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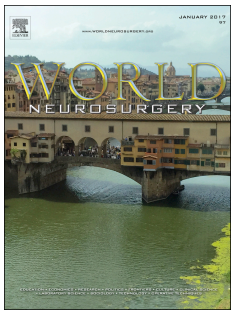


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Marvin Darkwah Oppong, MD, Daniela Pierscianek, MD, Yahya Ahmadipour, MD, Thiemo Florin Dinger, MD, Philipp Dammann, MD, Karsten Henning Wrede, MD, Neriman Özkan, MD, Oliver Müller, MD, Ulrich Sure, MD, Ramazan Jabbarli, MD

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# Intraoperative aneurysm rupture during microsurgical clipping: Risk re-evaluation in the post-ISAT era

Marvin Darkwah Oppong[1], MD; Daniela Pierscianek[1], MD; Yahya Ahmadipour[1], MD; Thiemo Florin Dinger[1], MD; Philipp Dammann[1], MD; Karsten Henning Wrede[1], MD; Neriman Özkan, MD; Oliver Müller[1], MD; Ulrich Sure[1], MD; Ramazan Jabbarli[1], MD

Affiliation: [1]Department of Neurosurgery, University Hospital, University of Duisburg-Essen, Essen, Germany

## CORRESPONDING AUTHOR:

Marvin Darkwah Oppong, MD

Department of Neurosurgery

University Hospital Essen

Hufelandstr. 55

D-45147 Essen

Germany

E-mail: marvin.darkwahoppong@uk-essen.de

Phone: +49 201 723 1230

Fax: +49 201 723 5909

## RUNNING TITLE

Risk evaluation for intra-OP aneurysm rupture

### ABBREVIATIONS

**95% CI** *95% confidence interval;* **ACOA** *anterior communicating artery*; **aOR** *adjusted Odds ratio;* **CT** *computed tomography* **DSA** *digital subtraction angiography*; **IA** *intracranial aneurysm*; **ICH** *intracerebral hemorrhage*; **IOAR** *intraoperative aneurysm rupture*; **IVH** *intraventricular hemorrhage*; **MCA** *middle cerebral artery*; **mRS** *modified Rankin scale*; **OR** *odds ratio*; **SD** *standard deviation*; **RIA** *ruptured intracranial aneurysm*; **SAH** *subarachnoid hemorrhage*; **SD** *standard deviation*; **UIA** *unruptured intracranial aneurysm;* **WFNS** *World Federation of Neurosurgical Societies federation*

## KEYWORDS

Aneurysm, intraoperative rupture, microsurgical clipping, rebleeding, subarachnoid hemorrhage

**Objectives**: Intraoperative aneurysm rupture (IOAR) is a common complication during intracranial aneurysm(s) (IA) surgery. In virtue of paradigm shift regarding IA selected for clipping in the post-ISAT era, we aimed to evaluate the risk factors and impact of IOAR in an institutional series of clipped ruptured (RIA) and unruptured (UIA) IA.

**Material and Methods**: All IA treated by microsurgical clipping at our institution between 2003 and 2016, were eligible for this study. Demographic, clinical and radiographic factors were correlated with occurrence of IOAR in univariate and multivariate analyses. Impact on outcome was analyzed for RIA and UIA separately.

**Results**: 903 clipped IAs were included in the final analysis (538 UIA and 365 RIA). IOAR occurred in 163 cases (18.1%), mostly during clipping of RIA (37.5% vs. 4.8%) In multivariate analysis, ruptured status (adjusted odds ratio [aOR] =10.46; p<0.001), sack size (aOR=1.05 per-mm-increase, p=0.038) and IA location in the anterior communicating artery (aOR=2.31, p<0.001) independently predicted IOAR. For RIA cases, IOAR was also independently predicted by rebleeding before therapy (aOR=3.11, p=0.033) and clinical severity of subarachnoid hemorrhage (aOR=1.18 per-WFNS-grade-increase, p=0.049). IOAR independently predicted poor outcome (aOR=1.83, p=0.042) after RIA surgery. In turn, IOAR impacted only the risk for cerebral infarct(s) (OR=3.75, p=0.003) and incomplete IA occlusion (OR=3.45; p=0.003) for UIA cases, but not the outcome (p=0.263).

**Conclusion**: IOAR was independently predicted by the ruptured status, location and size of IA, as well as by initial severity of aneurysmal bleeding and pretreatment rebleeding. Impact of IOAR differed between RIA and UIA cases.

## Introduction

Intraoperative aneurysm rupture (IOAR) is a common complication during intracranial aneurysm (IA) surgery. It occurs in 6 – 40% [1-11] of cases with ruptured intracranial aneurysm(s) (RIA) and in 1 -20% of cases with unruptured intracranial aneurysm(s) (UIA) [8, 10, 12, 13]. The risk dropped significantly after introduction of operative microscope (rates in pre-microscopic series > 50% [14, 15]). Even though microsurgical technique allows more control of actual bleeding [15], it still may become a real challenge even for an experienced neurosurgeon. Despite an 80-years history of neurovascular surgery, our knowledge about IOAR predictors is predominantly based on smaller cohorts collected in the pre-coiling era. Risk factors for IOAR include ruptured status of IA [8, 10, 12], initial severity of subarachnoid hemorrhage (SAH) [11], timing of surgery after SAH [6], experience of the vascular neurosurgeon [8, 12, 16] and location of IA [1, 2, 9, 10]. Regarding UIA cases, the data on IOAR are even sparser. In particular, one recent publication reported a thinner aneurysm wall (translucent aneurysm) as a predictor of IOAR in UIA [13]. Finally, the clinical value of IOAR for treatment success and functional outcome remains unclear [2, 3, 6, 8, 9, 11, 17].

The aim of the present study was to evaluate the risk factors for IOAR in a large post-ISAT institutional series of clipped RIA and UIA. Furthermore, we analyzed the impact of IOAR on treatment outcome.

## Material and Methods

This is a single institution retrospective study. All IA treated by microsurgical clipping at our institution between January 2003 and June 2016, were eligible for this study. This included RIA and UIA. The study was approved by the institutional review board.

### *Management of UIA*

Routine management of UIA included a pretreatment digital subtraction angiography (DSA) with further treatment allocation upon interdisciplinary consensus. All patients received a postoperative computed tomography (CT) scan of the head in the first 24

hours after treatment. Additional CT scans were performed if necessary. IA occlusion was checked by a second DSA during hospitalization.

*Management of RIA*

All patients with acute aneurysmal SAH were admitted to our neurosurgical intensive care unit. Initial diagnostic workup included CT scan of the head as well as DSA. All patients that underwent microsurgical clipping received a CT scan in the first 24 hours after treatment, as well as post-treatment DSA during the hospital stay. Additional CT scans were performed as needed.

Routine management of SAH included treatment of acute hydrocephalus by external ventricular or lumbar drainage, oral administration of nimodipine for 3 weeks and daily transcranial Doppler sonography for at least 2 weeks. Symptomatic vasospasm was treated by intra-arterial nimodipine application and, if necessary, by balloon dilatation. Persisting hydrocephalus was treated by ventricular peritoneal shunting.

*Data management*

Digital patients charts were reviewed for demographical, radiographical and clinical parameters. Data were included into an electronic database. In cases with acute SAH, the initial clinical severity was assessed in concordance to the World Federation of Neurosurgical Societies (WFNS) grading system [18]. The cases with pretreatment rebleeding in RIA as well as those with need for permanent shunting due to persisting hydrocephalus were recorded. Operative records were reviewed with regard to operating surgeon, IOAR occurrence and need for temporary clipping. Surgeons experience was judged by time since board exam at treatment date in years (for statistical analysis we dichotomized in > 2 years and ≤ 2 years). Calcification in IA wall was judged upon intraoperative findings and appearance on preoperative CT scans. Outcome was assessed according to the modified Rankin scale (mRS) [19] at 6 month after IA surgery. A mRS greater than 2 was defined as unfavorable functional outcome. Outcome parameters of RIA and UIA were analyzed separately.

Radiographic data was collected as follows:

- DSAs were screened for IA location, sack size (in mm) and post-clipping IA remnant. For further analysis, the IA from vertebral, basilar, posterior cerebral and posterior communicating arteries were merged into posterior circulation IA group;
- Post-treatment CT scans were reviewed by the senior author (RJ) blinded at this time for any clinical information with regard to occurrence of new cerebral infarcts. Lesions resulting from operative approach, drainage placement or intracerebral hemorrhage (ICH) were excluded.
- For SAH cases, the following radiographic data were recorded from the initial CT scans: severity of SAH using the original Fisher scale [20], presence of intraventricular hemorrhage (IVH) and ICH.

*Statistical analysis*

Statistical analysis was performed using SPSS Version 22 for Mac (IBM Corp.). Continuous variables are given in mean +/- standard deviation (SD). They were analyzed using the Student's t-test for normally distributed and the Mann–Whitney U test for non-normally distributed data. Categorical variables were analyzed using the Chi-Square-Test; for samples smaller than 5, the Fisher-Exact-Test was used. The value of differences between the IOAR rates between the neurosurgeons was utilized with the one-way ANOVA test (Friedman test). P-values smaller than 0.05 were defined as significant. Factors predictive for occurrence of IOAR in univariate analysis were included in final multivariate binary logistic regression analysis. Outcome endpoints were also analyzed in multivariate manner. Missing data were replaced using multiple implications.

## Results

A total of 903 clipped IA in 712 patients were included into the final analysis. 156 (21.9%) patients had more than one IA treated by clipping (including 18.1% with 2 and

3.8% with 3 and more clipped aneurysms). The majority of IA were UIA (n=538; 59.6%); accordingly, RIA accounted for 40.4% of the cases. More than two thirds of IA were harbored by female patients (636; 70.4%). Mean age was 53 years +/- 12 years (SD). Most of treated IA were located in the middle cerebral artery (MCA, see Figure 1). An IOAR occurred in 163 cases (18.1%).

*Predictors of IOAR*

The majority of IOAR occurred during clipping of RIA (37.5% vs. 4.8%; p< 0.001; Odds ratio (OR) = 11.83; 95% Confidence interval (95% CI) 7.57 – 18.51). IA location also showed substantial impact on IOAR risk (Figure 1). As compared to any other location, IA in the anterior communicating artery (ACOA) showed the highest risk for IOAR (p<0.001; OR=3.27; 95% CI 2.23-4.78, Table 1), whereat IA arising from the MCA had the lowest risk of IOAR (p<0.001;OR=0.41; 95% CI 0.29-0.58). Temporary clipping was more likely in case of IOAR (p<0.001; OR=4.71; 95% CI 2.10 – 10.53). Calcification of the IA had no impact on IOAR risk (p=0.103).

In multivariate analysis, RIA increased the risk for IOAR by 10.46 (adjusted OR [aOR]; p<0.001; 95% CI 6.65 -16.45). IA sack size (p=0.038; aOR=1.05 per mm size increase; 95% CI 1.01-1.09) and location in the ACOA (p<0.001; aOR=2.31; 95% CI 1.50-3.54) could also be shown to be independent risk factors. Male gender (p=0.025 in the univariate analysis) did not have independent predictive value on IOAR risk (p=0.583). The differences between the IOAR rates between the neurosurgeons (p=0.064) as well as influence of surgeons experience (> 2 years; p=0.271) did not reach statistical significance either.

Considering the above-mentioned risk factors, we re-calculated IOAR risk in different subgroups (Figure 2): clipping 50.5% of RIA in the ACOA was associated with IOAR, against 3.5% among UIA in the MCA (p<0.0001, OR=27.85, 95% CI 14.15 – 54.82).

Further, we evaluate IOAR-related risks factors separately for RIA and UIA cohorts.

*IOAR in RIA*

44.1% of SAH patients presented with an initial clinical severity measured by WFNS over 3 and 90% with a initial radiographic severity measured by original Fisher scale of 3 or 4. 42.8% had an IVH and 45.2% an ICH in initial CT scan.

Within the RIA cohort, we included the significant IOAR predictors from univariate analysis (see supplements table e1) into multivariate regression model. Accordingly, IA location in the ACOA (p=0.001; aOR=2.17; 95% CI 1.35-3.49), rebleeding before therapy (p=0.033; aOR=3.11; 95% CI 1.10-8.08) and higher initial clinical severity of SAH (p=0.049; aOR=1.18 per WFNS grade increase; 95% CI 1.01–1.39) were independent predictors of IOAR in the RIA cohort. In line with the analysis for the whole cohort, ruptured MCA aneurysms represented the group with the lowest risk of IOAR (vs. any other location, p=0.047; OR=0.65; CI 95% 0.42-0.99).

Regarding outcome, IOAR increased the risk of unfavorable outcome (p=0.009; OR=1.92; 95% CI 1.18-3.12). In multivariate analysis, this was independent of age, initial SAH severity and de novo infarcts (see table 2 for multivariate and supplements table e2 for univariate analysis of predictors of unfavorable outcome). Furthermore, IOAR was associated with in-hospital mortality among SAH patients (p=0.012; OR=2.06; 95% CI 1.16-3.64).

Finally, IOAR in RIA had no influence on infarct rate (p=0.082), residual aneurysm sack after clipping (p=0.380) or persisting hydrocephalus (p=0.061).

*IOAR in UIA*

In multivariate analysis (for univariate risk factors analysis see supplements table e1), the risk factors for IOAR in UIA were location in the ACOA (p=0.019; aOR=2.98; 95% CI 1.19-7.45) and sack size (p=0.046; aOR=1.07 per mm size increase; 95% CI 1.01-1.15). Consistently with RIA cohort, UIA in the MCA showed the lowest IOAR risk (vs. any other location, p=0.039; OR=0.44; 95% CI 0.20-0.98)

In the UIA cohort, IOAR did not show any impact on functional outcome at 6 month (p=0.263) and in-hospital mortality (p=0.144). However, IOAR increased the risk for

cerebral infarcts (p=0.003; OR=3.75; 95% CI 1.64-8.58) and post treatment residual IA sack (p=0.001; OR=3.45; 95% CI 1.56-7.65). Univariate analysis failed to identify additional risk factors for infarcts in UIA cases from our data (see supplements table e3).

## Discussion

The aim of this study was to identify the risk factors for IOAR. To our knowledge, we present the largest post ISAT single center series addressing IOAR risk during IA clipping. We identified location and size as well as ruptured IA status as independent risk factors for IOAR. Although male patients more frequently faced IOAR during IA clipping, but demographic characteristics failed to show independent predictive value for IOAR risk. Location in ACOA remained the main risk factor in separate assessment of RIA und UIA cases. Temporary clipping was more common in cases with IOAR. This most likely reflects the fact that aneurysm morphology is more complex in these cases or the IOAR itself urges for a temporay occlusion of the vessel. Regarding outcome, IOAR predicted infarcts and residual aneurysm sack after UIA clipping. In RIA cases, it independently predicted unfavorable outcome but had no impact on infarct rates.

### *IOAR risk: reconsidering the role in the modern post-ISAT neurovascular era*

Since the publication of the data from ISAT [21], there has been an increase of endovascularly treated IA. Presently, more than half of IA are being coiled in the largest neurovascular centers in North America and Europe [22-24]. However, most centers still hold to “clipping first” policy for MCA aneurysms [25]. ACOA aneurysms are in most large neurovascular centers primary considered for endovascular treatment. Further development of endovascular techniques like stenting and flow diversion makes even more ACOA aneurysms treatable by an endovascular approach [26]. IA at this location that are considered for open surgical approach, are more likely to be complex or harbored by patients with poor intracranial vessel structure [27]. In general, we apparently face a negative bias for non-MCA aneurysms selected for microsurgical clipping in the recent decade. This circumstance necessitates a reevaluation of risks related to IA clipping, especially IOAR.

*Predictors of IOAR in RIA*

IOAR in our series was most common in RIA cases. RIAs are known to be more prone to IOAR than UIA [10, 12, 28]. Compared to the largest pre ISAT trial by Leipzig et al. [10], recent clipping series show increased IOAR rates. Leipzig reported an IOAR rate of 10.7%, whereas in our series the rate was 37.5% comparable to recent published results (34.0% [11]). This might be an effect of the increase of endovascular treated RIAs [29] and therefore a raising complexity of non-MCA aneurysms selected for clipping at this point of time. In our RIA cohort, location of IA in the ACOA, higher initial severity of SAH and IA rebleeding before therapy independently predicted the risk of IOAR.

There are conflicting results regarding the role of IA location on IOAR risk. Higher rates of IOAR have already been reported for ACOA [1, 28] and for anterior cerebral aneurysms in general [9]. On the other hand, there are also reports showing no effect of IA location on intraoperative rupture risk [6, 11, 12]. Congruently with our data, MCA aneurysms have been reported to be safer regarding IOAR risk [1, 28]. Only one of the mentioned articles reports on post ISAT data and has a sample size of 100 [11]. This makes it difficult to draw a clear conclusion regarding the risk of IA location for IOAR.

The initial clinical severity of SAH has been connected to the risk of IOAR [11]. However, older series show no correlation between poor WFNS grade (>grade 3 or only grade 5) [2, 4, 10]. Our and prior published data [11] suggests that correlation between initial SAH severity [12] and IOAR risk more likely exists in gradually increasing manner, than in dichotomization into poor and good grade SAH.

Furthermore, IA rupture before treatment seems to be an important factor for intraoperative vulnerability of RIA and predilection to re-rupture. As reported by other authors, these aneurysms have an increased risk of IOAR [10, 28]. It has been reported that aneurysm showing a ‘spot sign’ during CT-Angiography as proof of actual bleeding during examination also have a higher risk of IOAR [11].

*Clinical Impact of IOAR in RIA*

In our cohort, IOAR independently predicted unfavorable outcome at six month for RIA cases. We also were able to show that it increases the risk of in-hospital mortality. Interestingly, we could not show any connection to surgical outcome (residual aneurysm after clipping), the incidence of infarcts and rate of persisting hydrocephalus requiring permanent shunting.

The impact of IOAR on outcome after SAH has been a topic of discourse for a long time. It might appear obvious that in the time before the introduction of the operation microscope the negative impact on outcome after IOAR was mostly connected to the permanent major vessel occlusion that was often necessary to control the bleeding [14, 15].

Some studies published after establishing of the operative microscope were able to show an association of IOAR and poor outcome [12, 17] some others showed only a connection for early stage IOAR and poor outcome [2, 3, 6]. There are also conflicting results showing no connection between outcome and IOAR [8, 9, 11].

*Predictors of IOAR in UIA*

UIA are commonly associated with a lower intraoperative rupture rate than RIA [8, 10, 12]. Our data confirmed this with an IOAR rate of 4.8% compared to 37.5% for RIA. Because of low incidence of IOAR during UIA clipping, it is often seen as negligible. In most previous series, the amount of UIA cases accounted for a small part of the whole cohort [8, 12]. In the largest pre ISAT series over 40% of the IA were unruptured [10]. However none of these studies focused on the risk factors of IOAR for UIA. One recent study reported that translucent walls as sign of weaker aneurysm wall in unruptured MCA aneurysms predicted IOAR [13]. However, this characteristic is only identifiable if the aneurysm is already at least partly exposed during operation. Our aim was to identify factors predicting IOAR before surgery. This is of special interest because of the trend towards higher identification rates of UIA cases due to improvement and higher availability of non-invasive imaging techniques [24]. In our cohort, IA size and location in

the ACOA independently predicted IOAR for UIA cases, whereas MCA aneurysms were less likely to rupture during surgery.

*Clinical Impact of IOAR in UIA*

IOAR did not influence the functional outcome at six month and in-hospital mortality. However, it increased the risk of cerebral infarcts after surgery. The reasons reported for ischemic complications following elective aneurysm surgery are multiple. They include age, previous medical conditions, intraoperative temporary clipping [30]. The occurrence of vasospasm after elective IA treatment is very rare and not necessarily connected to IOAR [31, 32]. Finally, IOAR was associated with higher risk of residual aneurysm sack after UIA clipping, but not in RIA.

## Limitations

Main drawback of this study is its retrospective design. We also did not include data regarding temporary clipping during surgery reported to impact IOAR risk [10]. Furthermore, the time of occurrence of the IOAR during the operation was not included into analysis. Especially rupture during very early stages of the operation (e.g. dura opening) is connected to poor outcome after IOAR in SAH patients [2, 3, 6]. However, very early intraoperative rupture occurs only in a very small group of patients. Furthermore, we did not perform MRI routinely after surgical clipping, which would increase the detection rate of cerebral infarction. In summary, we believe our data will increase the knowledge on risk factors related to IOAR in the current post-ISAT era with changed preferences regarding the IA treatment options.

## Conclusion

In our cohort, we confirmed the ruptured status, location in the ACOA and larger sack size as independent predictors of IOAR. Preoperative re-rupture of RIA and initial clinical

severity substantially increase IOAR risk in SAH patients. In addition, IOAR worsens the outcome after RIA surgery, but not for UIA cases. Unruptured MCA aneurysms carry the lowest risk of IOAR. Although rare for UIA cases, IOAR might lead to certain complications, like cerebral infarction and incomplete IA occlusion.

**Disclosure/Founding**

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**Figure legends**

Figure 1.: Number of aneurysms by parenting vessel and rate of intraoperative aneurysm rupture for the cohort of ruptured intracranial aneurysm.

*Abbreviations:* ACOA – anterior communicating artery; dACA – distal anterior cerebral artery; ICA –internal carotid artery; IOAR – intraoperative aneurysm rupture; MCA – middle cerebral artery; PC – posterior circulation.

Figure 2.: Number of aneurysms by parenting vessel and rate of intraoperative aneurysm rupture for the cohort of unruptured intracranial aneurysm.

*Abbreviations:* ACOA – anterior communicating artery; dACA – distal anterior cerebral artery; ICA –internal carotid artery; IOAR – intraoperative aneurysm rupture; MCA – middle cerebral artery; PC – posterior circulation.

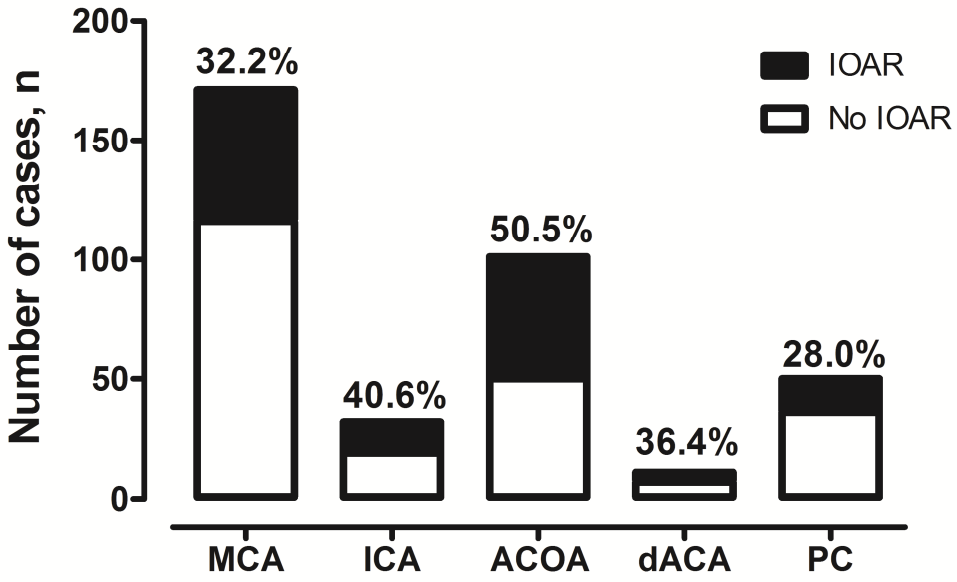
| Parameter | IOAR | | no IOAR | | | | |
|---|---|---|---|---|---|---|---|
| | n/mean | %/SD | n/mean | %/SD | p | OR | 95% CI |
| Age (years) | 53 | ±14 | 53 | ±12 | 0.806 | | |
| Male gender | 60 | 36.8% | 207 | 28.0% | 0.025 | 1.49 | 1.05 - 2.13 |
| Sack size (mm) * | 7.45 | ±5.09 | 6.34 | ±4.27 | 0.015 | | |
| RIA | 137 | 84.0% | 228 | 30.8% | <0.001 | 11.83 | 7.57 -18.51 |
| Location MCA | 68 | 41.7% | 471 | 63.6% | <0.001 | 0.41 | 0.29 - 0.58 |
| Location ACOA | 58 | 35.6% | 107 | 14.5% | <0.001 | 3.27 | 2.23 - 4.78 |
| Aneurysm calcification† | 12 | 11.5% | 97 | 18.1% | 0.103 | 0.59 | 0.31-1.12 |
| Residual aneurysm | 46 | 28.2% | 161 | 21.8% | 0.076 | 1.41 | 0.96 - 2.07 |
| De novo Infarct ‡ | 89 | 54.9% | 183 | 24.8% | <0.001 | 3.69 | 2.60 - 5.25 |

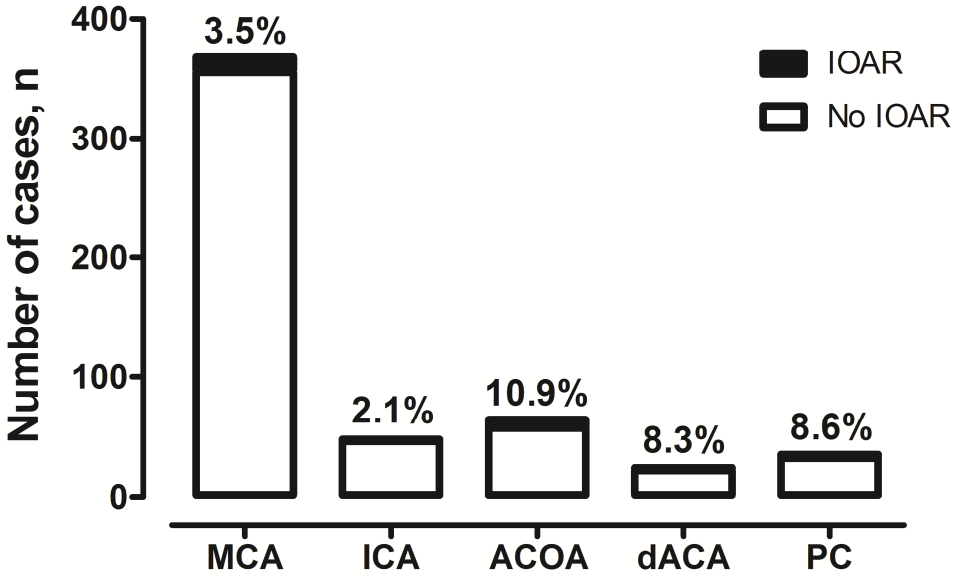
* data missing for 85 IA
† data missing for 263 IA
‡ 3 data missing for 3 IA

Table 1.: Univariate analysis of risk factors for IOAR and outcome parameters.

| Parameter | p | aOR | CI 95% |
|---|---|---|---|
| Age (years) | 0.004 | 1.03 | 1.01 - 1.05 |
| WFNS grade | 0.007 | 1.38 | 1.11 - 1.89 |
| Fisher grade | 0.153 | 1.12 | 0.85 - 2.72 |
| De novo infarct | <0.001 | 4.69 | 2.54 - 8.7 |
| IOAR | 0.042 | 1.83 | 1.02 - 3.25 |

Table 2.: Multivariate analysis of predictors of unfavorable outcome at 6 month follow-up in SAH cases.





- This article reports on intraoperative aneurysm rupture (IOAR)
- A large retrospective post ISAT cohort of patients with clipped intracranial aneurysm is analyzed
- IOAR was independently predicted by rupture status, location and size of the aneurysm
- IOAR affects the functional outcome of cases with ruptured aneurysm
- In cases with unruptured aneurysms it is associated with surgical outcome

## ABBREVIATIONS

**95% CI** *95% confidence interval;* **ACOA** *anterior communicating artery*; **aOR** *adjusted Odds ratio;* **CT** *computed tomography* **DSA** *digital subtraction angiography*; **IA** *intracranial aneurysm*; **ICH** *intracerebral hemorrhage*; **IOAR** *intraoperative aneurysm rupture*; **IVH** *intraventricular hemorrhage*; **MCA** *middle cerebral artery*; **mRS** *modified Rankin scale*; **OR** *odds ratio*; **SD** *standard deviation*; **RIA** *ruptured intracranial aneurysm*; **SAH** *subarachnoid hemorrhage*; **SD** *standard deviation*; **UIA** *unruptured intracranial aneurysm;* **WFNS** *World Federation of Neurosurgical Societies federation*

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