Neurosurgical Review

Secondary coiling after incomplete surgical clipping of cerebral aneurysms: a rescue strategy or a treatment option for complex cases? Institutional series and systematic review.

--Manuscript Draft--

Manuscript Number:	NREV-D-17-00317R1
Full Title:	Secondary coiling after incomplete surgical clipping of cerebral aneurysms: a rescue strategy or a treatment option for complex cases? Institutional series and systematic review.
Article Type:	Review
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Abstract:	Background Residual and recurrent intracranial aneurysms after surgical clipping present a persistent risk of bleeding. Secondary coiling after incomplete clipping represents a strategy to occlude the residual sac: feasibility, bleeding risk and outcome were evaluated through a systematic review of literature along with the series of two tertiary referral neurovascular centers. Methods Demographics, ruptured status, aneurysm morphology, topography, exclusion at surgery, timing of secondary coiling, complications, occlusion rate and outcome were analysed. Percentage of incidence and 95%CI were calculated for all variables. T-test was used for continue variables, whereas Fisher's test (two-sided) for categorical ones. Results Overall, 102 patients (92 cases from literature and 10 cases from institutional series) were included. Mean age at diagnosis was 52.94±12.17 years, and male/female ratio 0.5; 3/4 of aneurysms involved the anterior circulation, whereas ¼ the posterior circulation. An aneurysmal neck remnant was described in 58,43% of cases, an aneurysmal sac remnant in 29.21%, a regrowth in 12.36%. Residual aneurysm rupture was reported in 22% of cases. Complete/near-complete occlusion after secondary coiling was observed in 70% of cases, a partial in 25.56% and failure in 4.44%. Only one case of perforation was reported. Complications were comparable to standard endovascular procedures. Conclusions Aneurysms remnants after clipping are often observed in cases difficult anatomical locations. Their bleeding risk is not negligible. Secondary coiling is a rescue strategy to effective and safely secure the aneurysm remnant. Only in a minority of cases, it is a staged treatment after 'remodelling' of the aneurysm neck.
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Response to Reviewers:	DETAILED RESPONSE TO REVIEWERS Reviewer #1: The authors well summarized and made conclusions about the strategy to occlude the residual aneurysm after first clipping. Actually this is practically very important to prevent rupture of the An. I agree with the authors' opinion. -- We thank Reviewer #1 for his comments. Reviewer #2: The authors present a review article on secondary intracranial aneurysm embolization after incomplete surgical occlusion. Although the findings regarding frequency, location, and re-bleeding risk of incomplete IAs after clipping are not novel data on long-term clinical course of re-treated IAs (after clipping and combined secondary coil embolization) is of great interest. Unfortunately, the article lacks a read thread through the presentation of the results and discussion which makes it difficult to identify the main findings. -- We went through the whole manuscript and extensively reorganised results and discussion Main concerns and criticism is as follows: - Aneurysm remnants are divided in partial, complete and incomplete after microvascular clipping. Please adapt a most common used classification scheme such as the Sindou Classification. -- Data presentation of aneurysmal remnants was adapted to the Sindou classification. Tables references in the text and tables were changed accordingly - Aneurysm remnants after endovascular treatment should be stratified according to the Raymond and Roy classification. -- Data presentation of occlusion rate after coiling was adapted to the Raymond&Roy classification. Tables references in the text and tables were changed accordingly - Figures regarding rebleeding risk and risk of aneurysm regrowth from incompletely clipped IAs are missing in the result section but discussed in the discussion section. -- These figures were included in the Results. - The discussion section lacks a red thread, please revise and discuss only findings that are also presented in the results section. The authors are advised to focus on the question in the title: Is secondary coiling a valuable treatment option of incompletely clipped IA? Accordingly discussion of risk of rebleeding and regrowth could be removed.

-- Discussion was significantly revised and shortened, focusing on the research question as indicated by the reviewer. Discussion on rebleeding and regrowth was reduced.

- The overall number of figures should be reduced. Figure 1 is redundant if the authors refer to the Sindou classification.
-- Figure 1 was removed and figures were re-numbered accordingly.

Reviewer #3:
The authors present an interesting data collection. Unfortunately it is not well written and many questions remain unanswered. The discussion is confusing.
-- The paper was significantly re-edited and discussion shortened and focused more on the research question. We tried to enhance the thread through the presentation of the results and discussion.
1.What was the delay between clipping and coiling?
-- The timing of the secondary endovascular treatment was reported in 79/102 out of patients (77.4.%). In 31.65% the secondary treatment was immediate after surgery (during the same hospitalization), while in 68.35% coiling was delayed from 1 week to 26 years after surgery. These figures were detailed in the text.

2. What was the reason for detection of a residual aneuryms?
-- In most cases aneurysm residual was detected at postoperative DSA control or at follow-up angio-CT; in a minority of cases the residual was detected because of remnant bleeding (in about 21.69% of cases).

3. Is the postoperative angiography standard to control the clipping state?
-- Not all the authors specify which control was performed after surgery.
However, from our data collection, figures about postoperative DSA after the initial surgical treatment were reported in 89/102 cases (87,25%); data about postoperative radiological controls cannot be retrieved from literature in 13/102 cases (17,74%) .
Postoperative DSA after surgery was reported in 87/89 patients (97,75% CI); in 2/89 cases (2,25%) it was performed no postoperative DSA or other radiological exam.
Thus DSA is the standard control after surgical clipping as reported in the majority of papers. Most of authors recommend late angiographic follow-up review for incompletely obliterated aneurysms, while for completely clipped aneurysms such follow-up studies are not routinely performed. There is still no consensus about the required duration of angiographic follow-up after aneurysm incomplete clipping.
These data were specified in the text both in the results and discussion sections.

4. How many patients were retreated by coiling after re-rupture and what was the delay between clipping and rupture?
-- In the result section we added a paragraph dealing with ‘rebleeding risk and risk of aneurysm regrowth from incompletely clipped aneurysms’.
Specifically in 18/83 cases (21.69%) of aneurysm residual rupture of the remnant was observed. 5/11 cases (45.45%) were observed after aneurysmal regrowth. Re-bled aneurysms were treated with standard coiling in 17/18 cases (94,44%) and in a single case with stent-assisted procedure (5,56%).

5. I am wondering about the low rate of stent assisted coiling or using balloon remodeling as well as using flow diverter. Especially with respect to the postulated complexity of the residual aneurysms
-- Although it can appear surprisingly, to the best of our search, only a minority of reports indicate e remodelling technique. A possible explanation is that the most complex procedures were treated directly with FD devices (treatment with FD alone was not included in the analysis as we focused on coiling procedures only; this was specified in the methods).

6. About 4% of the clipped aneurysm is incomplete. What is the real indication for retreatment?
-- We better outlined in the paper that partial clipping corresponds to a remnant of the neck only, not amenable to reoperation without creating stenosis of the parent artery

	(Sindou I-II). In this cases most common attitude in literature is observation. Re-treatment is considered only if there is aneurysm morphological modification at follow-up. Whereas, incomplete clipping with remnants of the aneurysmal sack (Sindou III-IV) are generally considered for additional treatment if possible in an early stage. We specified these observations in the discussion 7. The authors state that coiling of residual aneurysm after initial clipping is safe with a complication rate which is comparable to "standard endovascular procedures". The authors have to compare with endovascular treatment of incidental or ruptured aneurysms. The overall complication rate of the secondary coiling from our data is about 1%, which is comparable to the rate of complications reported in literature for the endovascular treatment of a previously untreated aneurysms. -- This point was discussed. 8. For the clinical outcome the modified Rankin scale (mRs) should be used. It would also be important to know the diagnosis output (mRs before clipping, mRs before coiling). -- Clinical outcome was reported both according to GOS and mRs scorse as indicated by the reviewer. Text and tables were modified accordingly.. We agree with the reviewer that mRs before clipping/coiling would be a very interesting data to collect and analyse. However this is detailed only in a very small minority of the analysed papers. Therefore we was able to report only if a procedure-related clinical deterioration was present. This figure was included in the results. 9. A local ethical committee vote is also recommended for a retrospective study -- Ethical commitee approval was requested. This will be formally ratified on the 15th of February 2018 and attached to the submission. 10. Literature: The list is not clear - last reference followed by an additional reference 2. Alobaid ….. 34. Tsutsumi K, Ueki K, Kirino T (2001) Recurrent subarachnoid hemorrhage. Journal of neurosurgery 94:541-542 1016/j.surneu.2009.06.027 2. Alobaid A, Nossek E, Wagner K, Setton A, Dehdashti AR, Langer D, Chalif D (2017) Paradigms for single519 patient multimodality treatment for cerebral" --This was fixed. Editorial Team's Comments: 1) In a routine check for publishing ethics we found that the manuscript contains a number of sections taken from other published papers, most notably in the subsection ‘Rescue strategy or staged treatment?’ (paragraph 3rd and 4th), but also in subsection ‘Risk of bleeding and regrowth of the residual aneurysm’ (paragraph 1st – line 5 to line 10) and subsection ‘Conditions favouring aneurysm residual after clipping’ (paragraph 3rd- line 2 to line 6). -- Discussion was extensively rephrased and reorganised. Specific attention was payed to the abovementioned paragraphs which were modified. 2) As no human participants are directly involved in the study, contradicting statements regarding the informed consent taken from patients is mentioned in the manuscript. -- We simply meant that patients included from institutional series before the procedure signed an informed consent in which it is specified that medical information, in an anonymous way, can be used for scientific purposes.

Secondary coiling after incomplete surgical clipping of cerebral aneurysms: a rescue strategy or a treatment option for complex cases? Institutional series and systematic review.

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ABSTRACT

Background

Residual and recurrent intracranial aneurysms after surgical clipping present a persistent risk of bleeding.

Secondary coiling after incomplete clipping represents a strategy to occlude the residual sac: feasibility, bleeding risk and outcome were evaluated through a systematic review of literature along with the series of two tertiary referral neurovascular centers.

Methods

Demographics, ruptured status, aneurysm morphology, topography, ~~percentage of~~ exclusion at surgery, timing of secondary coiling, complications, occlusion rate and outcome were analysed.

Percentage of incidence and 95%CI were calculated for all variables. T-test was used for continue variables, whereas Fisher's test (two-sided) for categorical ones.

Results

Overall, 102 patients (92 cases from literature and 10 cases from institutional series) were included. Mean age at diagnosis was 52.94±12.17 years, and male/female ratio 0.5; 3/4 of aneurysms involved the anterior circulation, whereas ¼ the posterior circulation. An aneurysmal *neck remnant* ~~*partial exclusion*~~ ~~after surgery~~ was described in 58,43% of cases, a~~n *incomplete*~~n aneurysmal *sac remnant* in 29.21%, a *regrowth* in 12.36%. Residual aneurysm rupture was reported in 22% of cases. Complete/near-complete occlusion ~~(>95%)~~ after secondary coiling was observed in 70% of cases, a partial ~~(<95%) i~~in 25.56% and failure in 4.44%. Only one case of perforation was reported. Complications were comparable to standard endovascular procedures.

Conclusions

Aneurysms remnants after clipping are often observed in cases difficult anatomical locations. Their bleeding risk is not negligible. Secondary coiling is a rescue strategy to effective and safely secure the aneurysm remnant. Only in a minority of cases, it is a staged treatment after 'remodelling' of the aneurysm neck.

Keywords: failed aneurysm clipping, coiling, secondary coiling, aneurysm residual, aneurysm regrowth.

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INTRODUCTION

Residual and recurrent intracranial aneurysms can occur after surgical clipping, leading a persistent risk of regrowth and rupture or re-rupture. Several authors have emphasized the potential for these remnants to grow and to cause subarachnoid haemorrhage (SAH) in a delayed fashion[8,26,3]. Until the advent of the GDC, surgical reintervention was the only available treatment, but it was associated with higher risk than the first operation[13,25]. During the past two decades, however, advances in endovascular coiling techniques and technology have allowed some of these remnants to be treated safely with no open surgery[3,34].

The steady improvement in microsurgical technique has greatly enhanced the surgeons' ability to successfully occlude also complex intracranial aneurysms in a single clipping procedure. Anyway, in the setting of complex cases, secondary coiling after clipping could be an elective preoperatively planned option, as, both microsurgical and endovascular techniques continue to have their limitations, and certain aneurysm morphologies and locations remain exceedingly difficult to treat with a single modality[15,7,1]. In other contexts, a secondary coiling may represent a solution to obtain a complete aneurysm exclusion when it was not possible, for some reasons, at first surgery[2,6].

The aim of this study is to systematically review the pertinent literature concerning cases of secondary coiling after incomplete clipping along with the institutional experience on this topic of two Italian tertiary referral centers for neurovascular surgery, in order to identify its indications, efficacy, feasibility and limitations.

METHODS:

Literature review

A comprehensive review of the literature was performed with the following key-words "((intracranial OR cerebral OR brain) AND aneurysm AND clipping AND coiling))" to search in PubMed and Scopus databases.

The search strategy followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement where applicable, and this checklist was used in designing and reporting our review.

The last search was launched in December 2016.

All studies reporting patients who underwent a surgical clipping followed by a secondary coiling for the treatment of the residual aneurysm were first included. Case reports were not included in the

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analysis. Cases treated with flow-diverter devices were not included in the study as we focused on coiling techniques.

Two reviewers (G.M.D.P. and F.B.) independently collected data from the included articles. Any differences were resolved by consensus discussing with a third author (C.L.S.).

Then, English studies reporting detailed information regarding operative procedures (both surgical and endovascular), perioperative and postoperative complications, and aneurysm occlusion rates were included in the following analysis.

We evaluated the following variables: demographics, ruptured status, aneurysm morphology, topography and size, percentage of exclusion at first surgery, the entity of neck reduction after clipping, timing and modality (coiling, stent-assisted coiling and spontaneous thrombosis) of the secondary endovascular treatment, complications, final occlusion rate and clinical status at follow-up. We also explored, when reported, the prediction by the authors of an incomplete treatment at first surgery, in order to differentiate secondary coiling performed as a rescue strategies or as intentional treatments.

Peri-procedural complications studied were the occurrence of intraprocedural thrombosis (with or without transient hemiparesis), stroke (with permanent hemiparesis), and intraoperative rupture, and slippage of the clip.

With regards to localization we distinguished the aneurysms according to the vessel involved. Aneurysms were also divided in small (<1cm), large (>1cm<2.5cm) and giant (>2.5cm) according to what reported by the investigators.

The percentage of exclusion at first surgery was ~~divided~~ categorized ~~in~~ according the Sindou classification, with reference to presence of residual at the aneurismal neck or at the sac [32]. We identified the following four categories:

- ~~*partial*~~*Neck remnant*, corresponding to Sindou grades I and II, when the remnant is only at the aneurysmal neck~~clip occluded a portion of the aneurysm~~;
- ~~*i*~~*Sac remnant*~~*ncomplete*~~, corresponding to Sindou grades III and IV, when it is present a residual lobe from a multilobulated sac, or the residual portion of the sac is less than 75% of the initial aneurysmal size;
- *Failed*, corresponding to Sindou grade V, when clipping did not produce significant change in aneurysmal sac filling with the residual aneurism > 75% of the initial size. ~~*when the clip did not change the aneurysm filling, but might have narrowed neck (it is often the result of an attempt of complete clipping but clips blades do not cover fully the aneurysm's neck); and r*~~*R*egrowed aneurysms, when a~~the~~ fully occluded aneurysm at postoperative DSA appeared to be regrown and increased in size at controls. ~~**(Figure 1).**~~

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Radiologic outcomes for surgery or endovascular procedures were stratified into 3 levels on the basis of the degree of angiographic aneurysm obliteration, evaluated immediately after the secondary endovascular procedure and stratified according the Raymond–Roy classification [31]: *grade 1*) complete / near complete occlusion ~~(>95%)~~, defined as a lack of angiographic filling of the sac and the neck ~~or no filling of the sac but with small residual neck filling~~; *grade 2*) partial occlusion ~~(<95%)~~, defined as persistent angiographic filling at the aneurismal neck ~~of a small portion of the sac~~; *grade 3*) incomplete occlusion ~~(<90%)~~, defined as a persistent angiographic filling of a significant portion of the sac. Finally, clinical outcome was assessed both through the ~~Glasgow Outcome Scale~~ modified Rankin scale (~~GOS~~mRs) and Glasgow Outcome Scale (GOS).

Statistical analysis

Data were individually extracted for each patient. Percentage of incidence and 95% of confidence intervals (CI) were calculated for all considered variables and outcomes.

Quantitative variables were expressed as mean ± standard deviation and Student's t test was used to compare their means. Fisher's exact test (two-sided) was instead used to compare categorical variables. The associations were considered significant when $P<0.05$.

RESULTS

Institutional Series

Two institutional series was retrieved from the databases of two Italian tertiary referral centers for neurovascular surgery in Rome: 7 cases (3 males and 4 females with a mean age of 58.3± SD 8,0 years) from the "Catholich University of Rome School of Medicine, A. Gemelli Hospital", and 3 cases (1 male and 2 females with a mean age of 55.6±SD 5,9 years) from the "San Camillo Forlanini Hospital".

Data from the two institutional series was pooled with those retrieved from literature in order to provide an homogenous analysis (**Table 1**).

Systematic review: study selection and characteristics

Demographic, angiographic, and clinical features of the studies that met our inclusion criteria are summarized in **Table 1**.

According to our search strategy, articles in English language were retrieved through the electronic literature search. From the first search 698 articles were available in literature. Among these 110

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were reviews without original series, 13 were animal studies, 90 papers were case reports and 36 were not in English language.

Among the 449 articles left, 397 were primarily excluded by abstract reading and 52 were assessed for eligibility and analyzed in detail. After full text reading and a forward search from the bibliography of the selected papers, 11 articles published between 1998 and 2016 and reporting patients endovascularly treated for aneurysms incompletely clipped at first surgery were finally included in the review[2,3,6,7,16,22,25,27,30,20]; 92 patients were retrieved from literature analysis. Pooling these with the institutional series an overall of 102 patients were included in this study **(Figure 12).**

The pooled analysis of the main outcomes reported in the 11 included studies and institutional series is reported in **table 2**.

Demographics

Age was reported in 70/102 patients (68.6%), and the mean age at diagnosis was 52.94 ± 12.17 years (range 29-80). Sex was reported in 71 out of 102 patients (69.6%) and the male/female ratio was 25/46 (35.21% vs 64.79%).

Localization, size and ruptured status of the aneurysms

Localization of the aneurysms was reported in 93 out of 102 patients (91.17%). The most common location of aneurysms that needs a secondary endovascular treatment was represented by the anterior circulation. In particular, 37.63% originated from the ACoA and about 31% originated from the ICA distinguished in paraclinoid, Pcom origin, SHA origin, Acho origin and bifurcation segments. ACA was involved overall in about 3% of cases and MCA in 4%. Finally, about 24% of aneurysms treated with a secondary coiling involved the posterior circulation, especially the basilar artery (about 13% of cases).

Ruptured status was reported in 81 out of 102 patients (79.41%). Among them, 63/81 (77.78%; 95% CI 67.58-85.46) had an onset with subarachnoid hemorrhage (Table 1).

Size was instead reported only in little more than half of cases (63/102; 61.76%), with about the same percentage of small and large + giant aneurysms.

Percentage of exclusion and neck reduction at first surgery

The percentage of exclusion at first surgery was reported in 89 out of 102 patients (87.25%). Among them a ~~partial exclusion~~ neck remnant (Sindou grades I and II) was described in more than 50% of cases, a sac remnant ~~n incomplete~~ (Sindou grades III and IV) ~~exclusion~~ in about 29%, while

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a regrowth was observed in a little more than 12% of cases. No report of secondary coiling after a failed surgical procedure (Sindou grade V) was observed, for which re-operation is generally indicated.

Only in about half of patients included in this systematic review (50 out of 102 cases) was described by the authors the size of the neck reduction after the first clipping. In particular, in 48/50 out of them (96%; 95%CI 86.54-98.9) was reported a neck reduction larger than 50%.

Data concerning postoperative DSA after the initial surgical treatment is reported in 89/102 cases (87,~~.~~25% CI 79.41-92.40); data about postoperative controls cannot be retrieved from literature in 13/102 cases (12~~7~~,~~.~~754% CI 7.60-20.59). Postoperative DSA after surgery was reported in 87/89 patients (97,~~.~~75% CI 92.17-99.38); in 2/89 cases (2,~~.~~25% CI 0.62-7.83) it was performed no postoperative DSA or other radiological exam.

Secondary endovascular treatment and timing

A secondary selective coiling was reported in large majority of cases (95.1%; 95%CI 89.03-97.89), while a coiling procedure with adjuncts was described only in about 3% of cases (95%CI 1.01-8.29). In 2 cases, the incomplete exclusion after clipping was followed by a spontaneous thrombosis of the remnant.

Radiologic outcomes for endovascular procedures was a ~~complete / near complete occlusion (>95%)~~Raymond-Roy grade 1 in 70% of ~~–~~cases (95%CI 59.87-78.49), grade 2 ~~a partial occlusion (<95%)~~ in ~~–~~25.56%~~———~~ (95%CI 17.67-35.44), while a failed procedure (grade 3) with a persistent angiographic filling of a significant portion of the sac in 4.44% of cases~~——~~ (95%CI 1.74-10.88).

The timing of the secondary endovascular treatment was reported in 79/102 out of patients (77.4.%). In 25 cases (31.65%; 95%CI 22.45-42.55) the secondary treatment was immediate after surgery (during the same hospitalization), while in 68.35% (95%CI 57.45-77.55) was delayed from 1 week to 26 years.

Rebleeding risk and risk of aneurysm regrowth from incompletely clipped aneurysms

18/83 cases (15~~21~~.6~~69~~%; 95% CI 9.39-24.98~~—~~) of aneurysm residual after incomplete clipping presented a bleeding from the rupture of the remnant. Among the 26 patients with incomplete clipping with neck remnant (Sindou grades I and II), 2 (7.69~~8~~%; 95% CI 2.14-24.14~~—~~) presented

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bleeding; among the 52 patients with partial clipping with sac remnant (Sindou grades III and IV), 11 (21.15%; 95% CI 12.24-34.03) presented bleeding and among the 11 with aneurysmal regrowth, 5 (45.45%; 95% CI 21.27-71.99) presented bleeding. Re-bled aneurysms were treated with standard coiling in 17/18 cases (94.44%; 95% CI 74.24-99.01) and in a single case with a stent-assisted procedure (5.56%; 95% CI 0.99-25.76).

Complications of first surgery and secondary coiling, and clinical outcome.

The occurrence of complications after surgery was reported in 83 out of 102 patients (81.37%). A transient ischemia and a permanent stroke were reported in about 2.5% out of cases, respectively. An intraoperative aneurysm rupture was instead reported only in 1 case as well as the evidence of clip slippage in the post-operative imaging. Finally, a residual aneurysm rupture was reported in about 22% out of cases.

Only one case of aneurysm perforation was reported during the secondary coiling procedure (1.35%; 95%CI 0.24-7.27).

Clinical outcome was reported in 69/102 out of cases (67.64%). A GR was reported in about 67% out of cases, a MD in 13% and a SD in about 10%. The rate of mortality was overall 10.14% (7/69 out of patients; 95%CI 5-19.49). Clinical deterioration after the second (endovascular) procedure was reported in 1/62 cases (1.61%; 95% CI 0.29-8.59) and occurred after aneurysmal perforation during coiling.

Outcomes comparison between patients with ruptured and unruptured aneurysms, small versus large + giant aneurysms, and between aneurysms of the anterior and posterior circulation.

No statistically significant differences were observed in any outcomes comparison group (**supplementary tables 1, 2 and 3**).

DISCUSSION

The rate of incomplete aneurysm exclusion after microsurgical clipping has been estimated in literature to be as high as 4%[35,7,29].

From our analysis, it appears that insufficient surgical clipping ~~was the result of a partial exclusion~~resulted in a ~~(~~ remnant at the aneurysmal neck (Sindou grades I and II ~~that ensued a significant reduction of the aneurysm sac~~) in 52/89 cases (58.82%), ~~of~~ in ~~an incomplete exclusion~~

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(a remnant at the clipping did not modify aneurysm filling but reduced aneurysm necksac (Sindou grades III and IV) in 26/89 cases (29.21%) and of a regrowth (complete clipping at first surgery, confirmed by a postoperative DSA and appearance of a newly formed aneurysm at follow-up) in 11/89 cases (12.36%) **Figure 1).** Illustrative cases are showed in **figures 32-65.**

Risk of bleeding and regrowth of the residual aneurysm

The haemorrhagic risk associated with possibility that aneurysm remnants after incomplete clipping are at risk for haemorrhage and/or regrowth is wellhas been documented in literature by several studies documented [30]. Feuerberg et al. reported a 3.7% of incidence of rebleeding from residual aneurysms with a concomitant yearly rupture rate of up to 0.79%/year [11]. Other authors have also reported significant risk associated with residual or recurrent aneurysm remnants after microsurgical clipping[27]. Drake and Vanderlinden documented the adverse consequences of incomplete aneurysm treatment[9,10]. In the series by Drake and VanderlindenIn their series, 5 of 13a significant number of patients with large aneurysm remnants died as a result of experienced re-hemorrhage within 7 years of incomplete treatment, and showed that. That study also documented that these remnants could can increase in size and change morphology over time [9,10]. Lin et al. further refined the understanding of the risk associated with aneurysm remnantsOther experiences in literature displayed by demonstrating that the risk was not limited to large remnants but also appliedincludes also to neck remnants (Sindou grades I and II) as small as 1 to 2 mm [26].

Important is to notice that the rate of bleeding from aneurysm remnants and from aneurysmal regrowth is not negligible. Our data, in fact, showed that 18 out of 83 cases (21.69%) of aneurysm residual after incomplete clipping presented a bleeding from the rupture of the remnant (**Table 3)**. In particular, it is interesting to know that among the 11 patients who showed an aneurysmal regrowth, 5 presented a bleeding (45.45%); however, it should be acknowledged the selection bias behind this figure as most of the regrown aneurysms are discovered primarily because of bleeding.

Recent studies showed a 1.5% incidence of recurrent aneurysms in cases in which there was no residual after clipping[8,36]. Regrowth of aneurysm after clipping (with an initial negative postoperative DSA) may have several explanations: for example, a highly calcified neck or a nearly complete neck exclusion, with clip blades almost reaching the neck edge, might favour aneurysm slow fill even after clip placement, and over time cause aneurysmal recanalization[21,17,16].

About timing, from data analyses, it appears that remnants can bleed also several years after treatment. In fact, bleeding from a residual has been reported up to 26 years after initial treatment[30].

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Partial clipping that corresponds to a remnant at the aneurysmal neck only (Sindou I-II), is generally not amenable to reoperation without creating stenosis of the parent artery. In these cases most common attitude in literature is angiographic follow-up observation by means of DSA or angio-CT. Re-treatment is generally considered if there is aneurysm morphological modification at follow-up. Whereas, incomplete clipping with remnants of the aneurysmal sac (Sindou III-IV) are generally considered for additional treatment in an early stage [19,32].

DSA is the standard control after surgical clipping as reported in the majority of papers. Most of authors recommend late angiographic follow-up review for incompletely obliterated aneurysms, while for completely clipped aneurysms such follow-up studies are not routinely performed. There is still no consensus about the required duration of angiographic follow-up after aneurysm incomplete clipping [19].

Rescue strategy or staged treatment?

Complex, broad-necked aneurysms that may be difficult to treat with a single mode of therapy can be safely and successfully treated with a combination of endovascular and microsurgical techniques[2,10]. For patients with broad-based aneurysms that are difficult to access surgically without incurring significant morbidity, microsurgical clipping may be used as the initial procedure to create a smaller neck[3]. As suggested by Cockroft[7], a planned dual-modality approach allows for ~~the~~ a safer~~, more controlled, and more expeditious~~ treatment of complex~~/broad-based~~ lesions and ~~eliminates~~ reduces the need for an exceedingly ~~overly~~ aggressive single-modality treatment~~approach~~[7]. Conversely, ~~W~~when an aneurysm seems both unfavourable for direct coiling (e.g too broad-based) ~~for effective coiling, but is poorly located and~~and structurally unfavourable for microsurgical clipping, a planned approach of microsurgical partial clipping to reduce the size of the neck, followed by endovascular coiling ~~to obliterate the remainder of the aneurysm~~, may be a safe and effective alternative ~~to dangerously aggressive treatment with~~to a single modality [3]. When ~~arrangements are~~ planning is made ~~made~~ in advance, the patient may be taken directly to the angiography suite, and the combined procedure can be performed without delay[3,7].

However, this is true only in a minority of reports[3,7], and, as shown from literature data, in the majority of cases, the incomplete clipping is not an expected result and the secondary coiling is considered a rescue strategy in order to secure the aneurysm. In fact, a preoperative prediction of incomplete treatment was reported only in a minority of cases included in this systematic review (less than 5%). Moreover, only in about 1/3 of the reported cases the residual aneurysm is suspected

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at surgery and immediately treated with a secondary coiling; on the other hand, in about 70% of cases, the presence of a unexcluded part of the sac is identified later on the follow-up imaging and then the secondary coiling is delayed after the first surgery.

If an experienced surgeon leaves a remnant because of anatomic constraints, reoperation is unlikely to be beneficial[6]. In addition, to repeat surgery for aneurysms that develop in a patient with a prior craniotomy are often challenging due to scar tissue, cerebral spinal fluid (CSF) leaks, might make harder a clear view of the aneurysm site; the clip applied during the previous surgery can be an obstacle at subsequent operation; often it may be difficult or impossible to remove the clip when it is necessary, and aneurysm rupture and bleeding may occur during clip mobilization[3,28]. In other words, the presence of residual aneurysm reflects technical or anatomical difficulties of the prior operation, and the previously placed are an often an additional problem[3].

Coiling seems to offer a solution for some aneurysm remnants[5,28]. From a technical standpoint, remnant coiling usually is possible if the remnant is at least as deep as it is wide and if it is at least 2 mm in diameter [3].

Efficacy and safety

Secondary endovascular coil embolization resulted in complete aneurysmal occlusion (Raymond-Roy grade 1) in 70% of cases, whereas a persistent partial occlusion (Raymond-Roy grade 2) was still evident in about 25% of cases after the secondary procedure. In about 4.5% of cases an incomplete occlusion or the failure of the procedure (Raymond-Roy grade 3) was reported. There were no serious complications related to endovascular treatment and only one case of perforation was reported with associated clinical deterioration.

Clinical outcomes is generally favourable and there was no reported worsening of clinical status after procedure. Poor outcomes were significantly associated with a history of subarachnoid haemorrhage due to the rupture of the remnant.

The overall complication rate of the secondary coiling from our data is in fact little more than 1%, which is comparable to the rate of complications reported in literature for the endovascular treatment of a previously untreated aneurysms [4]. This data is particularly interesting as it underlines that previous surgery does not constitute an extra risk for endovascular coiling. Partial clipping also reduces the size of the neck, making compaction of the coil mass less complex and, above all, safer. The phase of coils compaction is the stage where lies the greatest risk; the metal clip at the base provides a reliable rigid support on which to build the cast.

Other advantages to this approach involve the information provided by the surgeon regarding the peri-aneurysmal environment, such as the presence of perforators[15].

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Timing of the secondary coiling

No clear data exists in literature on this topic[27]. However, this study discovered that in about 32% of cases, the secondary coiling was immediate after surgery (during the same hospitalization), while in about 68% was delayed in a time lapse ranging from 1 week to 26 years.

Anyway, only in a minority of patients that were immediately re-treated, it had been forecast before the clipping attempt (4/82; 4.9%), which was firstly aimed to remodel the aneurysm neck. In the majority of cases, instead, an incomplete clipping was demonstrated at post-operative angiographic studies, and an immediate endovascular treatment was then offered to the patients.

Our institutional experience, backed by many authors in literature[27,7,14,28,2], supports the idea that an incomplete clipping with neck narrowing it can alter flow dynamics with a higher flow jet toward the aneurysm dome increasing likelihood of rupture in some cases. Therefore second stage coiling should be completed soon after clip reconstruction or as soon as residual/regrowth is identified.

Complex aneurysm?

From our data the majority of cases of secondary coiling after incomplete clipping concerns small saccular aneurysms [33/63 cases – 52,38%]. This finding might seem surprising; however, if we carefully analyse that most cases are surgical failures, with a residual not expected or planned, this finding makes sense as large or giant aneurysms, as expected, are managed ‘a priori’ with combined therapies, often with extracranial-intracranial bypass followed by surgical trapping or endovascular obliteration of the aneurysm and the parent vessel. Conversely, larger aneurysms or fusiform or located in the posterior circulation are generally treated with endovascular intervention as primary treatment[33]. Thus, the aneurysm that most frequently undergoes a secondary coiling after clipping is the ‘common’ small -sized sacciform aneurysm (that from our data represent more than a half of cases, and along with large ones 93% of cases) for which a combined approach is not planned ab-initio and surgery is expected to exclude aneurysm one shot.

Conditions favouring aneurysm residual after clipping

From literature analysis it emerges that some anatomical locations are much more frequent than others. In particular, ICA-paraclinoid, BA and ACoA aneurysms are the most frequent sites for secondary coiling. Due to a limited surgical corridor and anatomical restraints, clips might not completely exclude the aneurysm. This scenario is encountered in carotid cave and paraclinoid aneurysms where part of the aneurysm extends beyond the dural ring and often the correct

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visualisation of aneurysmal neck might result difficult[24]. Moreover, in this anatomy often prevents the correct visualisation of the tips of the microsurgical clip and as a result a part of the aneurysm may still continue to fill. Similarly, in ACoA aneurysms, the rotation of the 'A1-ACoA-A2 complex' in the sagittal plane, associated to an elevated anatomical variability associated with this location (azygos A1/A2, duplications of ACoA, vascular hypotrophy or aplasia) can make difficult to fully control portions of aneurysm, especially if posteriorly projecting or embedded in brain parenchyma, resulting in a partial or incomplete clipping[23,12]. As in paraclinoid and ACoA, also BA aneurysm represent an anatomically challenging position as operative filed is narrow and deep and the aneurysm can be partially hidden by prominent perforators, that may preclude adequate circumferential dissection, or be embedded in eloquent brain parenchyma[12].

These observation are confirmed by our institutional data, that, according meta-analytic data from literature, places these three anatomical sites as the more at risk of incomplete clipping

Our data show also that residual aneurysm after clipping is more frequent if operated after SAH (63/81 – 77.8% cases in ruptured status versus 18/81 – 22.2% ~~–~~unruptured). Peri-aneurysmal dissection and appropriate brain relaxation are, of course more challenging if subarachnoid blood is present and thus this condition favours post-surgical residuals.

Several authors report of scissor-like deformation of surgical clips that consists in twisting of the clip blades and it is associated with incomplete clipping[17]. ~~Some aneurysms have a~~A highly calcified neck ~~that~~ might prevent ~~precludes~~ the correct closure of ~~the aneurysm~~the clip blades hence ~~and hence the aneurysm continues to fill even after clip placement. This~~ lead~~ing~~s to continued slow filling of the aneurysm ~~through a narrow neck~~[17,18]. A subsequent endovascular coil embolization of the aneurysm though the narrow calcified neck can help definitively thrombose the aneurysm.

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Limitations

This study presents several limitations. First, the majority of the included papers were case series including a small number of patients (only four papers report on a number of patients >10). In addition, the reported evidence is observational and non-comparative. Therefore, the proportions reported in this review only reflect the published cases and may be influenced by some form of publication bias. In particular about the bleeding rate of residuals, it should be acknowledged a selection bias as some failed clipping are discovered primarily because of bleeding; hence, their real bleeding rate cannot be accurately determined.

Moreover, we limited our research to the cases published since the nineties, before the endovascular coiling was not available earlier. Finally, clinical outcome at follow-up was available only in about

two-third of patients, therefore this study includes a not totally reliable evaluation of long-term prognosis.

CONCLUSIONS

The study confirms that the risk of bleeding from aneurysm remnants is not negligible, and it can also occur after several years from primary surgery. Remnants are more often observed when difficult anatomical locations (paraclinoid/BA) or SAH make aneurysm dissection more challenging, and proximal control not securable. Incomplete/partial clipping is not an expected result in the majority of cases, and the secondary coiling is considered a rescue strategy to secure the aneurysm remnant by the most of authors. Only in a minority of cases, this is considered as a staged treatment aimed to 'remodel' the aneurysm neck.

Since the field of vascular neurosurgery has continued to evolve, combined therapies can represent successful treatment strategies in cases of complex aneurysms or offer a feasible and safe option for the treatment of incompletely clipped aneurysms.

FIGURE LEGEND

~~**Figure 1.** Illustrative representation of different typologies of unsuccessful/partial surgical clipping at first surgery: *partial*, when the clip occluded a portion of the aneurysm; *incomplete* when the clip did not change the aneurysm filling, but might have narrowed neck (it is often the result of an attempt of complete clipping but clips blades do not cover fully the aneurysm's neck); *regrowth*, when the fully occluded aneurysm at postoperative DSA, appeared to be regrown at follow-up.~~

Figure ~~2~~1. Flow-chart of search strategy.

Figure ~~3~~2. *Illustrative case 1: a* 50 years old man presenting with intense nucal headache. Radiological examination showed SAH (HH4) secondary to ACoA aneurysm (a,b). Microsurgical clipping was attempted but early angiographic control enlightened a residual aneurysm due to partial clipping (c,d) with sac residual. Aneurysm residual was then completely coiled (e,f). The patient was discharged in good clinical and neurological condition.

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Figure 34. *Illustrative case 2:* A 59 years old woman presenting with SAH due to secondary to ACoP aneurysm (a,b). Microsurgical clipping was performed. Angiographic follow-up showed a

partial clipping (c,d), with a portion of the aneurysmal sac still perfused. Aneurysm that was then completely coiled (e,f).

Figure 45. *Illustrative case 3: incomplete* neck clipping of left A2 ruptured aneurysm (a,b). The residual aneurysm was endovascularly coiled (c,d).

Figure 56. *Illustrative case 4:* Right Vertebral artery angiography showing a clipped ruptured PICA aneurysm with a neck residual ~~(*partial*~~and partial exclusion of the sac~~)~~ (a). Stent assisted embolization with coils. Stent markers, coils and clips are clearly visible (b). post-procedural DSA showing the complete exclusion of the aneurysm and a patent vertebral artery (c).

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• *Funding:* None

• *Conflict of Interest:* None

• *Ethical approval*: Not required (literature review and retrospective case series)

• *Informed consent:* Yes, signed at the moment of procedure, stating that the patients authorises the use of medical information and imaging for scientific purposes in anonymous way.

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Table 1

Table 1: Demographic, angiographic, and clinical features of the studies that met inclusion criteria + institutional series

AUTHOR/ YEAR	N.OF CASES	MEAN AGE IN YEARS (±SD)	SEX	ARTERIAL SEGMENT INVOLVED	ANEURYSM SIZE	ANEURYSM MORPHOLOGY	RUPTURED STATUS	RESULT OF FIRST SURGERY	PREDICTED INCOMPLETE FIRST SURGERY	TYPE OF COILING	OCCLUSION RATE AFTER COILING (RAYMOND–ROY OCCLUSION CLASSIFICATION)	RESIDUAL ANEURYSM RUPTURE	COILING COMPLICATIONS	GOS AND MRS
ALOBAID 2016	4	50,25 (14,9)	F:2 M:2	ACA:2 ACoA:1 SHA:1	Small:1 Large:1 nr:2	Sacc 4	R:3 UR:1	SAC REMN:1 NECK REMN:3	N:4	Sel Coiling:4	Raymond-Roy 1: 3 Raymond-Roy 3: 1	1	None:4	MD (mRS 3-4):1 SD (mRS 5):1 D (mRS 6):1 nr:1
BENDOK 2002	5	56 (6,0)	F:1 M:4	ACoA:1 BA:1 ICA (paraclinoid):1 PICA:2	Small:1 Large:4	Sacc 4 Fus 1	R:3 UR:2	SAC REMN:1 NECK REMN:3 REGROWTH:1	N:4 Y:1	Sel Coiling:5	Raymond-Roy 1: 5	1	None:5	GR (mRS 0-2):2 SD (mRS 5):1 D (mRS 6):1 nr:1
CHOUDHRI 2013	6	66 (-)	F:1 nr:5	ACoA:2 ICA (paraclinoid):2 MCA:1 Pcom:6	Giant:1 nr:5	Sacc 1 nr5	UR:1 nr:5	NECK REMN:1 REGROWTH:1 nr:4	N:1 nr:5	Sel Coiling:6	Raymond-Roy 1: 1 nr:5	2	None:6	GR (mRS 0-2):1 nr:5
COCKROFT 2000	3	40,33 (10,3)	F1 M:2	BA:1 ICA (paraclinoid):1 VA:1	Small:1 Large:2	Sacc 3	R:2 UR:1	SAC REMN:1 NECK REMN:2	Y:3	Sel Coiling:3	Raymond-Roy 1: 3		None:3	GR (mRS 0-2):2 MD (mRS 3-4):1
HACEIN-BEY 1998	5	50,4 (11,8)	F:4 M:1	ACoA:2 BA:2 ICA (paraclinoid):1	Small:2 Large:3	nr 5	R:5	SAC REMN:3 NECK REMN:2	N:5	Sel Coiling:5	Raymond-Roy 1: 5		None:5	GR (mRS 0-2):5
HOH 2002	11	59 (-)	F:2 nr:9	Pcom:1 VA:1 nr:9	Large:2 nr:9	Fus 2 nr 9	R:1 nr:10	NECK REMN:2 nr:9	N:2 nr:9	Sel Coiling:11	Raymond-Roy 1: 5 Raymond-Roy 2: 6	1	None:1 nr:10	GR (mRS 0-2):1 D (mRS 6):1 nr:9
KANG 2004	13	65 (-)	F:1 nr:12	ACoA:6 BA:2 ICA (paraclinoid):2 MCA:1 Pcom:1 PICA:1	nr:13	Sacc 1 nr 12	R:10 UR:3	SAC REMN:10 NECK REMN:3	N:13	Sel Coiling:13	Raymond-Roy 1: 4 Raymond-Roy 2: 9	4	nr:13	GR (mRS 0-2):5 MD (mRS 3-4):1 SD (mRS 5):1

LAWTON 2003	6	34 (-)	F:1 nr:5	BA:2 ICA (paraclinoid):1 Pcom:2 VA:1	Large:1 nr:5	Fus 1 nr 5	nr:6	SAC REMN:5 REGROWTH:1		Sel Coiling:6	Raymond-Roy 1: 1 Raymond-Roy 2: 1 Raymond-Roy 3: 1 nr:3		None:1 nr:5	MD (mRS 3-4):1 nr:5
LIM 2008	6	54 (11,6)	F:5 M:1	Acho:1 ACoA:2 ICA (paraclinoid):2 PCom:1	Small:1 Large:1 nr:4	nr 6	R:6	NECK REMN:4 REGROWTH:2	nr:6	Sel Coiling:6	Raymond-Roy 1: 2 nr:4	2	None:6	MD (mRS 3-4):1 nr:5
MANGIAFICO 2005	12	55,58 (14,0)	F:9 M:3	ACoA:8 ICA (paraclinoid):1 MCA:1 Pcom:2	Small:6 Large:6	Sacc 2 nr 10	R:12	SAC REMN:2 NECK REMN:9 REGROWTH:1	N:12	Sel Coiling:10 Stent ass coil:2	Raymond-Roy 1: 10 Raymond-Roy 3: 2	3	None:11 Perforation:1	D (mRS 6):1 nr:11
RABINSTEIN 2002	21	50,57 (13,5)	F:13 M:8	ACoA:8 BA:4 ICA (paraclinoid):5 Pcom:1 PICA:1 VA:1	Small:12 Large:7 Giant:1 nr:1	nr 21	R:13 UR:8	NECK REMN:17 REGROWTH:4	N:21	Sel Coiling:21 Coil + sp thromb:2	Raymond-Roy 1: 15 Raymond-Roy 3: 6	4	None:21	GR (mRS 0-2):15 MD (mRS 3-4):1 SD (mRS 5):2 D (mRS 6):3
INSTITUTIONAL SERIES 'GEMELLI' HOSPITAL	7	58,28 (8,0)	F:4 M:3	MCA:1 ACoA:5 PCom:1	Small:6 Large:1	Sacc 7	R:5 UR:2	SAC REMN:1 NECK REMN:5 REGROWTH:1	N:7	Sel Coiling:7	Raymond-Roy 1: 7		None:7	GR (mRS 0-2):5 MD (mRS 3-4):1 SD (mRS 5):1
INSTITUTIONAL SERIES 'SAN CAMILLO' HOSPITAL	3	55,66 (5,9)	F:2 M:1	A1A2:1 ICA (BIFURCATION):1 PICA:1	Small:3	Sacc 3	R:3	SAC REMN:2 NECK REMN:1	N:3	Sel Coiling:2 Stent ass coil:1	Raymond-Roy 1: 2 Raymond-Roy 2: 1		None:3	GR (mRS 0-2):2 MD (mRS 3-4):1

OVERALL	102	52,94 (12,2)	F:46 M:25 nr:31	A1A2:1 ACA:2 ACho:1 MCA:4 ACoA:35 BA:12 ICA (bifurcation):1 ICA (paraclinoid):16 PCom:10 PICA:5 SHA:1 VA:5 nr:9	Small:33 Large:28 Giant:2 nr:39	Sacc 25 Fus 4 Diss 0 nr 73	R:63 UR:18 nr:21	SAC REMN:26 NECK REMN:52 REGROWTH:11 nr:13	N:78 Y:4 nr:20	Sel Coiling:99 Stent ass coil:3 Coil + sp thromb:2	Raymond-Roy 1: 63 Raymond-Roy 2: 23 Raymond-Roy 3: 4 nr:12	18	None:73 Perforation:1 nr:28	GR (mRS 0-2):51 MD (mRS 3-4):10 SD (mRS 5):7 D (mRS 6):7 nr:38

ACA: anterior cerebral artery; **ACho**: anterior choroidal artery; **MCA:** middle cerebral artery; **ACoA:** anterior communicating artery; **BA:** basilar artery; **ICA:** internal carotid artery; **PCom**: posterior communicating artery; **PICA**: postero-inferior cerebellar artery; **SHA**: superior hypophiseal artery; **VA:** vertebral artery; **Sacc:** saccular; **Fus**: fusiform; **Diss**: dissecting**; R:** ruptured; **UR**: unruptured**; NECK REMN:** neck remnant (Sindou I and II); **SAC REMN:** sac remnant (Sindou III and IV); **Sel Coiling**: selective coiling; **Stent ass coil**: stent assisted coiling; **Coil + sp thromb**: coiling + spontaneous thrombosis; GR:51
GOS: Glasgow outcome scale; **MD**:moderate disability; **SD**: severe disability; **D**:death; **nr**:not reported.

Table 2. Pooled Analysis of the Main Outcomes Reported in the 11 Included Studies + institutional series, Grouped as Reported in the First Column.

		Cumulative		
Outcome measured		**Raw number**	**Percentage**	**95% CI**
Demographics	**mean age±st.dev**	70/102	52.94±12.17	
	male sex	25/71	35.21	25.12-46.82
Subarachnoid hemorrhage		63/81	77.78	67.58-85.46
Localization	**ICA paraclinoid**	16/93	17.2	10.88-26.13
	ICA bifurcation	1/93	1.08	0.19-5.84
	basilar artery	12/93	12.9	7.54-21.21
	vertebral artery	5/93	5.38	2.32-11.97
	ACoA	35/93	37.63	28.46-47.79
	ACA	2/93	2.15	0.59-7.51
	SHA	1/93	1.08	0.19-5.84
	PICA	5/93	5.38	2.32-11.97
	MCA	4/93	4.3	1.69-10.54
	Pcom	10/93	10.75	5.95-18.67
	A1A2	1/93	1.08	0.19-5.84
	Acho	1/93	1.08	0.19-5.84
Size	**small**	33/63	52.38	40.27-64.22
	large	28/63	44.44	32.85-56.68
	giant	2/63	3.17	0.87-10.86
Exclusion at first surgery	**Neck Remnant (Sindou I-II)**	52/89	58.43	48.05-68.11
	Sac Remnant (Sindou III-IV)	26/89	29.21	20.78-39.36
	Regrowth	11/89	12.36	7.04-20.79
Neck reduction > 50% at surgery		48/50	96	86.54-98.9
preoperative prediction of incomplete treatment		4/82	4.88	1.91-11.88
Timing of secondary coiling	**immediate**	25/79	31.65	22.45-42-55
	delayed	54/79	68.35	57.45-77.55

Secondary treatment	**selective coiling**	97/102	95.1	89.03-97.89
	stent-assisted coiling	3/102	2.94	1.01-8.29
	spontaneous thrombosis	2/102	1.96	0.54-6.87
Angiographic Outcome after secondary coiling	**Raymond-Roy 1**	63/90	70	59.87-78.49
	Raymond-Roy 2	1	25.56	17.67-35.44
	Raymond-Roy 3	4/90	4.44	1.74-10.88
Complications of surgery	**Transient ischemia**	2/83	2.41	0.66-8.37
	residual aneurysm rupture	18/83	21.69	14.18-31.7
	Stroke	2/83	2.41	0.66-8.37
	intraoperative rupture	1/83	1.2	0.21-6.51
	sleapage of the clip	1/83	1.2	0.21-6.51
Complications of secondary coiling	**Perforation**	1/74	1.35	0.24-7.27
Clinical outcome (GOS and mRS) at discharge	**GR (mRS 0-2)**	46/69	66.67	54.93-75.65
	MD (mRS 3-4)	9/69	13.04	7.02-22.97
	SD (mRS 5)	7/69	10.14	5-19.49
	VS	0/69	0	0-5.27
	D (mRS 6)	7/69	10.14	5-19.49

Table3: Residual aneurysm rupture according to different failed surgical clipping

ANEURYSM EXCLUSION AT FIRST SURGERY	N. OF CASES	N. RUPTURES OF RESIDUALS	% RUPTURES OF RESIDUALS
SAC REMNANT	26	2	8%
NECK REMNANT	52	11	21%
REGROWTH	11	5	45%
TOTAL	89	18	20%

Figure 1

Click here to download Figure fig2.jpg

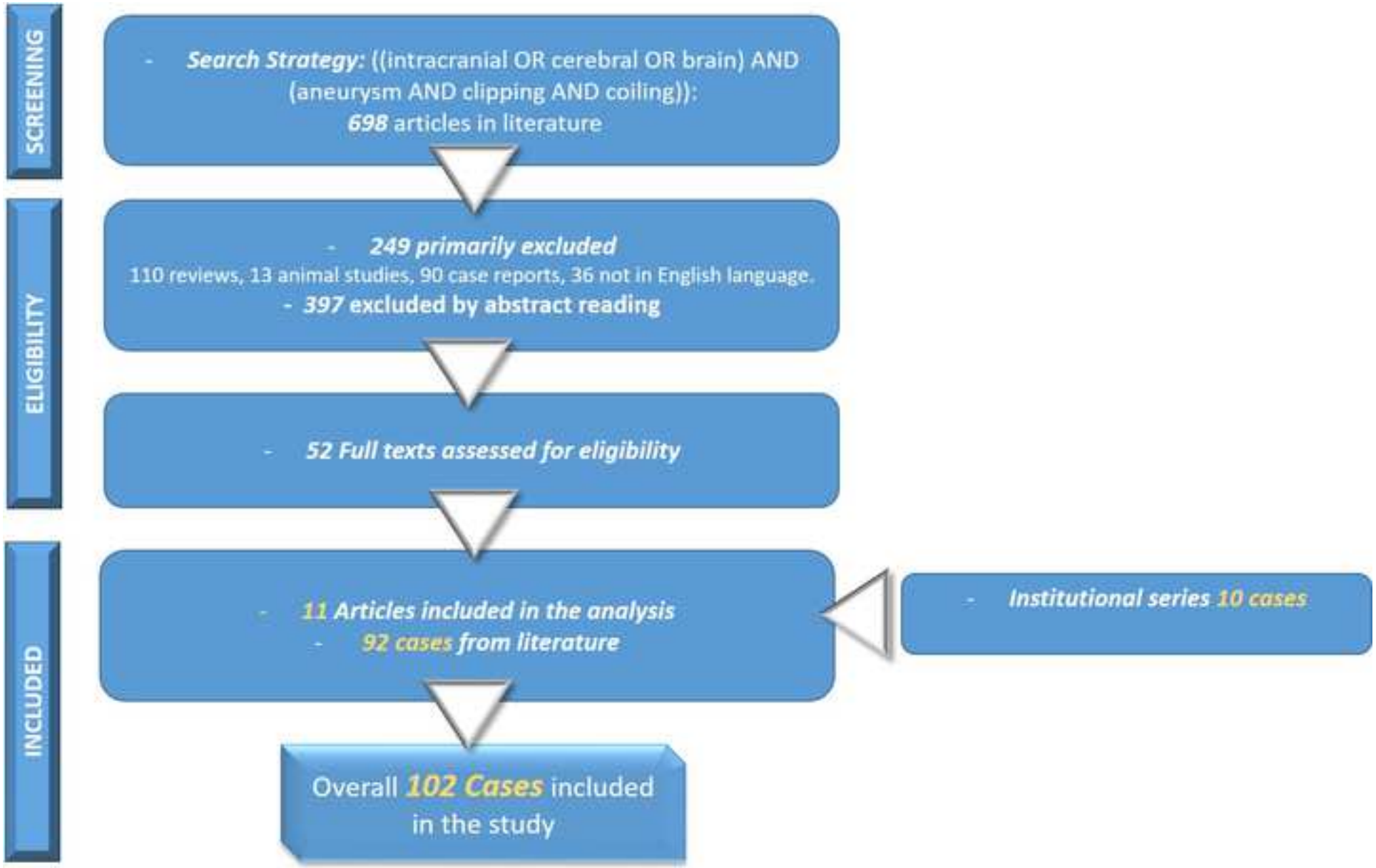

Figure 2

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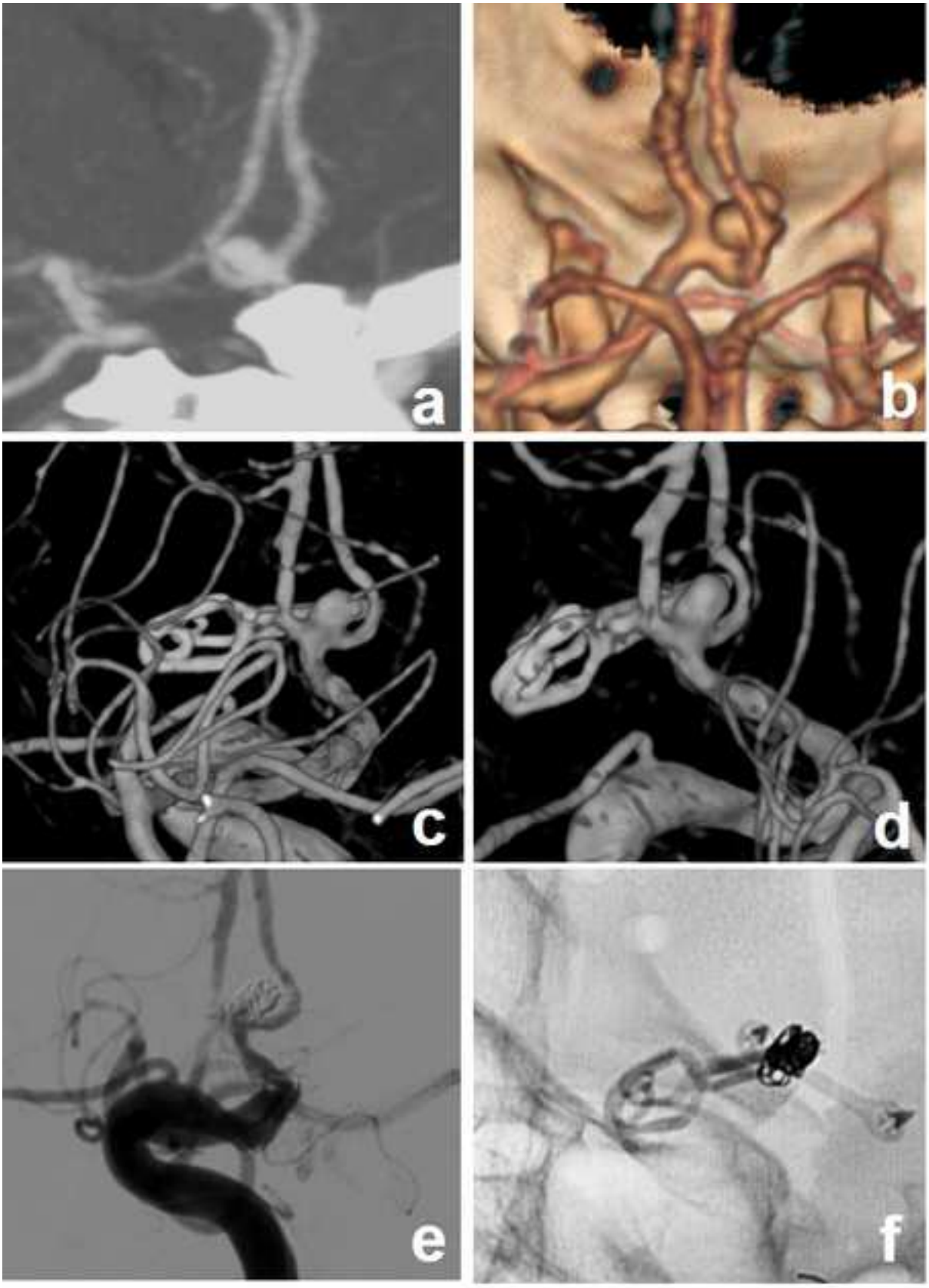

Figure 3

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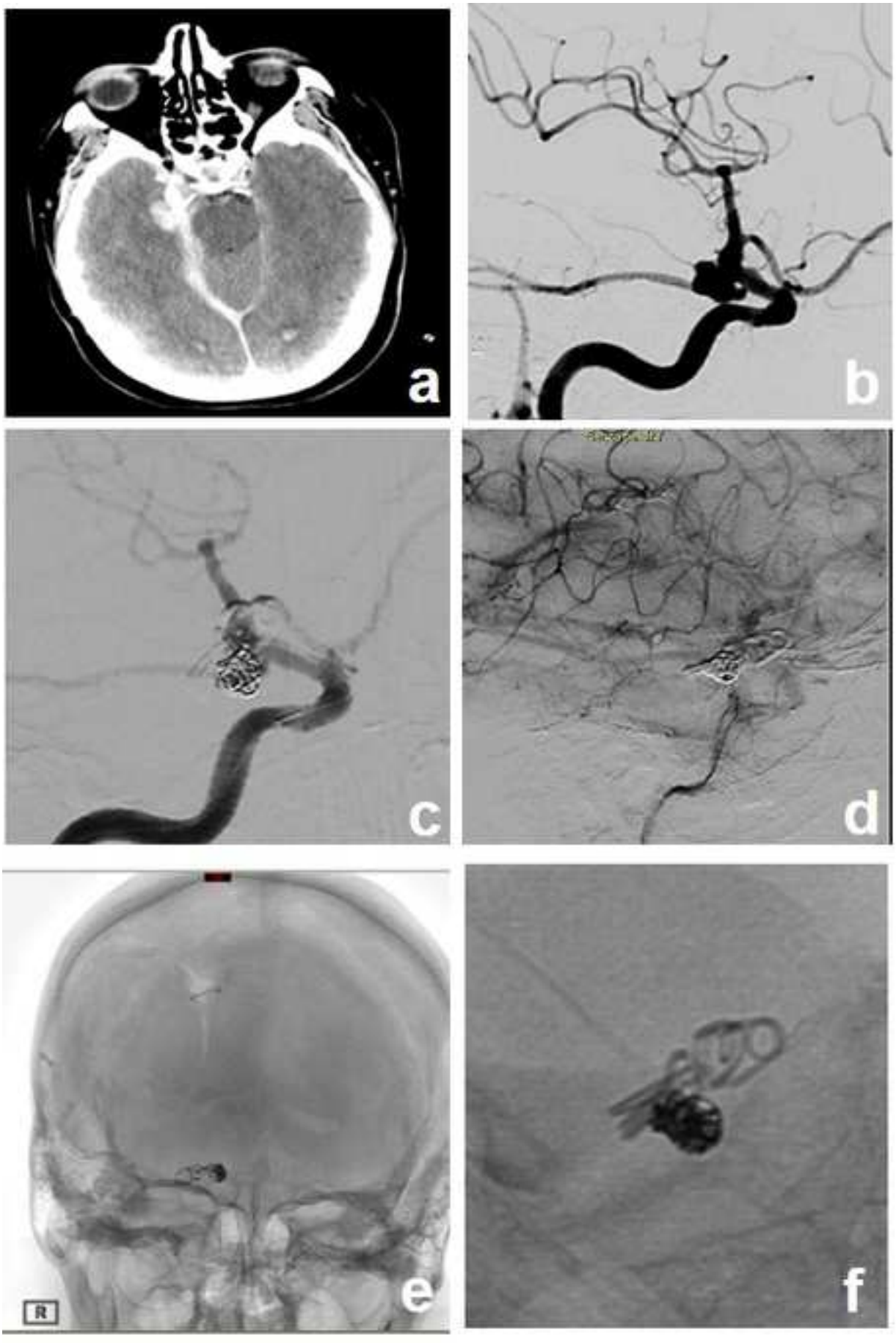

Figure 4

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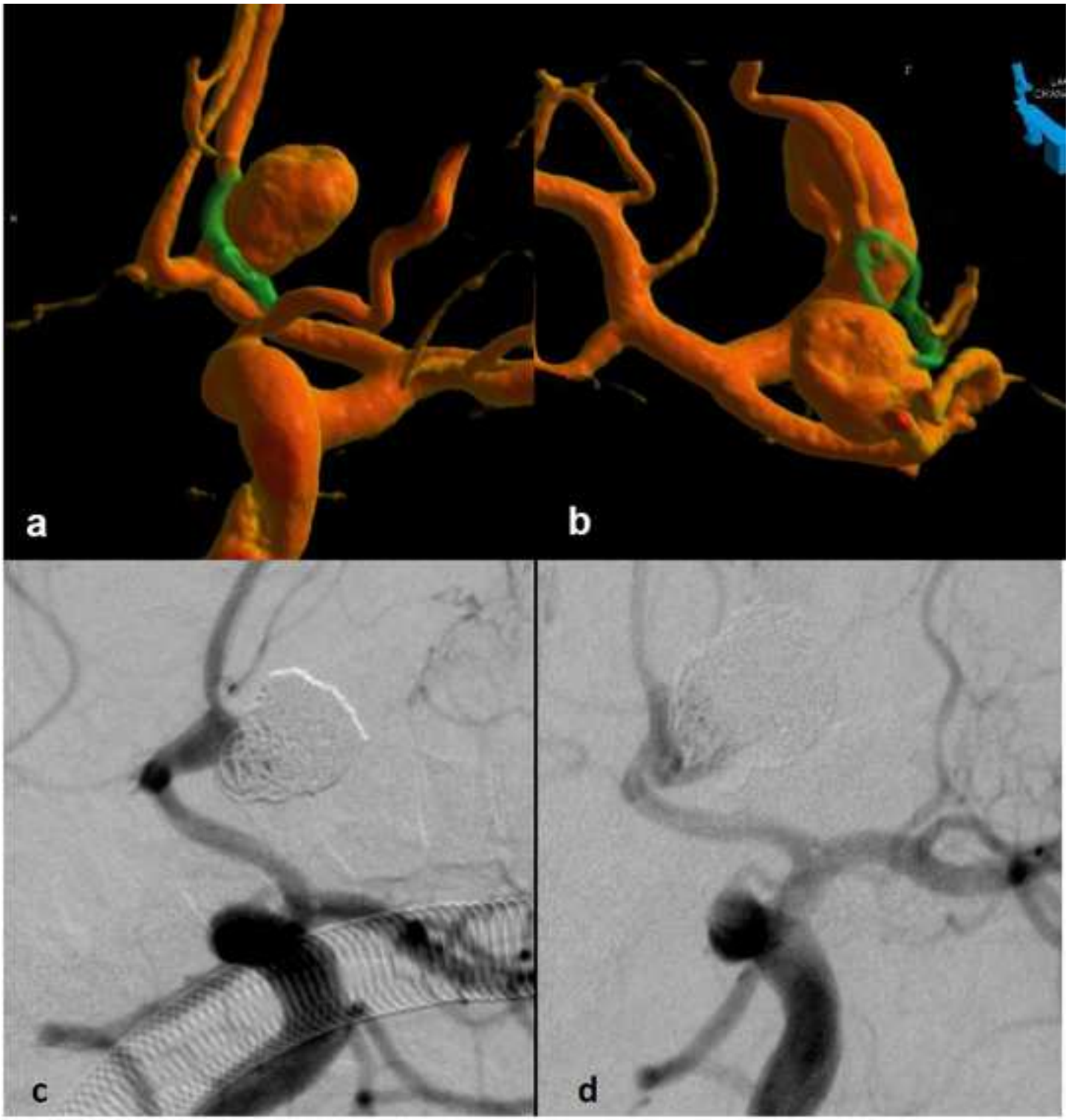

Figure 5

Click here to download Figure fig6.jpg

Supplementary Table 1. Outcomes Comparison Between Ruptured Versus Unruptured Aneurysms.

		Ruptured (n=63)		Unruptured (n=18)		P value
		Raw number	Percentage (95% confidence interval)	Raw number	Percentage (95% confidence interval)	
Localization	ICA paraclinoid	5/63	7.94 (3.44-17.27)	9/18	50 (29.03-70.97)	**0.0028**
	ICA bifurcation	1/63	1.59 (0.28-8.46)	0/18	0 (0-17.59)	1.00
	Basilar artery	9/63	14.29 (7.7-24.97)	1/18	5.56 (0.99-25.76)	0.68
	Vertebral artery	2/63	3.17 (0.87-10.86)	1/18	5.56 (0.99-25.76)	0.54
	ACoA	27/63	42.86 (31.4-55.14)	6/18	33.33 (16.28-56.25)	0.80
	ACA	2/63	3.17 (0.87-10.86)	0/18	0 (0-17.59)	1.00
	SHA	0/63	0 (0-5.75)	1/18	5.56 (0.99-25.76)	0.23
	PICA	5/63	7.94 (3.44-17.27)	0/18	0 (0-17.59)	0.57
	MCA	3/63	4.76 (1.63-13.09)	0/18	0 (0-17.59)	1.00
	Pcom	7/63	11.11 (5.49-21.2)	0/18	0 (0-17.59)	0.33
	A1A2	1/63	1.59 (0.28-8.46)	0/18	0 (0-17.59)	1.00
	Acho	1/63	1.59 (0.28-8.46)	0/18	0 (0-17.59)	1.00
Size	small	25/46	54.35 (40.18-67.85)	8/15	53.33 (30.12-75.19)	1.00
	large	21/46	45.65 (32.15-59.82)	5/15	33.33 (15.18-58.29)	0.78
	giant	0/46	0 (0-7.71)	2/15	13.33 (3.74-37.88)	0.06
Exclusion at first surgery	Neck Remnant (Sindou I-II)	40/63	63.49 (51.15-74.28)	11/18	61.11 (38.62-79.69)	1.00
	Sac Remnant (Sindou III-IV)	17/63	26.98 (17.58-39.03)	4/18	22.22 (9-45.21)	1.00
	Regrowth	6/63	9.52 (4.44-19.26)	3/18	16.67 (5.84-39.22)	0.43
Neck reduction > 50%		32/33	96.97 (84.68-99.46)	8/9	88.89 (56.5-98.01)	1.00
Preoperative prediction of incomplete treatment		3/57	5.26 (1.81-14.37)	1/18	5.56 (0.99-25.76)	1.00
Timing of secondary coiling	immediate	14/54	25.93 (16.12-38.93)	5/18	27.78 (12.5-50.87)	1.00
	delayed	40/54	74.07 (61.07-83.88)	13/18	72.22 (49.13-87.5)	1.00
Secondary treatment	Selective coiling	60/63	95.24 (86.91-98.37)	16/18	88.89 (67.2-96.9)	1.00
	Stent assisted coiling	3/63	4.76 (1.63-13.09)	0/18	0 (0-17.59)	1.00
	Spontaneous thrombosis	0/63	0 (0-5.75)	2/18	11.11 (3.1-32.8)	**0.05**

Angiographic outcome after secondary coiling	**Raymond-Roy 1**	48/59	81.36 (69.62-89.26)	10/18	55.56 (33.72-75.44)	0.52
	Raymond-Roy 2	9/59	15.25 (8.24-26.52)	7/18	38.89 (20.31-61.38)	0.12
	Raymond-Roy 3	2/59	3.39 (0.93-11.54)	1/18	5.56 (0.99-25.76)	0.56
Complication of surgery	**Transient ischemia**	2/62	3.23 (0.89-11.02)	0/18	0 (0-17.59)	1.00
	Residual aneurysm rupture	14/62	22.58 (13.96-34.41)	2/18	11.11 (3.1-32.8)	0.51
	stroke	1/62	1.61 (0.29-8.59)	1/18	5.56 (0.99-25.76)	0.41
	Intraoperative rupture	1/62	1.61 (0.29-8.59)	0/18	0 (0-17.59)	1.00
	Sleapage of the clip	1/62	1.61 (0.29-8.59)	0/18	0 (0-17.59)	1.00
Complication of secondary coiling	**perforation**	1/53	1.89 (0.33-9.94)	0/15	0 (0-20.39)	1.00
Clinical outcome (GOS and mRS) at discharge	**GR (mRS 0-2)**	30/50	60 (46.18-72.39)	16/17	94.12 (73.02-98.95)	0.29
	MD (mRS 3-4)	8/50	16 (8.34-28.51)	0/17	0 (0-18.43)	0.18
	SD (mRS 5)	7/50	14 (6.95-26.19)	0/17	0 (0-18.43)	0.19
	VS	0/50	0 (0-7.13)	0/17	0 (0-18.43)	1.00
	D (mRS 6)	5/50	10 (4.35-21.36)	1/17	5.88 (1.05-26.98)	1.00

Supplementary Table 2. Outcomes Comparison Between patients harboing aneurysms of the anterior and posterior circulation.

		Anterior circulation (n=71)		Posterior circulation (n=22)		P value
		Raw number	Percentage (95% confidence interval)	Raw number	Percentage (95% confidence interval)	
Subarachnoid hemorrhage		47/63	74.6 (62.66-83.72)	16/18	88.89 (67.2-96.9)	0.69
Size	small	26/47	55.32 (41.25-68.59)	7/16	43.75 (23.1-66.82)	0.29
	large	19/47	40.43 (27.64-54.66)	9/16	56.25 (33.18-76.9)	0.61
	giant	2/47	4.26 (1.17-14.25)	0/16	0 (0-19.36)	1.00
Percentage of exclusion at first surgery	Neck Remnant (Sindou I-II)	43/67	64.18 (52.22-74.6)	9/22	40.91 (23.26-61.27)	0.40
	Sac Remnant (Sindou III-IV)	16/67	23.88 (15.27-35.33)	10/22	45.45 (26.92-65.34)	0.21
	Regrowth	8/67	11.94 (6.18-21.83)	3/22	13.64 (4.75-33.33)	1.00
Neck reduction > 50%		35/37	94.59 (82.3-98.5)	9/9	100 (70.09-100)	1.00
Preoperative prediction of incomplete treatment		1/60	1.67 (0.29-8.86)	3/22	13.64 (4.75-33.33)	0.07
Timing of secondary coiling	immediate	17/59	28.81 (18.84-41.38)	8/20	40 (21.88-61.34)	0.60
	delayed	42/59	71.19 (58.62-81.16)	12/20	60 (38.66-78.12)	0.83
Secondary treatment	Selective coiling	68/71	95.77 (88.3-98.55)	20/22	90.91 (72.19-97.47)	1.00
	Stent assisted coiling	2/71	2.82 (0.78-9.7)	1/22	4.55 (0.81-21.8)	0.56
	Spontaneous thrombosis	1/71	1.41 (0.25-7.56)	1/22	4.55 (0.81-21.8)	0.42
Angiographic outcome after secondary coiling	Raymond-Roy 1	46/62	67.74 (55.37-78.05)	13/19	68.42 (46.01-84.64)	1.00
	Raymond-Roy 2	12/62	19.35 (11.43-30.85)	6/19	31.58 (15.36-53.99)	0.38
	Raymond-Roy 3	4/62	6.45 (2.54-15.45)	0/19	0 (0-16.82)	0.57
Complication of surgery	Transient ischemia	2/64	3.13 (0.86-10.7)	0/19	0 (0-16.82)	1.00
	Residual aneurysm rupture	12/64	18.75 (11.06-29.97)	6/19	31.58 (15.36-53.99)	0.37
	stroke	2/64	3.13 (0.86-10.7)	0/19	0 (0-16.82)	1.00
	Intraoperative rupture	0/64	0 (0-5.66)	1/19	5.26 (0.94-24.64)	0.23
	Sleapage of the clip	1/64	1.56 (0.28-8.33)	0/19	0 (0-16.82)	1.00
Complication of	perforation	1/59	1.69 (0.3-9)	0/15	0 (0-20.39)	1.00

secondary coiling						
Clinical outcome (GOS and mRS) at discharge	**GR (mRS 0-2)**	33/50	66 (52.15-77.56)	13/19	68.42 (46.01-84.64)	1.00
	MD (mRS 3-4)	8/50	16 (8.34-28.51)	1/19	5.26 (0.94-24.64)	0.43
	SD (mRS 5)	6/50	12 (5.62-23.8)	1/19	5.26 (0.94-24.64)	0.66
	VS	0/50	0 (0-7.13)	0/19	0 (0-16.82)	1.00
	D (mRS 6)	3/50	6 (2.06-16.22)	4/19	21.05 (8.51-43-33)	0.18

Supplementary Table 3. Clinical outcome comparison between patients harboing small versus large+giant aneurysms.

		Small (n=33)		Large+Giant (n=30)		P value
		Raw number	Percentage (95% confidence interval)	Raw number	Percentage (95% confidence interval)	
Subarachnoid hemorrhage		25/33	75.76 (58.98-87.17)	21/28	75 (56.64-87.32)	1.00
Localization	**ICA paraclinoid**	3/33	9.09 (3.14-23.57)	8/28	28.57 (15.25-47.06)	0.18
	ICA bifurcation	1/33	3.03 (0.54-15.32)	0/28	0 (0-12.06)	1.00
	Basilar artery	2/33	6.06 (1.68-19.61)	6/28	21.43 (10.21-39.54)	0.15
	Vertebral artery	3/33	9.09 (3.14-23.57)	1/28	3.57 (0.63-17.71)	0.62
	ACoA	17/33	51.52 (35.22-67.5)	6/28	21.43 (10.21-39.54)	0.13
	ACA	0/33	0 (0-10.43)	1/28	3.57 (0.63-17.71)	0.46
	SHA	1/33	3.03 (0.54-15.32)	0/28	0 (0-12.06)	1.00
	PICA	2/33	6.06 (1.68-19.61)	2/28	7.14 (1.98-22.65)	1.00
	MCA	2/33	6.06 (1.68-19.61)	0/28	0 (0-12.06)	0.49
	Pcom	1/33	3.03 (0.54-15.32)	6/28	21.43 (10.21-39.54)	0.10
	A1A2	1/33	3.03 (0.54-15.32)	0/28	0 (0-12.06)	1.00
	Acho	0/33	0 (0-10.43)	0/28	0 (0-12.06)	1.00
Exclusion at first surgery	**Neck Remnant (Sindou I-II)**	24/33	72.73 (55.78-84.93)	20/30	66.67 (48.78-80.77)	0.84
	Sac Remnant (Sindou III-IV)	5/33	15.15 (6.65-30.92)	5/30	16.67 (7.34-33.56)	1.00
	Regrowth	4/33	12.12 (4.82-27.33)	5/30	16.67 (7.34-33.56)	0.73
Neck reduction > 50%		20/22	90.91 (72.19-97.47)	20/20	100 (83.89-100)	1.00
Preoperative prediction of incomplete treatment		1/32	3.13 (0.55-15.74)	3/29	10.34 (3.58-26.39)	0.35
Timing of secondary coiling	**immediate**	8/32	25 (13.25-42.11)	8/27	29.63 (15.85-48.48)	0.78
	delayed	24/32	75 (57.89-86.75)	19/27	70.37 (51.52-84.15)	1.00

Secondary treatment	**Selective coiling**	29/33	87.88 (72.67-95.18)	29/30	96.67 (83.33-99.41)	0.85
	Stent assisted coiling	3/33	9.09 (3.14-23.57)	0/30	0 (0-11.35)	0.24
	Spontaneous thrombosis	1/33	3.03 (0.54-15.32)	3/30	10 (3.46-25.62)	0.35
Angiographic outcome after secondary coiling	**Raymond-Roy 1**	27/33	81.82 (65.61-91.39)	24/30	80 (62.69-90.49)	1.00
	Raymond-Roy 2	4/33	12.12 (4.82-27.33)	5/30	16.67 (7.34-33.56)	0.73
	Raymond-Roy 3	2/33	6.06 (1.68-19.61)	1/30	3.33 (0.59-16.67)	1.00
Complication of surgery	**Transient ischemia**	0/33	0 (0-10.43)	1/28	3.57 (0.63-17.71)	0.46
	Residual aneurysm rupture	5/33	15.15 (6.65-30.92)	6/28	21.43 (10.21-39.54)	0.74
	stroke	1/33	3.03 (0.54-15.32)	0/28	0 (0-12.06)	1.00
	Intraoperative rupture	0/33	0 (0-10.43)	1/28	3.57 (0.63-17.71)	0.46
	Sleapage of the clip	0/33	0 (0-10.43)	1/28	3.57 (0.63-17.71)	0.46
Complication of secondary coiling	**perforation**	1/33	3.03 (0.54-15.32)	0/28	0 (0-12.06)	1.00
Clinical outcome (GOS and mRS) at discharge	**GR (mRS 0-2)**	18/26	69.23 (50.01-83.5)	15/24	62.5 (42.71-78.84)	1.00
	MD (mRS 3-4)	2/26	7.69 (2.14-24.14)	4/24	16.67 (6.68-35.85)	0.66
	SD (mRS 5)	2/26	7.69 (2.14-24.14)	2/24	8.33 (2.32-25.85)	1.00
	VS	0/26	0 (0-12.87)	0/24	0 (0-13.8)	1.00
	D (mRS 6)	4/26	15.38 (6.15-33.53)	3/24	12.5 (4.34-31)	1.00