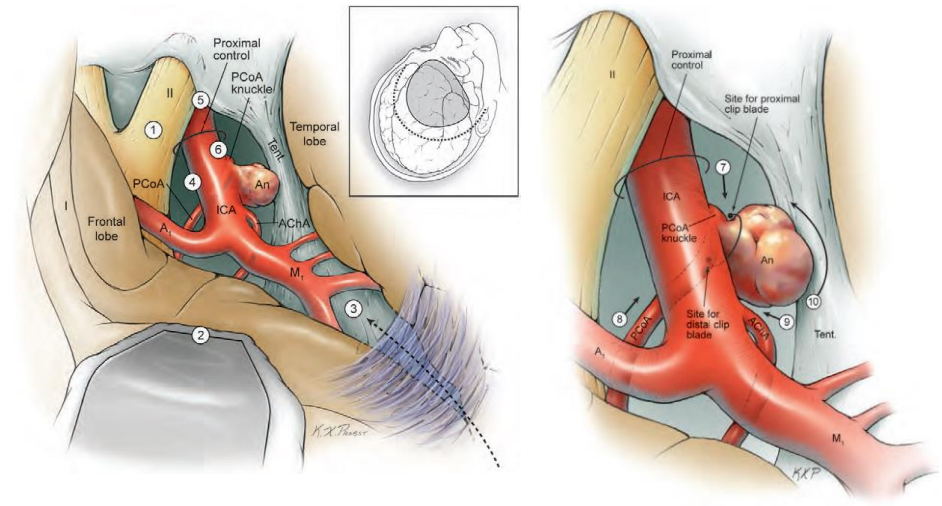


Figure (15) Dissection strategy for pcom aneurysm; Michael T 2011

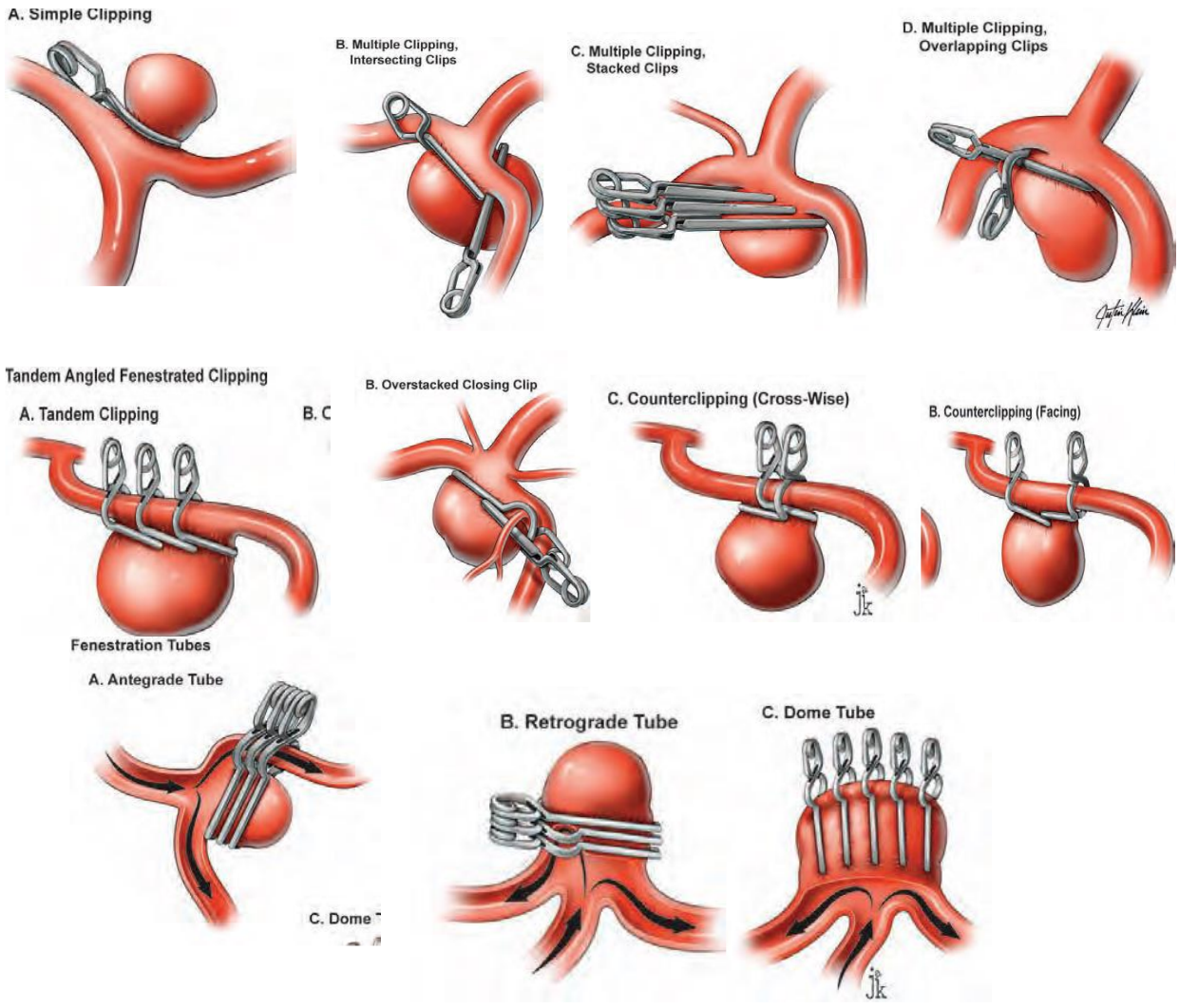


Figure (16) Different technique for microsurgical clipping; Michael T 2011

2.4.5 Screening for Intracranial Aneurysms:

Of the whole population, about 2% harbor cerebral aneurysms. In most of cases, the aneurysm is not prone to rupture and usually remains asymptomatic throughout their life. Given the serious consequences of intracranial aneurysmal rupture with catastrophic consequences, with up to a 50% mortality rate even with the best available management and the emergence of new technologies that can aid diagnosis and treatment before rupture, more attention to screening unruptured cerebral aneurysms is mandatory. [16]

Screening asymptomatic without risk factors or even those with acquired risk factors, such as smoking or alcohol abuse do not seem to provide any benefits.[10] Screening the entire population for IAs is not logical, since most of them do not harbors IAs. Furthermore, treating all diagnosed IAs is unnecessary since most of them will never harm the patients, parallel to the cost, time, and potential hazards of screening tools. On the contrary, waiting till IAs rupture is not justifiable, as that leaves most patients dead or disabled. [16]

Screening IAs in patients with positive family history of ruptured intracranial aneurysm is controversial. For patients with one affected first-degree relative, the Stroke Council of the American Heart Association does not recommend screening aneurysms. [142] Screening patients with positive two or more family members with intracranial aneurysms is more complexed. Several studies [16, 78] advocate screening for such patient population, based on the higher rupture rates. But more recent studies indicate that screening does not have a significant reduction of the morbidity or mortality rates for those patients. Therefore, the decision of whether or not to screen is best decided on a case-by-case basis. [20]

This conflict leads to a major clinical dilemma that should be resolved in future research when more is learned about the risk of IAs rupture and the techniques for diagnosis and management of intracranial aneurysms are improved. Screening should also be considered for patients with rare conditions (e.g. autosomal dominant polycystic kidney disease) that are associated with an increased risk of aneurysms. However, it should be based on their overall health. In patients with a history of aneurysmal subarachnoid hemorrhage, the annual rate of new aneurysm formation is between 1 and 2 percent, and the risk of aneurysmal rupture appears to be increased. [37] Therefore, surveillance of these patients with magnetic resonance angiography or intra-arterial digital subtraction angiography may be justified. [20]

2.4.6 Outcome of cerebral aneurysms treatment:

Meta-analysis of multicenter randomized studies includes ISAT that compares the outcomes of ruptured cerebral aneurysms treated either via microsurgical clipping or by endovascular therapy, illustrates that the Initial clinical outcomes indicate little differences between endovascular and surgical treatment for aneurysms of the anterior circulation but that coiling results yield better outcomes for those of the posterior circulation. The effect on mortality rates is not statistically different across the two treatments. Rebleeding rates within the first month were higher in patients allocated to endovascular coil embolization. [77, 86]

Regarding the occlusion of ruptured aneurysms, microsurgical clipping procedure is significantly superior. Initial subtotal obliteration is stated in 1.6% of the microsurgical cases versus 19.1% of the endovascular cases. In ISAT, the complete occlusion rate in the

endovascular group (discharge until over 2 years) was 66% of the treated aneurysms. Retreatment was performed on 17.4% of the patients who underwent endovascular therapy and on 3.8% of the patients who underwent surgical clipping. Long term follow ups indicated that endovascular coiling had a higher risk of rebleeding than clipping (6.1% versus 0.4%), but the risk was low and remained similar to the risk of SAH from another aneurysm. [17, 86,154]

For unruptured cerebral aneurysms, endovascular coiling and surgical clipping have similar risk ratios of mortality, bleeding, cerebral ischemia, independence in daily activities, and further investigation is needed on quality of life and cognitive outcome. Despite the major advances in endovascular techniques, it still bears a lower rate of occlusion and microsurgical clipping is still the most efficient procedure. [116,148]

Long term rupture rates for unruptured aneurysms in patients without a history of SAH and aneurysms located in the internal carotid artery, Acom or ACA, or MCA were 0%, 2·6%, 14·5%, and 40% for aneurysms less than 7 mm, 7–12 mm, 13–24 mm, and 25 mm or greater, respectively, compared with rates of 2·5%, 14·5%, 18·4%, and 50%, respectively, for the same-size categories involving posterior circulation and Pcom aneurysms. These rates often equal or exceed the risks associated with surgical or endovascular repair of comparable lesions. Patients' age is a strong predictor of surgical outcomes, and the size and location of an aneurysm predict both surgical and endovascular outcomes. [116,154]

The most durable treatment modality for aneurysm is that which could exclude it completely from circulation, but the complete microsurgical closure of an aneurysm cannot be achieved in all cases, and thus the reported rate of clip remnants varies from 1.6% to 42%. [3, 60,104,121]

The presence of a clip remnant on postoperative angiography may have far-reaching clinical consequences, with a risk of rebleeding in 1.9% of cases and a regrowth risk of 1.83% per year. [27,132] Evolution of potentially safer and less invasive endovascular therapies is also associated with the risk of aneurysm recurrence or recanalization, and varies over a wide range from 17% to 60%. Consequently, follow-up imaging after coil embolization is routinely performed to identify recurrent aneurysms before they rupture. [105]

Many scores have been used as outcome measures of intracranial aneurysms treatment for decades: the Glasgow Outcome Scale (GOS), Karnofsky Performance Scale (KPS), the modified Rankin scale (mRS), and Functional Status Examination (FSE). All these scores are valuable instruments for assessing the patient recovery after aneurysms treatment and the impact of SAH. [63, 70, 71,103] However, not all of them evaluate the efficacy of treatment and the variety of the scales which make it impossible to compare the results of different studies. [61]

The frequency and variability of recurrence rates vary widely around the world. Also, human decision-making under conditions of uncertainty is a complex, poorly-understood process [99] especially when it comes to tremendous responsibility for those who make decisions that impact the lives of others and potentially life-long consequences for individuals as those decisions made within a doctor–patient and doctor-doctor relationship, which is particularly true in the management of cerebral aneurysms.[73] Such a matter requires comprehensive and accessible information on treatment efficacy and raises an urgent need for high quality

evidence and stratification scale to clearly evaluate the safety and efficacy of these techniques, in order to determine which treatment provides the best quality and outcomes for patients.

Score	Description
1	Death
2	Persistent vegetative state Patient exhibits no obvious cortical function.
3	Severe disability Conscious but disabled. Patient depends on others for daily support.
4	Moderate disability Disabled but independent. Patient is independent as far as daily life. Disabilities include varying degrees of dysphasia,hemiparesis,or ataxia as well as intellectual and memory deficits and personality changes
5	Good recovery Resumption of normal activities even though there may be minor neurologic or psychological deficits.

Table (2) Glasgow outcome score, Kim DH 2005

Score	*Description*
0	*No symptoms at all*
1	*No significant disability despite symptoms; able to carry all usual duties and activities.*
2	*Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance*
3	*Moderate disability; requiring some help, but able to walk without assistance*
4	*Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance*
5	*Severe disability; bedridden, incontinent and requiring constant nursing care and attention*
6	*Dead*

Table (3) Modified Rankin scale, Kim DH 2005

2.5 Summary and trends for the future:

From the overview on the review of the literature, it can be concluded that:

- In the past decade a lot of progress has been achieved to improve the modalities and techniques to treat cerebral aneurysms; microsurgical clipping become more efficient, less invasive and direct toward eliminating cerebral aneurysms with minimal trauma to the brain, normal vessels and surrounding tissues through improved orientation and understanding the brain microanatomy, advance in microscope and microinstruments parallel to improved handling under high power of magnification through tiny gabs, at the same time, progress in endovascular techniques become

more complexed from just coil packing to use of ballon or stent and flow diverters with the thromboembolic risk and still carry a low aneurysm occlusion rate.

- The exact mechanism for cerebral aneurysms formation is still unclear, the role of inflammatory and genetics process should be extensively examined. So, it might be possible to develop pharmaceutical therapies that would reverse the process of IA formation
- When aneurysm is formed, some aneurysms rupture while others do not. Many studies have focused on the morphological characteristics of aneurysms on 3D angiography to predict rupture risks. Other researches correlate some morphological characteristics with the histology of the aneurysms wall in order to determine more reliable indicators for the degree of resilience of the aneurysm wall to rupture. All available data, however, is suggestive rather than conclusive. Integration of both, meticulous examination of the aneurysm tissue provided during microsurgical clipping by histochemical and immunological studies and the newly developed investigation tools such as the ultra-high-field MRI, that would probably enable examination of the aneurysm wall for weak spots, would allow for more reliability when classifying IAs as either stable or rupture-risk harboring.
- Prevention of rebleeding after SAH is a big challenge. Also, the efficacy of antifibrinolytic therapy such as aminocaproic acid and tranexamic acid to prevent rebleeding and the benefit of statin to control the growth of the aneurysm is still conflicting.
- Issues like the pathogenesis of vasospasm due to SAH and why vasospasm and delayed cerebral ischemia occur in rupture aneurysm SAH and rarely occur in patients with SAH after rupture of an AVM or perimesencephalic SAH, have not been entirely elucidated.
- Screening for cerebral aneurysm represents a clinical dilemma, as only about 2% of the whole population is expected to harbor IAs. In most cases, however, it will not rupture or harm the patient. Also, it is an expensive and time-consuming procedure that bears the hazards of radiation exposure. Despite that, waiting till an aneurysm rupture occurs is not justifiable, as it consequences can be catastrophic. Identifying the genetic factors associated with IAs could make screening for them as fast and as smooth as a simple blood test, resulting in a higher percentage of patients with IAs being identified early. Until that happens; a low threshold to investigate patients with any CNS symptoms should be adopted.
- Preventive medicine is the best route. Despite that, there is no solid indication to treat unrupture cerebral aneurysm due to missing real rupture risk.
- All scores are routinely used to evaluate outcomes after cerebral aneurysms treatments, and only measure recovery after any brain insult, irrespective to the efficacy of the treatment modality in eliminating the absolute and relative risk of aneurysm ruptures. So an urgent need arises for high quality evidence and stratification scale to clearly evaluate the safety and efficacy of these techniques and to determine which treatment provides the best quality and outcomes for patients.

- Advances in endovascular technology might provide for the development of new polymer-coated stents and flow diverters which do not require cotreatment with antiplatelet drugs. Furthermore, it is not impossible that some of today's science fiction might come true resulting in scientific breakthroughs in the future, whereby we witness Nano robots navigating throughout our cerebral arteries to treat IAs or strengthen their walls.

3. Material and methods:

3.1 Publication I: Outcome of cerebral aneurysms treatment; new scoring system.

3.1.1 What is the best score that can be used to evaluate the outcome of intracranial aneurysms treatment? Is it the Glasgow outcome score (GOS), the modified Rankin score (mRS), Karnofsky performance scale (KPS), functional status examination (FSE) or something else? All these scores have been validated for evaluating the patient outcome and recovery from any brain insult i.e. stroke, head trauma, tumor, etc. Although, they are also applied to evaluate outcomes for patients after cerebral aneurysms treatment, unfortunately, they are not viable to evaluate the efficacy of treatment in eliminating aneurysms from the circulation and subsequently eliminating the risk of aneurysm ruptures, which is the main aim of treatment.

Up till now, no available score is specified to evaluate the outcome of cerebral aneurysms treatment, as the optimal score should evaluate both the patient outcome (safety of the procedure) and the efficacy of treatment parallel to each other. Dissociation between the patient outcome and the degree of aneurysm closure, during the discussion of cerebral aneurysms treatment results, leads to a lot of conflicts and inconvenience. Therefore, the author has created a new score specified to evaluate both the safety and efficacy of the cerebral aneurysms treatment.

3.1.2 Nomenclature:

BRS score indicates the first letter of the author's and his mentors' first names, where B stands for the author Bahaa Ghareeb Hassanin, R stands for the Egyptian mentor Professor Roshdy Elkhyat, and BR stands for the German mentor and head of the department Professor Alexander Brawanski and S stands for the cerebrovascular mentor Professor Karl Michael Schebesch.

3.1.3 Description of the scoring system:

The main risk of harbouring intracranial aneurysms is the risk of rupture with subsequent SAH. The goal of any treatment is to exclude the aneurysm from cerebral circulation to prevent its rupture. The most efficient treatment modality is that which eliminates the risk of rupture with the best patient outcome. The proposed scoring system is based on these two parameters: efficacy of treatment and patient outcome. These factors were determined based on the follow-up angiography and/or 3DCT, Glasgow Come Score (GCS) and neurological examination of the patient.

BRS Score:

-Efficacy of the treatment:

Based on 3D rotational follow up angiography/ or 3D CT, the efficacy of treatment was determined to be: *(Table 4)*

A: Complete elimination of the aneurysm.

B: Small residual at the aneurysm neck less than 3mm.

C: Residual bleb3mm or more at the aneurysm neck, or shows regrowth on follow up, or required retreatment.

Table (4) BRS Score

score	Description
A	Complete elimination of the aneurysm from the circulation.
B	Small residual at the base less than 3mm.
C	Residual 3mm or more or show growth on follow up or required retreatment.

-Patient outcome:

Based on the patient Glasgow come score (GCS) and neurological examination, either positive (+) or negative (-) charges are added to the above efficacy category.

Positive charge (+): indicates patient with GCS 15, with no neurological deficit.

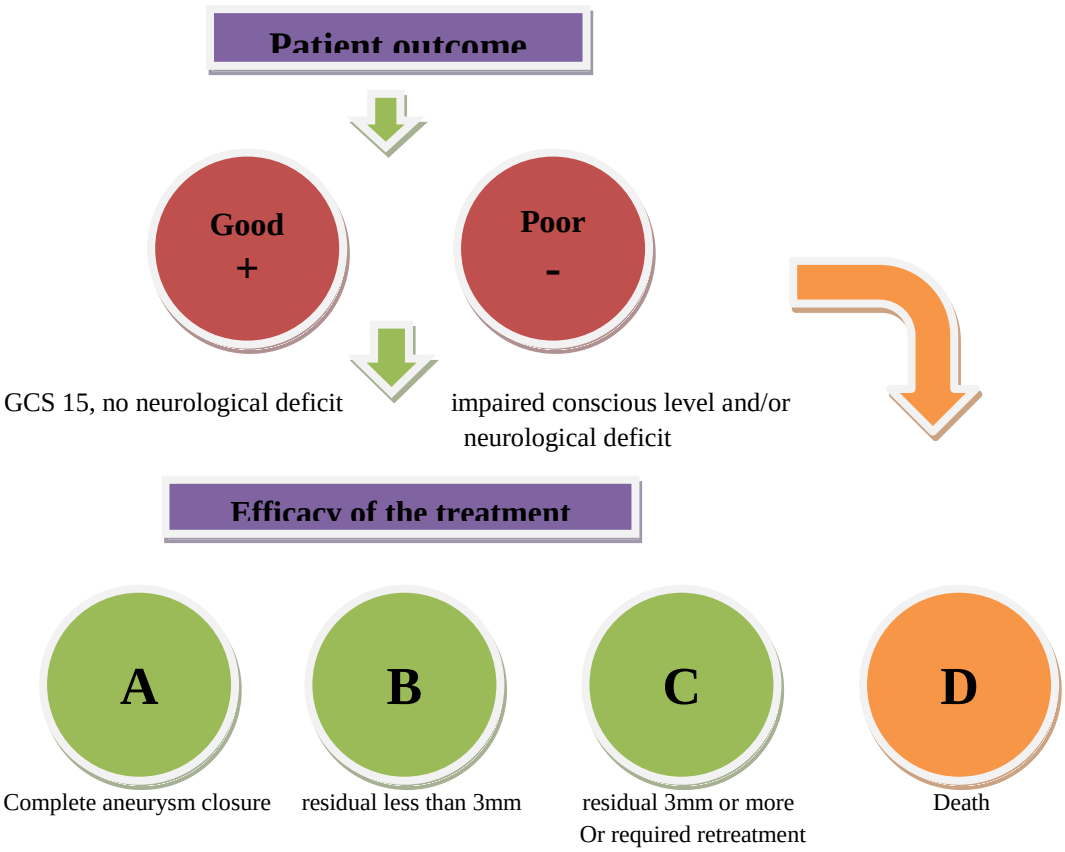
Negative charge (-): indicates patient with impaired levels of consciousness and/or with neurological deficits.

So the full score will be as follow: ***Table (5)***

Score	Description	Numerical score
A+	GCS15, No neurological deficit, complete aneurysm elimination from the circulation.	7
A-	DCL and/or Neurological deficit, complete aneurysm elimination from the circulation.	4
B+	GCS15, No neurological deficit, small residual at the base less than 3mm.	6
B-	DCL and/or Neurological deficit, small residual at the base less than 3mm.	3
C+	GCS15, No neurological deficit, residual 3mm or more /or show growth on follow up /or required retreatment.	5
C-	DCL and/or Neurological deficit, residual 3mm or more /or show growth on follow up /or required retreatment.	2

Interpretation of the score: ***Table (6)***

Score	Numerical equivalent	Indication
A+	**7**	Excellent efficacy with good patient outcome.
B+	**6**	Fair efficacy with good patient outcome.
C+	**5**	Inefficient with good patient outcome.
A-	**4**	Excellent efficacy with patient impairment.
B-	**3**	Fair efficacy with patient impairment.
C-	**2**	Inefficient with patient impairment.
D	**1**	Death.



3.2 Publication II: The extended BRS (exBRS) score to evaluate the outcome of cerebral aneurysms treatment.

3.2.1 Objective:

The first score specified to evaluate the outcome after cerebral aneurysms treatment, the BRS score, previously published by the author, has a limited value as a measure for the description of neurological impairment especially in neurologically impaired patients as those after SAH insult, which is confusing when it comes to classifying patient outcome and recovery after brain insult in patients with rupture aneurysms. Therefore, the authors has created a new more extended score to evaluate the efficacy of the treatment modalities parallel to a more specific, standardized and objective description of the degree of patient recovery and outcome.

3.2.2 Nomenclature:

Extended BRS score as it is based on the previous BRS score published by the author but with a more extended measure to the neurological state and patient recovery.

3.2.3 Description of the scoring system:

The proposed scoring system is based on two parameters: efficacy of treatment and patient outcome; the efficacy of the treatment is measured by the degree of aneurysm elimination from the circulation based on the follow-up angiography. Patient outcome and recovery are based on consciousness level and neurological examination of the patient

Extended BRS Score: ***(Table 7)***

- **Patient outcome:**

According to the patient GCS and the neurological examination, the patient can be stratified into the following category in descending order of the best outcome;

Grade (5); Competent *patient*; with the best outcome, with GCS15 and without neurological deficit.

Grade(4); independent patient with GCS15 and mild neurological deficit, which do not interfere with the patient's daily activities, and these include memory impairment, aphasia/dysphasia, sensory impairment, cranial nerve affection, and motor affection of one limb up to hemiparesis grade 4/5.

Grade (3); Dependent *patient*; with moderate to severe neurological affection that required assistance in accomplishing the daily activity. These include impaired level of conscious and/or motor affection hemiparesis grade 3/5 or more.

Grade(2); *Vegetative patient*; absence of responsiveness and awareness due to overwhelming dysfunction of the cerebral hemispheres, with sufficient sparing of the diencephalon and brain stem to preserve autonomic and motor reflexes and sleep-wake cycles.

Grade (1); *Death*

Extended BRS Score: ***Table (7)***

Score	Finding	Description
5	GCS15, No neurological deficit.	Competent**.**
4	GCS15 with mild neurological impairment which include; memory impairment, aphasia/dysphasia, sensory impairment, cranial nerve affection one limb motor affection up to hemiparesis G4/5.	Independent**.** **(**Mild impairment)
3	Impaired level of conscious and/or motor affection more than one limb; hemiparesis G 3/5 or more.	Dependent. (moderate to severe impairment**)**
2	absence of responsiveness and awareness due to overwhelming dysfunction of the cerebral hemispheres, with sufficient sparing of the diencephalon and brain stem to preserve autonomic and motor reflexes and sleep-wake cycles	Vegetative.
1	Death.	Death.

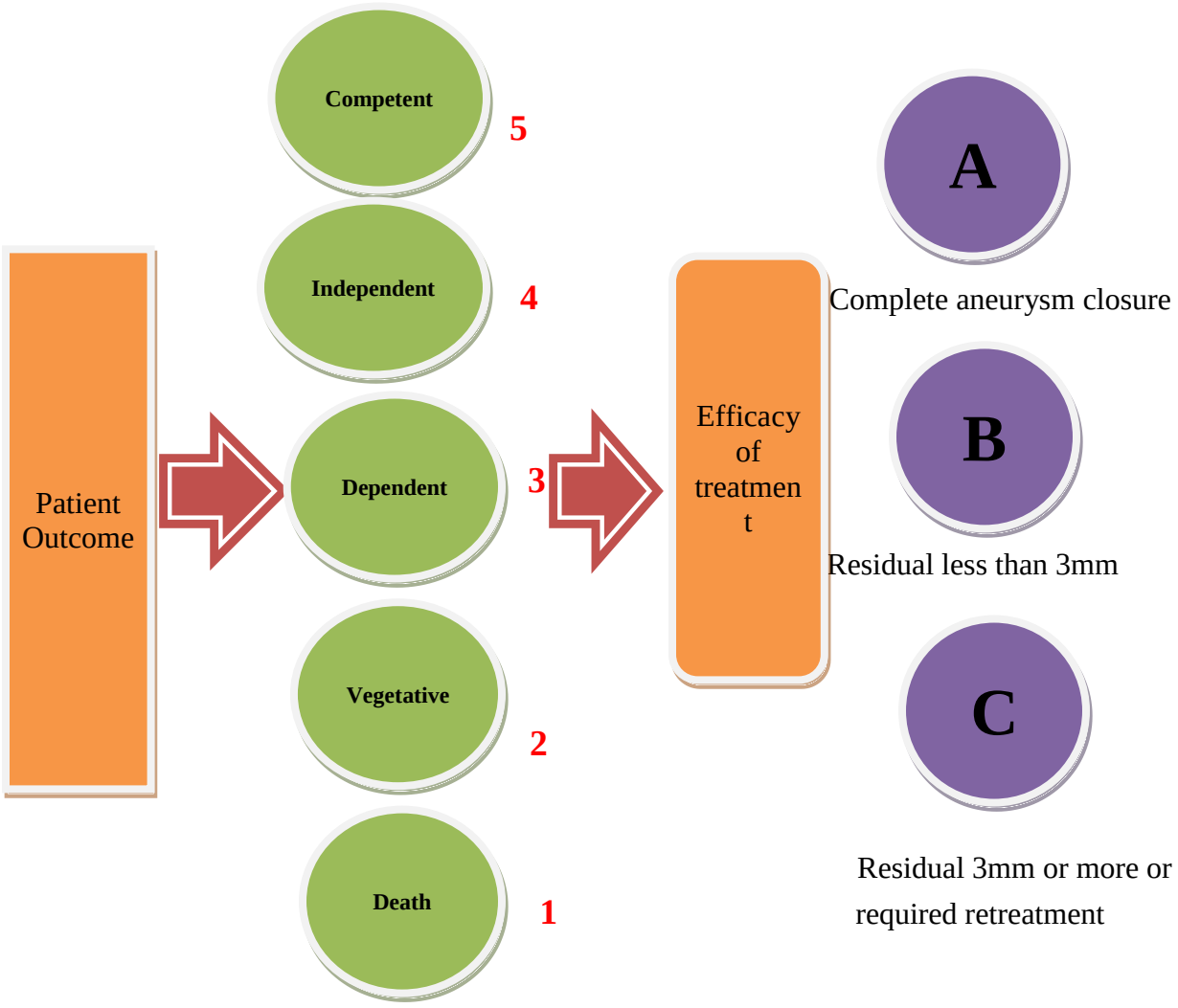
- **Efficacy of the treatment:**

For each of the above categories from grade 5 to grade 2, either A, B or C will be added;

- **A**: this indicates complete aneurysm elimination from the circulation.
- **B**: this indicates small residual at the aneurysm neck less than 3mm.
- **C**: this indicates residual 3mm or more, or shows regrowth on follow up or required retreatment.

So the final score will be; ***Table (8);***

Score	Finding	Numerical equivalent
5A	Competent, complete elimination of the aneurysm from the circulation.	13
5B	Competent, small residual at the aneurysm base less than 3mm.	12
5C	Competent, residual 3 mm or more or growth on follow up or retreatment	11
4A	Independent, complete elimination of the aneurysm from the circulation.	10
4B	Independent, small residual at the aneurysm base less than 3mm.	9
4C	Independent, residual 3 mm or more or growth on follow up or retreatment.	8
3A	Dependent, complete elimination of the aneurysm from the circulation.	7
3B	Dependent, small residual at the aneurysm base less than 3mm.	6
3C	Dependent, residual 3 mm or more or growth on follow up or retreatment.	5
2A	Vegetative, complete elimination of the aneurysm from the circulation.	4
2B	Vegetative, small residual at the aneurysm base less than 3mm.	3
2C	Vegetative, residual 3 mm or more or growth on follow up or retreatment.	2
1	Death.	1



3.3 Assessment of the new scores:

1) The accuracy and predictive value of the new score to the patient outcome and efficacy of treatment, in comparison with the commonly used scores, was studied using the Receiver operating characteristic (ROC) curve.
2) To evaluate the significance and reliability of the new score, it was retrospectively applied on a sample of patients with intracranial aneurysms divided into ruptured and unruptured groups, that were treated either via microsurgical clipping or endovascular intervention at Regensburg university hospital and the illustrated results were highly comparable to the high-quality internationally published ones.

3.4 Data analysis:

Data was analysed using IBM SPSS Statistics for Windows version 20.0 and Medcalc version 18.6. Quantitative data is expressed as means ± standard deviation, median, and range. Qualitative data is expressed as numbers and percentages. Chi-square ($\chi 2$) test was used for comparison of qualitative variables. Receiver operating characteristic (ROC) curve was constructed for the studied old and new scores, in predicting the outcome and efficacy of intracranial aneurysms, and the area under the ROC curve value with 95% CI was calculated. A 5% level was chosen as a level of significance in all statistical tests used in the study.

4. Results:

4.1 statistical *analyses of the validity and predictive value of the new* scores in comparison with traditional scores by ROC reveal the following:

- High specifity and sensitivity of the new scores to evaluate the efficacy of the treatment modalities with AUC are so close to 1.0 and high significant p-value. In comparison with the traditionally-used score which was not significant at all.
- The new scores are significant as well as the traditional scores used to evaluate patient outcome but BRS score is not expressive for the severity of neurological impairment especially for rupture aneurysms group. The ex BRS score is highly significant as well as the traditional scores to evaluate the patient outcome and differentiate it into different degree of neurological impairment.

Table (9): Receiver operating characteristic (ROC) curve of old and new scores in predicting efficacy of treatment

Score	Cutoff	AUC	95% CI	Sensitivity	Specificity	P-value
Complete aneurysm closure						
GOS	≤ 4	0.507	0.429 - 0.585	1.47	100	0.896
Modified Rankin score	>1	0.507	0.429- 0.585	1.47	100	0.896
BRS Score	>6	0.982	0.949 - 0.996	97.79	100	<0.001*
Extended BRS Score	>12	0.982	0.949 - 0.996	97.79	100	<0.001*
Residual less than 3mm						
GOS	> 4	0.507	0.429 - 0.585	100	1.43	0.904
Modified Rankin score	≤ 1	0.507	0.429- 0.585	100	1.43	0.904
BRS Score	≤ 6	0.96	0.918- 0.984	100	95	<0.001*
Extended BRS Score	≤ 12	0.96	0.918- 0.984	100	95	<0.001*
Residual 3mm or more						
GOS	> 4	0.506	0.428 - 0.584	100	1.23	0.962
Modified Rankin score	≤1	0.506	0.428 - 0.584	100	1.23	0.962
BRS Score	≤ 6	0.941	0.894 - 0.972	100	81.6	<0.001*
Extended BRS Score	≤ 12	0.941	0.894 - 0.972	100	81.6	<0.001*
The need for retreatment						
GOS	> 4	0.506	0.428 - 0.584	100	1.23	0.962
Modified Rankin score	≤1	0.506	0.428 - 0.584	100	1.23	0.962
BRS Score	≤ 5	0.982	0.948 - 0.996	100	97.55	<0.001*
Extended BRS Score	≤ 11	0.982	0.948 - 0.996	100	97.55	<0.001*

*** Statistically significant**

Figure (17): Receiver operating characteristic (ROC) curve of old and new scores in predicting complete aneurysm closure

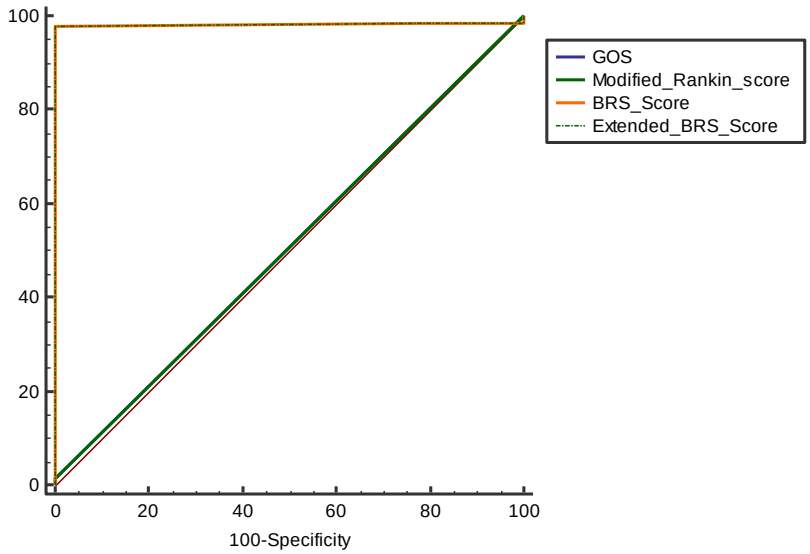


Figure (18): Receiver operating characteristic (ROC) curve of old and new scores in predicting residual less than 3mm

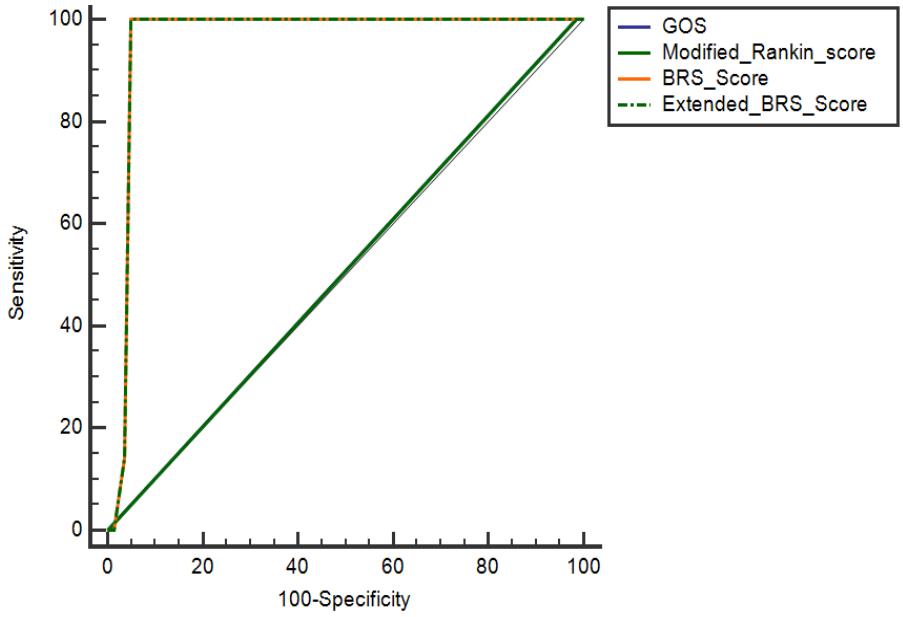


Figure (19): Receiver operating characteristic (ROC) curve of old and new scores in predicting residual 3mm or more

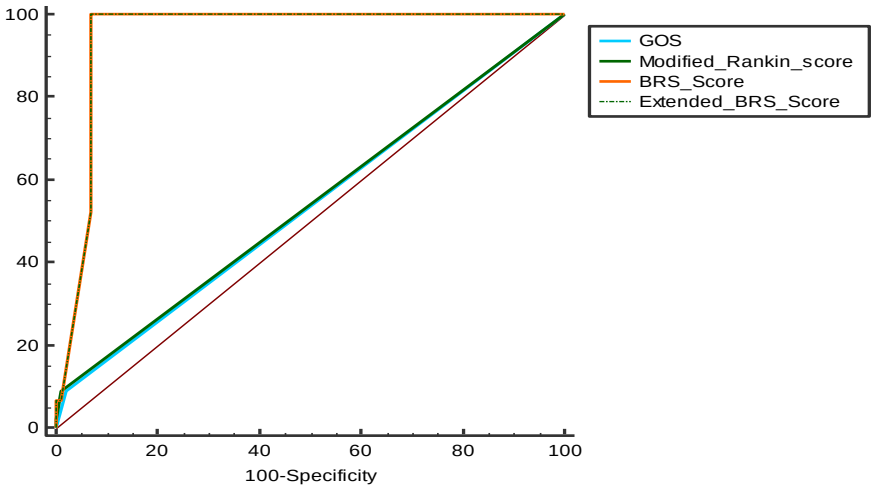


Figure (20): Receiver operating characteristic (ROC) curve of old and new scores in predicting retreatment

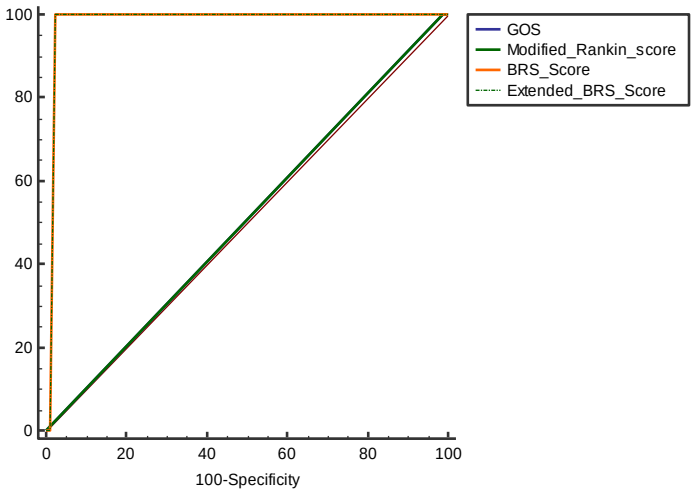
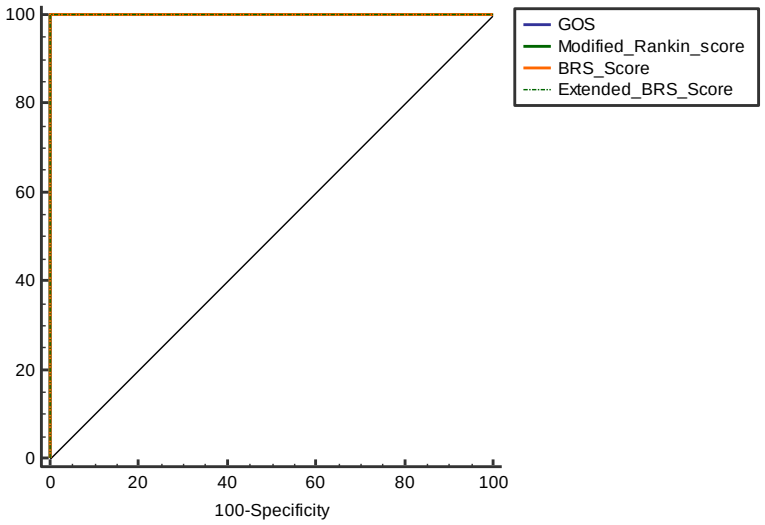


Table (10): Receiver operating characteristic (ROC) curve of old and new scores in predicting outcome

Score	Cutoff	AUC	95% CI	Sensitivity	Specificity	P-value
Neurological deficit						
GOS	**≤ 4**	**1**	**0.978 to 1**	**100**	**100**	**<0.001***
Modified Rankin score	**>1**	**1**	**0.978 to 1**	**100**	**100**	**<0.001***
BRS score	**≤ 4**	**1**	**0.978 to 1**	**100**	**100**	**<0.001***
Extended BRS score	**≤ 10**	**1**	**0.978 to 1**	**100**	**100**	**<0.001***

*** Statistically significant**

Figure (21): Receiver operating characteristic (ROC) curve of old and new scores in predicting neurological deficit



4.2 *To assess the reliability and significance of the new scores*, the scores are retrospectively applied to a 532 patients harbouring 622 intracranial aneurysms (62 patients have multiple aneurysm; all are asymptomatic unruptured aneurysm, only 6 patient have unruptured aneurysm incidentally discovered with ruptured one); 313 aneurysms were unruptured and 309 aneurysms were ruptured; in the ruptured group, 130 aneurysms treated with microsurgical clipping and 179 aneurysms treated with interventional endovascular techniques. For the unrupturd aneurysms group, 168 aneurysms treated with microsurgical clipping and 145 aneurysms treated with interventional endovascular techniques and the traditional results are as follows:

Table (11): Distribution of the studied patients by gender, age, family history and treatment group (No.=622).

Characteristics	Summary statistics
Gender	
Male	**196 (31.5%)**
Female	**426 (68.5%)**
Age(years)	
Mean± S.D.	**53.9 ± 11.58**
Median (Range)	**53 (9 - 86)**
Positive family history	
No	**611 (98.2%)**
Yes	**11 (1.8%)**
Treatment groups	
Clipping ruptured	**130 (20.9%)**
Clipping unruptured	**168 (27%)**
Coiling ruptured	**179 (28.8%)**
Coiling unruptured	**145 (23.3%)**

Figure (22): Distribution of the studied patients by treatment group (No=622).

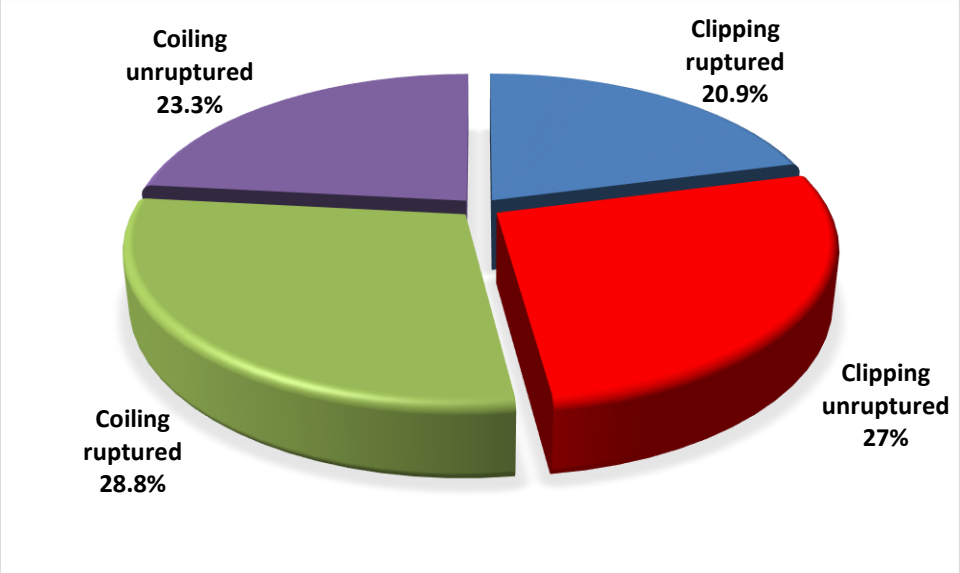


Table (12): comparison between the four treatment groups regarding outcome and efficacy

Parameter	clipping ruptured (N=130)	clipping unruptured (N=168)	coiling ruptured (N=179)	Coiling unruptured (N=145)	P-value
No residual in Follow up **No** **Yes**	**11 (8.5%)** **119 (91.5%)**	**32 (19%)** **136 (81%)**	**68 (38%)** **111 (62%)**	**50 (34.5%)** **95 (65.5%)**	**<0.001 ***
Residual less than 3mm **No** **Yes**	**122 (93.8%)** **8 (6.2%)**	**140 (83.3%)** **28 (16.7%)**	**115 (64.2%)** **64 (35.8%)**	**101 (69.7%)** **44 (30.3%)**	**<0.001 ***
Residual 3mm or more **No** **Yes**	**127 (97.7%)** **3 (2.3%)**	**163 (97%)** **5 (3%)**	**175 (97.8%)** **4 (2.2%)**	**139 (95.9%)** **6 (4.1%)**	**0.744**
Retreatment **No** **Yes**	**126 (96.9%)** **4 (3.1%)**	**163 (97%)** **5 (3%)**	**157 (87.7%)** **22 (12.3%)**	**120 (82.8%)** **25 (17.2%)**	**<0.001 ***
Post-operative GCS 15 **No** **Yes**	**30 (23.1%)** **100 (76.9%)**	**0 (0.0%)** **168 (100%)**	**45 (25.1%)** **134 (74.9%)**	**0 (0.0%)** **145 (100%)**	**<0.001 ***
Post-operative GCS 12-14 **No** **Yes**	**124 (95.4%)** **6 (4.6%)**	**168 (100%)** **0 (0.0%)**	**173 (96.6%)** **6 (3.4%)**	**145 (100%)** **0 (0.0%)**	**0.005***
Post-operative vegetative **No** **Yes**	**124 (95.4%)** **6 (4.6%)**	**168 (100%)** **0 (0.0%)**	**177 (98.9%)** **2 (1.1%)**	**145 (100%)** **0 (0.0%)**	**0.001***
Death **No** **Yes**	**113(86.9%)** **17 (13.1%)**	**168 (100%)** **0 (0.0%)**	**143 (79.9%)** **36 (20.1%)**	**145 (100%)** **0 (0.0%)**	**<0.001 ***
Post-operative Neurological deficit **No** **Yes**	**107 (82.3%)** **23 (17.7%)**	**166 (98.8%)** **2 (1.2%)**	**152 (84.9%)** **27 (15.1%)**	**141 (97.2%)** **4 (2.8%)**	**<0.001 ***

P- Value was calculated by Chi Squa

*** Statistically significant**

Table (13): Distribution of the studied patients by old and new scores (No=622).

Characteristics	Summary statistics
GOS	
1	**55 (8.8 %)**
2	**10 (1.6%)**
3	**33 (5.3 %)**
4	**28 (4.5%)**
5	**496 (79.8%)**
Modified Rankin score	
1	**497 (79.9%)**
2	**17 (2.7%)**
3	**34 (5.5 %)**
4	**11 (1.8%)**
5	**9 (1.4%)**
6	**54 (8.7%)**
New score	
A-	**47 (7.6 %)**
A+	**359 (57.7%)**
B-	**19 (3.1 %)**
B+	**83 (13.3 %)**
C-	**3 (0.5%)**
C+	**56 (9%)**
D	**55 (8.8 %)**
New score	
1	**55 (8.8 %)**
2C	**1 (0.2%)**
2A	**7 (1.1%)**
3B	**7 (1.1%)**
3A	**27 (4.3%)**
4C	**3 (0.5%)**
4B	**9 (1.4%)**
4A	**15 (2.4%)**
5C	**56 (9%)**
5B	**83 (13.3%)**
5A	**359 (57.7%)**

Table (14): comparison between the four treatment groups regarding old and new scores

Score	clipping ruptured (N=130)	clipping unruptured (N=168)	coiling ruptured (N=179)	Coiling unruptured (N=145)	P-value
GOS					
1	**18 (13.8%)**	**0 (0.0%)**	**37 (20.7%)**	**0 (0.0%)**	**<0.001***
2	**7 (5.4%)**	**0 (0.0%)**	**3 (1.7%)**	**0 (0.0%)**	
3	**19 (14.6%)**	**0 (0.0%)**	**14 (7.8%)**	**0 (0.0%)**	
4	**6 (4.6%)**	**2 (1.2%)**	**14 (7.8%)**	**6 (4.1%)**	
5	**80 (61.5%)**	**166 (98.8%)**	**111 (62%)**	**139 (95.9%)**	
Modified Rankin score					
1	**80 (61.5%)**	**166 (98.8%)**	**111 (62%)**	**140(96.6%)**	**<0.001***
2	**3 (2.3%)**	**0 (0.0%)**	**10 (5.6%)**	**4 (2.8%)**	
3	**16 (12.3%)**	**2 (1.2%)**	**15 (8.4%)**	**1 (0.7%)**	
4	**8 (6.2%)**	**0 (0.0%)**	**3 (1.7%)**	**0 (0.0%)**	
5	**6 (4.6%)**	**0 (0.0%)**	**3 (1.7%)**	**0 (0.0%)**	
6	**17 (13.1%)**	**0 (0.0%)**	**37 (20.7%)**	**0 (0.0%)**	
BRS score					
A-	**29 (22.3%)**	**2 (1.2%)**	**15 (8.4%)**	**1 (0.7%)**	
A+	**73 (56.2%)**	**133 (79.2%)**	**59 (33%)**	**94 (64.8%)**	**<0.001***
B-	**3 (2.3%)**	**0 (0.0%)**	**13 (7.3%)**	**3 (2.1%)**	
B+	**3 (2.3%)**	**26 (15.5%)**	**33 (18.4%)**	**21 (14.5%)**	
C-	**0 (0.0%)**	**0 (0.0%)**	**3 (1.7%)**	**0 (0.0%)**	
C+	**4 (3.1%)**	**7 (4.2%)**	**19 (10.6%)**	**26 (17.9%)**	
D	**18 (13.8%)**	**0 (0.0%)**	**37 (20.7%)**	**0 (0.0%)**	
Extended BRS score					
1	**18 (13.8%)**	**0 (0.0%)**	**37 (20.7%)**	**0 (0.0%)**	
2C	**0 (0.0%)**	**0 (0.0%)**	**1 (0.6%)**	**0 (0.0%)**	**<0.001***
2A	**6 (4.6%)**	**0 (0.0%)**	**1 (0.6%)**	**0 (0.0%)**	
3B	**1 (0.8%)**	**0 (0.0%)**	**6 (3.4%)**	**0 (0.0%)**	
3A	**18 (13.8%)**	**0 (0.0%)**	**9 (5%)**	**0 (0.0%)**	
4C	**0 (0.0%)**	**0 (0.0%)**	**2 (1.1%)**	**1 (0.7%)**	
4B	**1 (0.8%)**	**0 (0.0%)**	**6 (3.4%)**	**2 (1.4%)**	
4A	**6 (4.6%)**	**2 (1.2%)**	**6 (3.4%)**	**1 (0.7%)**	
5C	**4 (3.1%)**	**7 (4.2%)**	**19 (10.6%)**	**26 (17.9%)**	
5B	**3 (2.3%)**	**26 (15.5%)**	**33 (18.4%)**	**21 (14.5%)**	
5A	**73 (56.2%)**	**133 (79.2%)**	**59 (33%)**	**94 (64.8%)**	

P- Value was calculated by Chi Square test

*** Statistically significant**

Figure (23): comparison between the four treatment groups regarding GOS

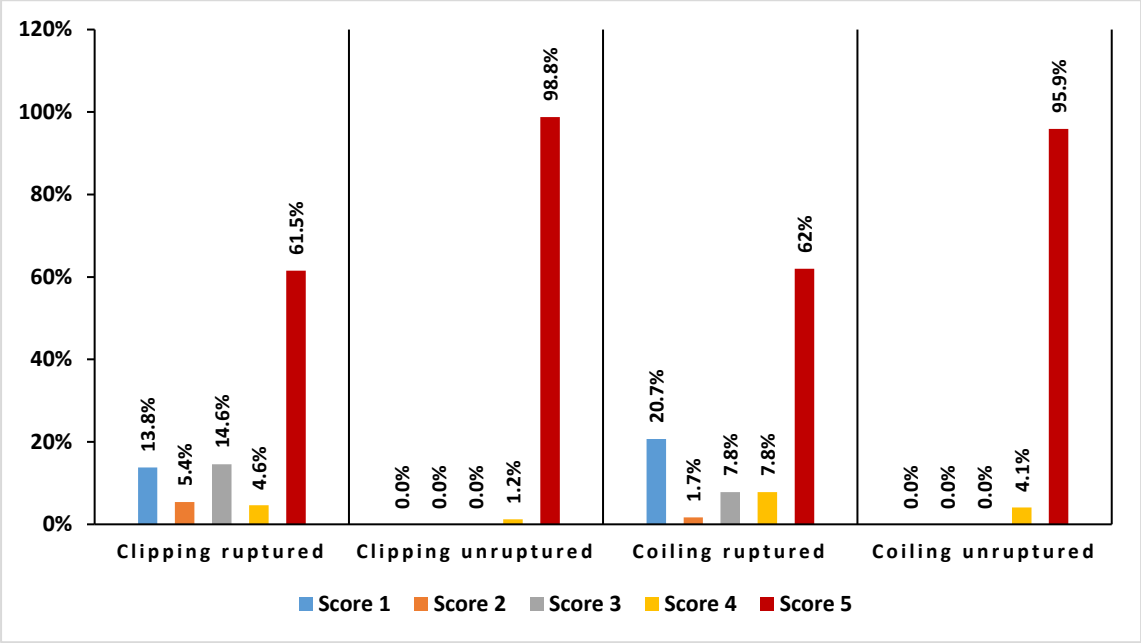
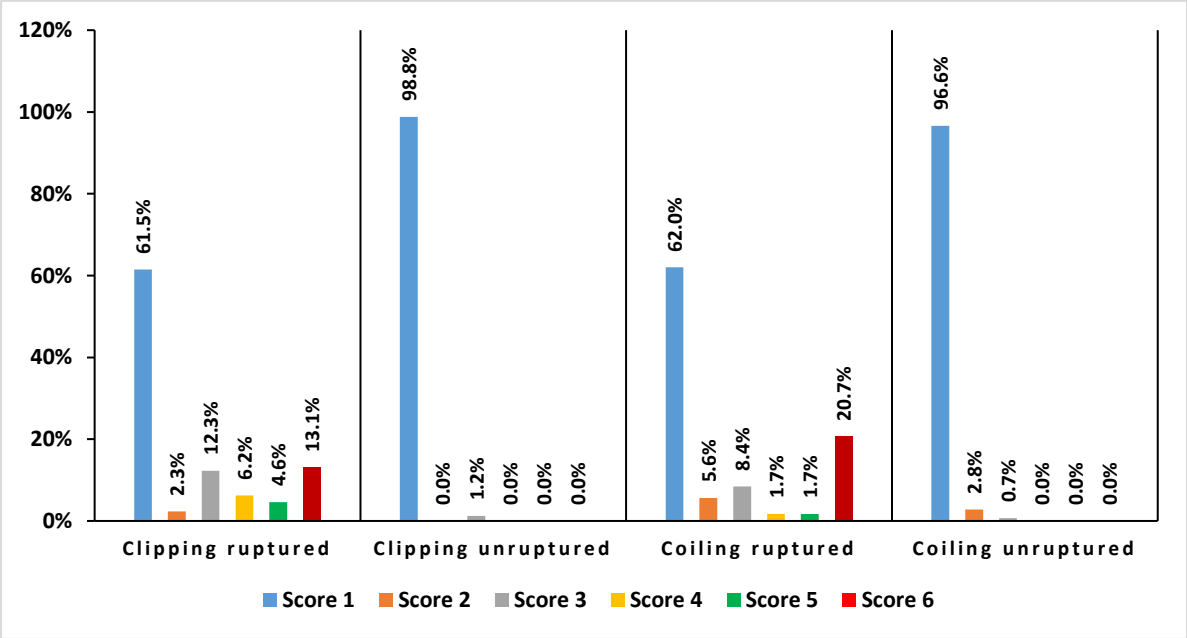


Figure (24): comparison between the four treatment groups regarding Modified Rankin score



After application of the new score the results are as follows:

4.3 Outcome with BRS score (Publication I):

For unruptured aneurysms group:

According to the new score; 1- good patient outcome was 98.8% (n=166) for clipping group; complete aneurysm occlusion "BRS score A+" was 79.2% (n=133), partial aneurysm closure with neck remnant less than 3mm "BRS score B+" was 15.5% (n=26) and aneurysm residual at the neck 3mm or more or required retreatment "BRS score C+" was 4.2% (n=7). compared to endovascular group; good patient outcome was 97.2% (n=141); complete aneurysms closure "BRS score A+" was 64.8% (n=94), partial aneurysm closure with neck remnant less than 3mm "BRS score B+" was 14.5% (n=21) and neck remnant 3mm or more or required retreatment "BRS score C+" was 17.9% (n=26).

2- patient impairment was 1.2% (n=2) in clipping group, all was complete aneurysm closure "BRS score A-".compared to 2.8% (n=4) in endovascular group; 0.7% (n=1) was complete aneurysm closure "BRS score A-" and 2.1% (n=3) was partial aneurysms closure with neck residual less than 3mm "BRS score B-".

By the traditionally used score; best outcome; GOS 5 and mRankin 1 was 98.8%, 98.8% (n=166) for clipping group and 95.9% (n=139), 96.6% (n=140) for endovascular group respectively. Poor patient outcome was; for clipping group 1.2% (n=2) GOS 4 and 1.2% (n=2) mRankin scale3. For endovascular group was 4.1% (n=6) GOS 4 and 2.8% (n=4) m Rankin scale 4 and .0.7% (n=1) mRankin scale 3.

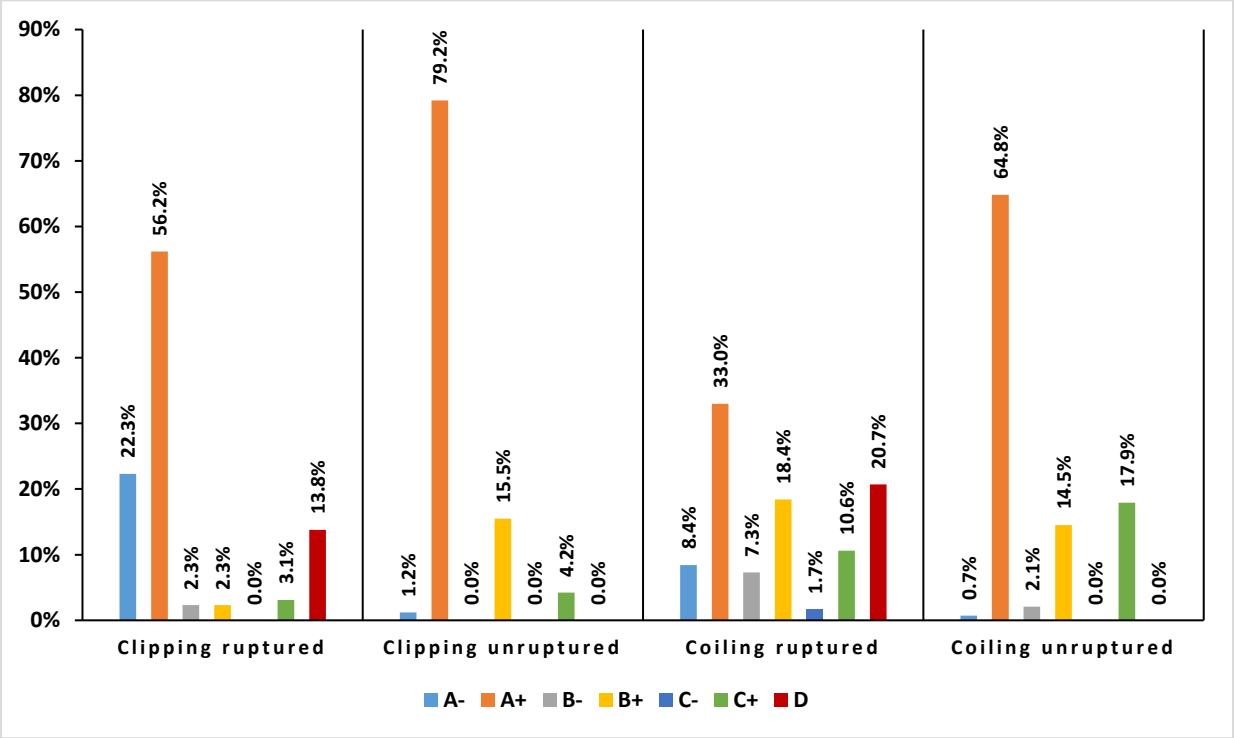
For rupture aneurysms group:

By new score: 1- good patient outcome was 61.5% (n=80) for clipping group; complete aneurysm closure "BRS score A+" was 56.2% (n=73), partial aneurysm closure with neck remnant less than 3mm "BRS score B+" was 2.3% (n=3) and aneurysm residual at the neck 3mm or more or required retreatment "BRS score C+" was 3.1% (n=4). compared to endovascular group; good patient outcome was 62% (n=111); complete aneurysms closure "BRS score A+" was 33% (n=59), partial aneurysm closure with neck remnant less than 3mm "BRS score B+" was 18.4% (n=33) and neck remnant 3mm or more or required retreatment "BRS score C+" was 10.6% (n=19).

2- patient impairment was 24.6% (n=32) in clipping group, complete aneurysm closure BRS "score A-" was 22.3% (n=29) and 2.3% (n=3) was partial aneurysms closure with neck residual less than 3mm "BRS score B-" .compared to 17.3% (n=31) in endovascular group; 8.4% (n=15) was complete aneurysm closure "BRS score A-", 7.3% (n=13) was partial aneurysms closure with neck residual less than 3mm "BRS score B-" and 1.7% (n=3) neck residual 3mm or more or required retreatment "BRS score C-". Mortality "BRS score D" was 13.8% (n=18) for clipping group and 20.7% (n=37) for endovascular group.

By the traditionally used score; best outcome; GOS 5 and mRankin 1 was 61.5% (n=80) for clipping group and 62% (111) for endovascular group in both scores. Poor patient outcome was 24.7% (n=32) for clipping group and 17.3% (n=31) in endovascular group by both scores in different degree of neurological impairment. Mortality was 13.8% (n=18) for clipping group and 20.7% (n=37) in endovascular group by both scores.

Figure (25): comparison between the four treatment groups regarding BRS score



4.4 Outcome with Extended BRS Score (publication II):

For unruptured aneurysms group:

According to the new score;

1- good competent patient outcome was 98.8% (n=166) for clipping group; complete aneurysm occlusion "exBRS score 5A" was 79.2% (n=133), partial aneurysm closure with neck remnant less than 3mm "exBRS score 5B" was 15.5% (n=26) and aneurysm residual at the neck 3mm or more or required retreatment "exBRS score 5C was 4.2% (n=7). Compared to endovascular group; good competent patient outcome was 97.2% (n=141); complete aneurysms closure "exBRS score 5A" was 64.8% (n=94), partial aneurysm closure with neck remnant less than 3mm "exBRS score 5B" was 14.5% (n=21) and neck remnant 3mm or more or required retreatment "exBRS score 5C" was 17.9% (n=26).

2- Patient impairment: all was independent patient outcome exBRS score 4 (mild neurological impairment). was 1.2% (n=2) in clipping group, all was complete aneurysm closure "exBRS score 4A".compared to 2.8% (n=4) in endovascular group; 0.7% (n=1) was complete aneurysm closure "exBRS score 4A", 1.4% (n=2) was partial aneurysms closure with neck residual less than 3mm "ex BRS score 4B" and neck residual 3mm or more "exBRS score 4C" was 0.7% (n=1).

For rupture aneurysms group:

By the new score:

- Microsurgical clipping group;

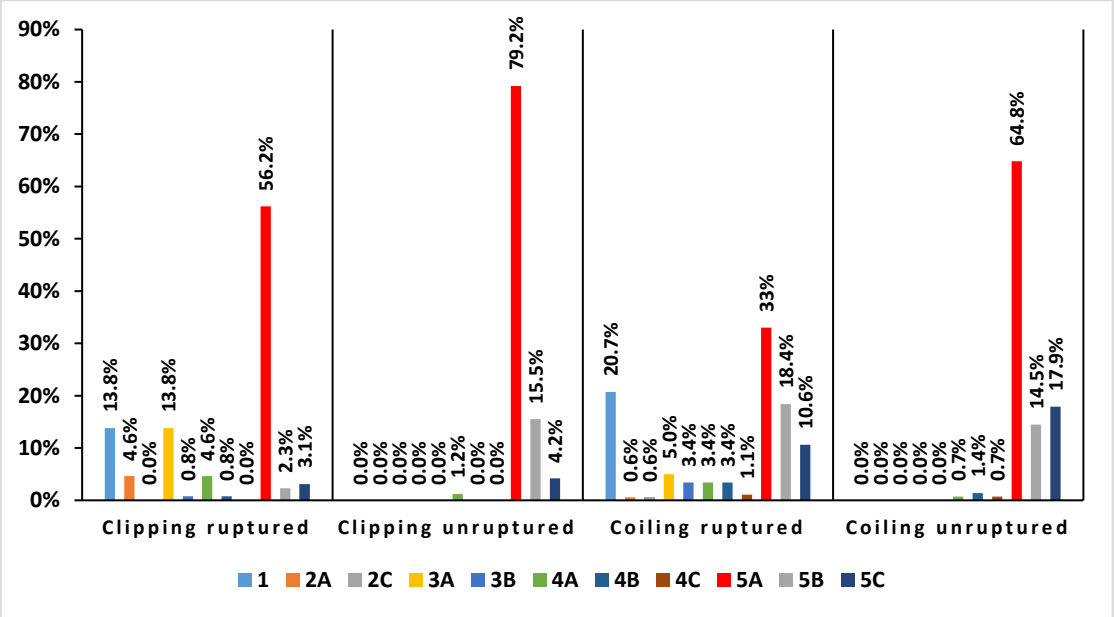
1- Good competent patient outcome was 61.6% (n=80) for clipping group; complete

aneurysm closure "exBRS score 5A" was 56.2% (n=73), partial aneurysm closure with neck remnant less than 3mm "exBRS score 5B" was 2.3% (n=3) and aneurysm residual at the neck 3mm or more or required retreatment "exBRS score 5C was 3.1% (n=4).
2- Patient impairment was 24.6% (n=26) as follows:
- Independent patient with mild neurological impairment exBRS 4 was 5.4% (n=7); complete aneurysm closure "exBRS score 4A" was 4.6% (n=6) and 0.8% (n=1) was partial aneurysms closure with neck residual less than 3mm "exBRS score 4B.
- Dependant patient with moderate to severe neurological impairment exBRS 3 was 14.6% (n=19); complete aneurysm closure "exBRS score 3A" was 13.8% (n=18), 0.8% (n=1) was partial aneurysms closure with neck residual less than 3mm "exBRS score 3B.
- Vegetative patient exBRS score 2 was and 4.6% (n=6), all was complete aneurysm closure "exBRS 2A".
-Mortality exBRS score 1 was 13.8% (n=18).

- Endovascular group:

1- Good patient outcome was 62% (n=111); complete aneurysms closure "exBRS score 5A" was 33% (n=59), partial aneurysm closure with neck remnant less than 3mm "exBRS score 5B" was 18.4% (n=33) and neck remnant 3mm or more or required retreatment "exBRS score 5C was 10.6% (n=19).
2-poor patient outcome was 17.5% (n=31) as follow;
-Independent patient with mild neurological impairment 7.9% (n=14); complete aneurysm closure "exBRS score 4A was 3.4% (n=6), 3.4% (n=6) was partial aneurysms closure with neck residual less than 3mm "exBRS score 4B" and 1.1% "(n=2) neck residual 3mm or more or required retreatment "exBRS score 4C".
-Dependant patient with moderate to severe neurological impairment 8.4% (n=15); complete aneurysm closure "exBRS score 3A" was 5% (n=9), 3.4% (n=6) was partial aneurysms closure with neck residual less than 3mm "exBRS score 3B".
-Vegetative patient was 1.2% (n=2); complete aneurysm closure "exBRS score 2A" was 0.6% (n=1), 0.6% (n=1) was neck residual 3mm or more or required retreatment "exBRS 2C".
-Mortality exBRS score 1 was 20.7% (N=37).

Figure (26): comparison between the four treatment groups regarding Extended BRS score



5. Discussion:

The selection of 3mm as the cut parameter between the second and third grade of efficacy is based on 26 studies, describing the growth rate of aneurysms 3 mm and smaller, 5 mm and smaller, and 7 mm and smaller, respectively, whereas rupture rates were reported in 7, 11, and 13 studies for aneurysms 3 mm and smaller, 5 mm and smaller, and 7 mm and smaller, respectively. The annualized growth rate was less than 3% in all. The annualized rupture rate was 0%, less than 0.5%, and less than 1% for the 3 size categories, respectively. [3, 4]

The studied group for which the score was applied, has a results in line with the international published studies i.e. ISUIA, ISAT, either in the patient outcome, rate of occlusion and the need for retreatment; so the score is highly specific and illustrative to summarized all aspect of aneurysm treatment in a sharp numerical score.

Significance of the new scores:

- Combine the neurological performance and the radiographically confirmed occlusion. The new BRS score is an easy applicable score to predict precisely the outcome after aneurysm treatment.
- This score can be applied to patients as early as the discharge date with the base line follow up angiography, also can follow the course of treatment once it is applied on each follow up at 6 months, one year…etc. So, not only does it evaluate the outcome at once, but also it follows the aneurysm on long term treatment with clear, sharp and numerical score. Score improvement or regression will give a significant indication about the long term efficacy of treatment, aneurysm regrowth, coil compaction, and clip slipping.

- With a simple sharp numerical score applied to aneurysms data, many conflicts can be easily resolved, i.e. the best treatment for each aneurysm location**,** and to decide which group will need to be followed up. So, decreasing the cost and hazard of exposure to radiation and any newly developed techniques, in the future, will be clearly evaluated, i.e. endovascular, genetic, etc…
- This score is applicable for patients with single or multiple aneurysms, as it is applied to each aneurysm separately, even the conflicting group with multiple aneurysms in whom the unruptured aneurysm are incidentally discovered with ruptured ones who have recovered with neurological impairment, BRS score will fit them very well (where the + charge will represent no recent neurological impairment and – charge will represent recent impaired level conscious or neurological deficit).

Comparing our two new scores; both scores Combine the neurological performance and the radiographically confirmed occlusion and are easy applicable scores to predict precisely the outcome after aneurysm treatment. BRS score is simpler, but has alimited value to differentiate the degree of neurological impairment especially for rupture aneurysms; exBRS score has the advantage of more significant ability to classify different degrees of neurological impairments from complete neurological intact patients passing through mild, moderate and sever neurological impairments.

Compared with the traditionally used scores such as GOS, and mRankin scale, extended BRS score can efficiently measure patient outcome with high index in stratifying the degree of neurological impairment, with the advantage of its ability to measure the efficacy of treatment modality, an advantage not provided by other scores.

The patient outcome part of the extended BRS score is based on sharp solid clinical signs which aren't subjected to any bias or interobserver conflict or changes that may occur with the commonly used scores. The point that makes the patient outcome part of the extended BRS score a golden measurement tool for the patient and brain recovery, not only in patients with cerebral aneurysms but for all patients with brain insults.

Limitation of the study:

Retrospective application of the scores, dependence on learning curve for the radiologists and application of these score to a large sample of patient with cerebral aneurysms is recommended.

6. Conclusion:

The new scores are the first available score, specified to evaluate outcomes after treatment of cerebral aneurysms, combine the neurological performance and the radiographically confirmed occlusion. These score are simple, easy applicable, reliable and allow for a standardized and objective description of the efficacy of treatment modality and patient recovery that can be used to evaluate the current modalities, i.e. microsurgical clipping, endovascular intervention or any further modality that may be developed in the future.

These scores reflect the real image of efficacy in treating cerebral aneurysms without confusion. They will play a significant role in resolving many conflicts that arise during the discussion concerning cerebral aneurysms treatment.

Acknowledgment:

I owe the deepest gratitude to the ***Egyptian Ministry of High Education, Mission sector*****,** which financed my two-year scholarship at the department of Neurosurgery, Regensburg University hospital.

I am deeply indebted to my fellowship mentor ***Prof. Dr. Alexander Brawanski***. I am very grateful to him for his continuous support, advice and encouragement and invaluable guidance during my work. He saved me a lot of time by always being available. He pushed me forward and set appropriate timelines, which kept the work on track without periods of deceleration. His good sense of humor, even when providing his constructive criticism, improved the working atmosphere remarkably. I am very appreciative of his intelligence and his constant offers to help even before being asked.

I give my heartfelt thanks to the entire staff of neurosurgery, intervention neuroradiology and anesthesiology for their friendly attitudes, which created such a pleasant working environment.

Last, but not least, I would like to thank my parents, brother, sister and my wife for their unconditional love and support which strengthened my resolve to complete this work. I feel indebted to them all, especially my wife, Rahma, who willingly assumed all household responsibilities while being pregnant and sacrificed her time and effort to allow me the time to focus solely on my work. I cannot find the words to express my gratitude.

Bahaa G. Hassanin
Regensburg, 2019

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A;

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