Research Article

Brainstem Cavernomas: Functional Results and Prognosis Long-Term Follow-Up Cohort of Patients Treated Non-Operatively and Operatively

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Abstract

Introduction: Cerebral cavernous malformation (CCM) is an abnormally large collection of low flow vascular channels without brain parenchyma intervening between the sinusoid vessels. Brainstem Cavernoma Malformations (BSCMs) account for 0.5 to 0.9 % in the literature. Functional results, bleeding and subsequent bleeding have been reported in several studies in the literature relative to the management both for surgery and non-operative treatment. Our study aimed to evaluate long term functional outcomes of patients treated both operatively and non-operatively.

Materials and Methods: A cohort of 44 patients has been followed for 29 years either retrospectively and prospectively. The retrospective period extended from October 1992 to September 2020 while the prospective one was the one year follow-up (FU) till September 2021. Data have been collected from patients' archived files, schedule visits to the physician and phone calls. Patients in whom the diagnosis of BSCMs have been confirmed clinically and by image findings were included in our study. Functional status were assessed using both modified Rankin Scale (mRs) score over an interval from 0 to 5 and Karnosky Index (KI) from 0 to 100. Muscle strength was assessed by muscular testing over an interval from 0 to 5. Zero meant absence of muscular contraction while 5 was normal muscle motion. Magnetic Resonance Imaging (MRI) was systematically carried out in patients who had not got imaging control for 2 years. During FU period each patient who presented a new and sudden clinical symptom related to the involvement of brainstem was reassessed clinically and image work-up to rule out a rebleeding episode. Univariate analysis was conducted for establishing statistical significance between early haemorrhages, rebleeding, clinical and demographic features.

Results: Forty patients presented 57 bleeding episodes. Thirteen patients (29.54 %) underwent surgery. Thirteen ones had eighteen recurrent bleeding episodes, i.e. a rate of 31.69 ± 0.65 SD. Initial average mRs score was 0.67 ± 0.79 SD for the conservative treatment group while the operated on patients had 2.15 ± 1.14 SD. Postoperatively, mRs score was 2.07 ± 1.44 SD. Final FU mRs was 0.93 ± 00 SD and 1.81 ± 00 SD for non-operative and operative treatment respectively. Surgery reduced the rate of rebleeding (*p=0.04*). The long-term functional outcome improvement was similar between non-operative and operative treatment (*p=0.27*). The predictive factors of bleeding and rebleeding reported were woman gender (*p=0.0074*) and pons location (*p=0.0001*) while age and Zabramski radiologic type were not significant.

Conclusion: Our finding sustains similar functional outcomes to both non-operative and operative treatment. Nevertheless, surgery reduced the rate of rebleeding and remains largely related to the precise patient selection regarding clinical, radiologic and microsurgery features.

Keywords: Cavernomas, Brainstem, Bleeding, Surgery, Conservative, Follow-up.

Abbreviations: *KRTI1* = Krev interaction protein tapped protein 1; *PDCD10* = Programmed Cell Death protein 10

1. Introduction

Cerebral Cavernomas Malformations (CMs), cavernous angiomas (CA) or cerebral hemangiomas (CH) are a set of abnormally large collection of low flow vascular channels without brain parenchyma intervening between sinusoidal capillaries (1). In 1846 Karl Von Rokitanski described for the first the CA. In 1863 Virchow described precisely its histopathological features. In 1927 Kufs described the first family case. In 1966 McCORMICK recognised cavernomas as being one of the great classes of Cerebral Vascular Malformations (CVM) that encompass Arterio-Venous Malformations (AVM), Developmental Venous Abnormalities and capillary telangiectasias. In 1976 the study published by Yasargil and Voigt opened the modern era of the history of cavernomas implementing microsurgical approach. In 1997 Houtteville confirmed the dynamic feature of CA changing over time under the influence of hemorrhagic factors and angiogenic growth (1).

Overall prevalence of cerebral CMs accounts in general population accounts of 0.4 to 4% (2). BSCMs prevalence is estimated at 0.5 to 0.9 % (3). The clinical feature of BSCMs is highly variable both in its symptomatic aspects and in the naturel history of its clinical evolution. The annual bleeding rate of BSCMs with neurologic impairement accounts for 2.7 to 5 % per patient-year, twice more than other locations(2). Rebleeding episodes lead to severe neurologic deficits most often irreversible including brainstem neurovegetative disorders(1).

Most of BCMs lesions are sporadic however 20 % of hereditary family cases with a dominant character resulting in the presence of multiple unsystematized locations(2). Family cases are more symptomatic than sporadic ones. Three genes encoding specific proteins have been identified as being causative of cavernomas development: Cerebral Cavernomas Malformation genes 1 and their respective proteins *CCM1* (*KRIT1*), *CCM2* (*CCM2 protein*), *CCM3* (*PDCD10*) whose mutations of ones of these 3 genes can lead to a cerebral cavernomatosis indicating a relatively high genetic penetrance (2).

BSCMs are diagnosed in young or adult subjects, can develop de novo or even spontaneously regress during follow-up period. A comprehensive history is of critical importance to avoid potentially morbid interventions(4). The gold standard of diagnosis work-up is magnetic resonance imaging (MRI). BSCMs are critical lesion that require a timely and proper intervention(4).Surgical management remains controversial in the literature although it was the first treatement approach. However with microsurgery techniques in one hand and aid tools such as neuronavigation, intraoperative potentials evoked, functional tractography, several studies reported the benefit of surgery(2). Surgery highly reduces rebleeding rate but surgical resection of BSCMs remains highly morbid. The question related to the functional outcome and rebleeding rate of those patients has been reported in the literature however there is controversial related to the benefit of conservative versus surgery in long-term follow-up(1).

2. Materials and Methods

A literature review was performed through electronic search in PubMed, PMC, HINARI, Google Scholar and Embase. The keywords used for literature review were as follow: Brainstem, Cavernomas, surgery, non-operative, conservative, surgical treatment, microsurgery, malformations, hemorrhage and bleeding, rebleeding, natural history. Literature review could allow to select only studies related BSCMs. Our study is an observational cohort both retrospectively and prospectively from 1992 to 2021. The retrospective period extended from October 1992 to September 2020 however the prospective one extended from October 2020 to September 2021. During our study period 44 patients diagnosed with BSCMs have been followed in single neurosurgery department of NICE (France). Data have been collected from patients' archived files, during schedule visits to the physician and lastly by phone call. There was any code for sporadic BSCMs however the family case was identified Q.28.3 in the International Classification of Disease 10 (*ICD10*). Were included in our study patients who consented freely, in whom the diagnosis of BSCMs was confirmed by imaging and who were followed clinically and radiologically by MRI during our study period. Were excluded in our study lost patients to FU, those who opted out of tracking and those who had supra-tentorial lesion without brainstem involvement.

The concept of family cavernomas has been systematically sought and a complete anamnesis made it possible to obtain clinically significant brutal neurologic symptoms after an initial episode was previously recorded and therefore considered as a rebleeding till imaging rules out. Initial physical examination included the assessment of functional independence score using both mRs and KI. The modified Rankin scale was evaluated on a scale of 0 to 6 with 0 indicating no symptoms and 5 severe disability and 6 death (Table 1).

The KI was evaluated on a scale of 0 to 100 while 0 indicating death and the maximum 100 meaning a patient able to carry out normal living activities. Clinical assessment included initial neurologic examination at the onset of hemorrhage, immediate neurologic status for those operated on and long-term physical examination including neurologic sequelae both operative and non-operative group.

Diagnosis criteria included both clinical and imaging findings. MRI was the main diagnosis tool with specific sequences allowing to carry out Zabramski classification for dating the BSCM hematoma(1). Non-operative treatment was carrying out for paucisymptomatic patients who underwent only one bleeding episode whose lesion was small in size and located in an anatomical eloquent area. Surgery was performed in case of 2 bleeding episodes and the outcrop of the lesion on the pial surface of brainstem. In addition, age, symptoms, lesion size and safe entry zone were included.

Table 1: Modified Rankin scale score.

Score	Description
0	No symptoms
1	No significant disability, able to carry out usual activities, despite some symptoms
2	Slight disability, able to look after own affairs without assistance, but unable to carry out previous activities
3	Moderate disability, requires some help, but able to walk unassisted
4	Moderately severe disability, unable to attend to own body needs without assistance or unable to walk unassisted
5	Severe disability requiring constant nursing care and attention, bedridden, incontinent
6	Death

Modified Rankin scale is assesses functional independence score ranging from 0 to 6. Zero indicates no symptoms while 5 a severe disability possible and 6 means death.

3. Results

Both operative and non-operative patients demographic and clinical features are summarized in table 2 and 3 however clinical and imaging features of operative group are on table 4. The BSCMs revealed bleeding event in 40 patients (90.9%) with neurologic signs most often while 4 patients had performed MRI having led to an incidental diagnosis. Physical examination depicted cranial nerves palsy in 28 patients (63.63 %) with monocular or mixed diplopia being the highest, facial nerve palsy in 7 patients (15.9 %), facial hypoesthesia in 4 patients, and swallowing disorders in 2 patients and cerebellar syndrome in 8 patients (18.18%). Motor deficit was found in 18 patients (40.9 %), hemi paraesthesia or/ and hemi paresis was found 8 patients (18.18%). The initial mRs score and KI were respectively 1.81±1.14 SD and 82±10.69 SD both operative and non-operative patients. Pre-operative mRs score was 2.15±1.14.

Table 2: Patients demographic and clinical features both non-operative and operative group.

Patient number	N= 44
Average age/ year at diagnosis	45
Family cavernoma in patients	10/44
Bleeding rate in female (Bleeding/F)	39/19
Bleeding rate in in male (Bleeding/M)	18/18
Revealing mode : neurologic deficit	36 (81.81 %)
Cranial nerves palsy	28 (63,63 %)
Motor deficit	18 (40.9 %)
Sensitive deficit	8 (18.18%)
Cerebellar syndrome	8 (18.18%)

Early hemorrhage episode/Patients	40/44
Rebleeding rate/Patients	17/44
Early KI both operative and non-operative	82±10.69 SD
Early mRs score both operative and non-operative	1.81±1.14 SD
KI preoperatively	76±9.23 SD
KI postoperatively	75±9.23 SD
Patients mRs preoperatively ≤ 2	31
Patients mRs postoperatively ≥ 2	6/13

Table 2 shows patients demographic and clinical features. Female have presented 81.81 % of bleeding rate. Neurologic deficits were the common revealing signs. mRs and KI showed a good functional outcome both operative and non-operative group.

In our study, there was an overall 57 bleeding episodes in 40 patients. Thirty patients presented only one hemorrhage episode. Six and 2 patients presented respectively 2 and 3 bleeding episodes. One patient presented the highest rate of bleeding i.e. 6 altogether. The annual bleeding rate was 3.82±2.27 SD patient-year. Thirteen patients presented rebleeding during FU i.e. 18 rebleeding episodes with overall rebleeding rate estimated to 31±0.65 SD (%). Patients from operative group presented at least one bleeding episode preoperatively which was causative of neurologic deficit.

Twenty tree pons lesion locations were predominant (52.27%) followed by mesencephalon, cerebral peduncle and bulbo-pontic junction i.e. 36.36 %, 18.18% and 9.09 % respectively. Twelve lesions were located in left pons, 10 in right pons and a last median one. Five mesencephalon lesion locations were reported (11.36 %) with 2 in left side mesencephalon and 3 in right side. Eight cerebral peduncle locations were found either 4 at right side and 4 at left one. Four bulbo-pontic lesion locations were reported i.e. 3 in left side and the last one in right. Tree mesencephalo-thalamic lesions and one mesencephalo-pontic lesion were too reported (Table 3). Average size of lesions was 13.42±0.3 SD mm. Lesions were superficial in 18 patients i.e. 6 in operative group. Deep lesion locations without outcrop of pial surface were reported in 23 patients i.e. 5 in operative group. In addition there were some extra-brainstem locations most often supratentorial in 22.72 % of cases reported. Developmental Vein Abnormality (DVA) was associated in 15 BSCMs patients (34%).

Table 3: Operative group imaging features.

Number		N=13
Average lesion size (mm)		13.42±6.84 SD
AVD associated to BSCMs		15
Locations	Mesencephalon	5
	Cerebral peduncle	8
	Pons	23
	Medullar bulb	5
	Thalamus	3
Pia matter and ependymal location distance (mm)		4.23±2.73 SD
Average time between diagnosis and surgery for 8 patients operated on in subacute period (day)		12±9.91 SD
Average time between diagnosis and surgery for 6 patients operated on after 3 months (day)		40±9.07 SD
Average time between diagnosis and surgery for patients operated on in overall series (months)		3.32±6.48SD

Table 3 showed operative group characteristics. The highest BSCMs location were pons. DVA were associated with BSCMs in 15 cases.

Thirteen patients underwent surgery (29.54%). The average time between diagnosis and surgery was 12±9.91 SD days for patients operated on in sub-acute period with extremes of 24 hours to 30 days. Six patients have been operated on far from hemorrhage event when rebleeding occurred with intervals ranging from 5 months to 3 years. Median or lateral transvermien suboccipital approach was the highest surgical procedure performed in 8 out of 13 patients operated on. Left subtemporal approach was performed in 5 patients whose lesions were located in cerebral peduncle. Each resected BSCMs was then addressed to histopathological analysis and all of them has been confirmed.

Average FU period was 127.08 months i.e. 29 years. Long-term FU reported an overall mRs score of 0.93±00 SD. Non-operative long-term FU had a mRs score of 0.67±0.79 SD. Patients operated on had a preoperative mRs score of 2.15±1.14 SD. This latter had an average immediate post-operative mRs score of 2.07±1.44 SD. In thirteen operative patients six out of them presented a mRs score equal or more than 4 ± 00 SD whose 4 were remained stationary. Three operative group patients deteriorated post-operatively whose one out of 3 went from 3 to 4 mRs who was remained as functionally dependent. This last one was the only case of death i.e. 4 years after surgery. Twenty non-operative patients had a mRs score of 5.1 ±0.5 SD whose 9 out of them were remained stationary and the remainder recovers completely. The initial KI (iKI) reported in our study was 82±10.69 SD. Operative patients preoperative iKI's was 75±35 SD. This latter remained almost stationary immediately after surgery to 76±10 SD. KI at final FU was 90±10 SD regarding overall cohort while 85±0.9 SD was reported in operative group.

Functional sequelae was reported in 17 patients whose 7 non-operative patients had cranial nerves palsy i.e. 4 diplopias, 1 left ptosis and 2 left facial nerves palsy. Five operative patients presented a cranial nerves palsy sequelae i.e. 2 left diplopias, 2 right facial nerves palsy and a last one swallowing disorders. Long tract fibers sequelae lesions were reported altogether in 8 patients i.e. 5 right hemiparesis, 1 left hemiparesis and a last 3 hemi paresthesia. Five patients had cerebellar syndrome sequelae both non-operative and operative group. Multivariate regression analysis was carried out for statistical evaluation of our cohort. A confidence interval of 95% was set and Chi2 test has been carrying out for statistical significance. Statistical outcome highlighted surgery reduced the bleeding and rebleeding rate (*p=0.04*). Both non-operative and operative group depicted good functional outcomes at final long-term FU, but not statically significant for those operated on (*p=0.11*). Otherwise, the non-operative group depicted good long-term FU functional outcome statistically significant (p=0.00014).

4. Discussion

BSCMs bleeding and rebleeding events are a well-recognized causes of functional disability and death on one hand and represent an imposing neurosurgical challenge to find a proper management strategy way(1). Current guidelines lack of evidence-based practice regarding treatment indication either non-operative or operative (3). The average time of surgery lacks too consensus as well (3). In addition several studies have reported functional outcomes but long-term functional outcome both operative and non-operative patients was lacking in literature review (5). In our study, average time between diagnosis and surgery for 8 patients operated on in sub-acute period was 12±9.91 SD while the remainder was operated on from 3 months to 3 years. This finding is similar to those reported in the literature. Gross and *al* reported a surgical deadline between 4 to 6 weeks (6). Some authors suggested to operate on patients in sub-acute phase after clots have liquefied (6). In a multivariate analysis, surgical treatment within 6 weeks was associated to a good clinical outcome with Glasgow Outcome Scale (GOS) improving at final FU (P=0.002) (7). The average annual bleeding rate was 3.32± 2.27 SD per patient-year. Gross and *al* found an annual bleeding rate from 2.33 to 4.1 % similar to our finding (6). Same authors reported an annual rebleeding rate from 5 to 22.9 %. The age group of 26 to 40 years presented the highest bleeding and rebleeding rate i.e. 15 and 8 respectively in our study. However, age was not a significant risk factor (p= 0.267). Female gender presented the highest bleeding and rebleeding rate i.e. 39 and 13 respectively. Female gender was too a significant risk factor (p= 0.0074) in our study. This fact could be related to hormonal discrepancies and remained to be clarified in further coming studies. Pons bleeding rate locations (52.27%) were predominant and significant (P=0.00093). Zabramski type III was the highest finding in our study related to bleeding and rebleeding i.e. 22 and 12 respectively. However, Zabramski type was not statistically significant (p=0.34). The overall rebleeding rate reported during FU period was 18, most of them occurring within the five first years from disease on-set. The annual rebleeding rate was 31.69 % in our series. Pandey and al found 31.5 % rebleeding per patient-year (8). TASLIMI and *al* reported 20.4 % rebleedings rate in addition to an annual bleeding rate of 2.96 %(9). These findings were similar to our study. TSALMI and *al* reported decreasing of bleeding risk within time even though this has been confirmed in supratentorial cavernomas with a median of rebleeding at 8 months (p < 0.001)(9).

Peng Hu and *al* reported a rebleeding rate of 21.5 % in the absence of proper treatment (10). In a meta-analysis conducted by Horne and *al* in 2015 encompassing 7 cohort studies, 1620 patients diagnosed with intracranial brain cavernomas. The main goal of this survey was to carry out FU till the first symptomatic intracranial hematoma occur within 5 years (11). The bleeding rate within 5 years accounted for 8 % in brainstem (1). When comparing those findings to the rebleeding rate; this latter could be 10 fold. They concluded no relationship between gender and bleeding rate in contrary of our findings (12). Overall, 46.15 % of patients operated on presented a slight preoperative symptoms improvement in sub-acute postoperative phase i.e. preoperative and postoperative mRs being respectively 2.15 versus 2.07. Four patients (30.7 %) operated on remained stationary with a mRS score of 1.75±0.4. Three patients (23.07 %) operated on deteriorated whose one out of them die secondary to neurovegetative disorders 4 years later after surgery. Gross and *al* reported 23.7 % of immediately postoperative morbidities and 10.5 % at long-term FU (6). Ferroli and *al* reported in a cohort of 52 patients operated on 21 % of postoperative surgical morbidities (13). Wang and *al* reported 28 % of postoperative complications (14). Aba and al reported in a cohort of 260 adult patients operated on a permanent neurologic impairment of 36% postoperatively (15). These literature data are closely similar to our findings.

5. Case Illustration

64 year-female diagnosed with right pons cavernoma in March 2021 revealed by a first bleeding episode which resulted in left arm paresthesia and persistent dizziness. She had an initial mRs score of 2/6. CT image finding depicted evident cerebral vascular hemorrhage located in right bulbo-pontic junction. MRI showed a cavernoma lesion features (*figure1*). Clinical course initially conducting conservative management was marked by a rebleeding recurrence on May 17th with noisier symptomatology encompassing left proportional hemi paresis 3 out of 5, a binocular diplopia, swallowing disorders, dysphonia and an high intracranial pressure syndrome. Then the mRs improved only by one point (mRs 3/6). MRI finding control on May 18th showed evidence right latero-pontic hematoma of 32 mm on cavernoma with mass effect on the trunk (*figure 2*). Surgery was indicated on criterion of rebleeding, worsening of initial symptoms, mass effect on the trunk and lesion's outcrop to the pial surface. Surgery was planned on May 27th with the help of neuronavigation by median sub-occipital approach (*figure 2*). Surgical outcomes depicted worsening of left hemi paresis, left foot elevator plegia, binocular diplopia, inter nuclear ophtalmoplegia, right peripheral facial nerve palsy. Postoperatively the mRs was 4/6. At 2 months FU symptoms improved considerably i.e. hemi paresis regresses from 3 to 4 out of 5 and a mRs score at 4 out of 6.
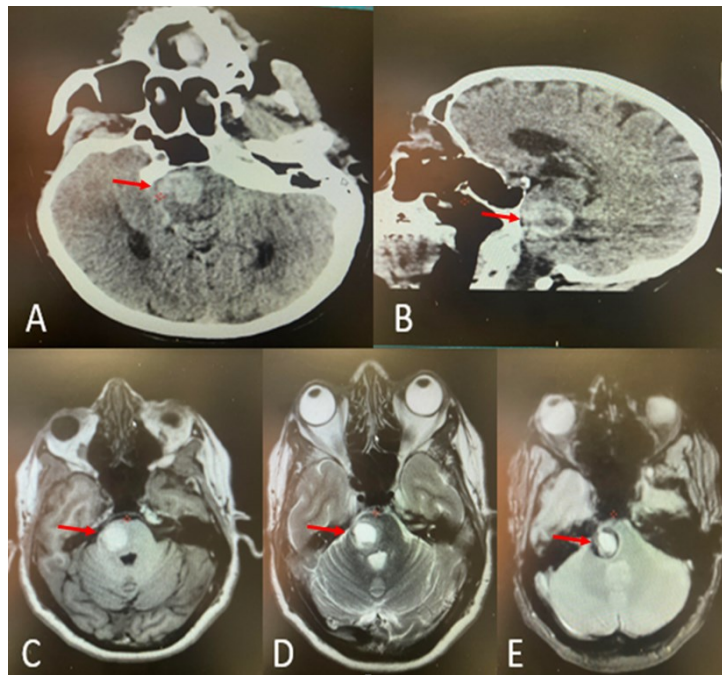

Figure 1*: Image findings; (A) Axial cerebral CT-scan and (B) sagittal showing a right pons cavernoushematoma; (C) MRI T1-weighted depicted a hematoma on cavernoma; (D) IRM T2- weighted and (E) SWAN showed a right pons cavernoma (Zabramski I et al).*
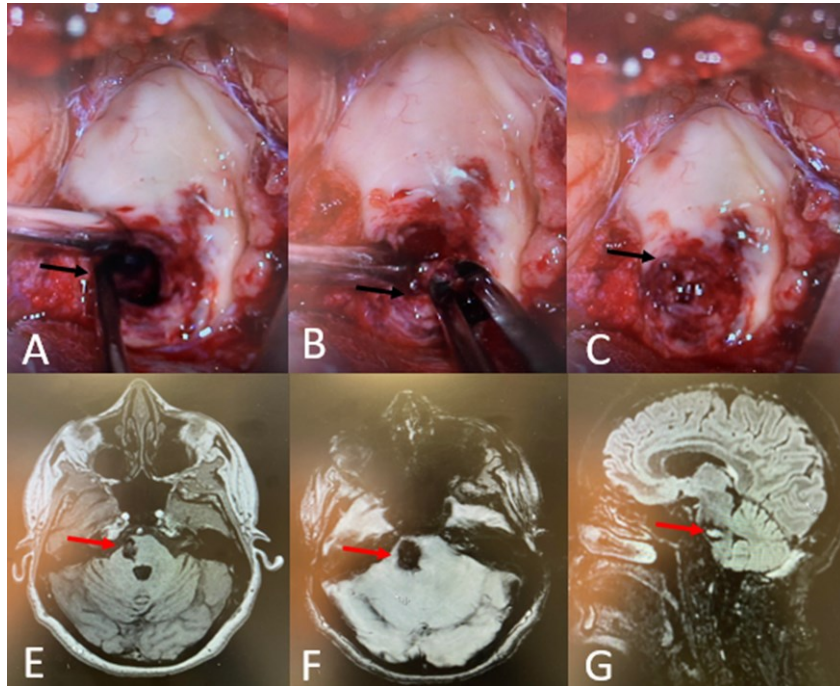
Figure 2: Intraoperative images and postoperatively MRI findings; (A) Intraoperative view of the right lateropontine cavernoma; (B) Intraoperative image showing excision of the cavernoma; (C) Intraoperative image after resection showing the cavity of the cavernoma; (E) Follow-up MRI at 1 month, T1-weighted showing a hyposignal reflecting the resection cavity of the lateropontine cavernoma; (F)Hyposignal SWAN sequence from the resection pocket; (G) Hypersignal Fluid-attenuatedinversion recovery (FLAIR) sequence of the resection pocket.

6. Limitation

Our study had certain limitations related to its retrospective component which was the source of sampling bias in one hand and other hand the size of our sample as well. Patients changed group from conservative to surgery when subsequent bleedings and surgery criteria were met. This permutation between treatment groups emphasized study bias and provides the necessity of randomized Controlled Trails for carrying out a fair comparison between treatment modalities and patients' functional outcome. Patient's loss of FU and those who gave up the FU were missing data that could be the source of study bias.

7. Conclusion

Our study despite obvious limitations related to sample size and its retrospective component provided important findings which were similar to those reported in the literature. Both Cavernomas angiomas pons location and female sex were predictive factors of bleeding and subsequent bleeding statistically significant respectively (*p=0.0001; p=0.0074*). Age and Lesion size were not predictive factors of bleeding and subsequent bleedings. Rebleeding rate was reduced in patients operated on significantly (*p=0.04*). Long-term follow-up of functional disability using mRs and KI score resulted in good functional outcome for both treatment modality but not statistically significant (*p=0.27*). Randomised Controlled Trials are needed to carry out high level evidence studies comparing long-term functional outcomes and effectiveness between non-operative and operative treatment.

Conflict of Interest

The authors declare no conflict of interest.

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