

Contemporary adverse event profile of microsurgery for intracranial unruptured aneurysms in high-volume microsurgical centers: the international PRAEMIUM study

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OBJECTIVE Objective values on procedural risk are essential to facilitate informed consent and optimize clinical decision-making in patients with unruptured intracranial aneurysms (UIAs). While robust heuristics, such as the PHASES (population, hypertension, age, size of aneurysm, earlier subarachnoid hemorrhage, and site of aneurysm) score, are established for predicting rupture risk, contemporary and granular benchmarks for procedural safety remain scarce. The multinational Prediction of Adverse Events After Microsurgery for Intracranial Unruptured Aneurysms (PRAEMIUM) study aims to comprehensively characterize contemporary adverse event rates following microsurgical treatment at high-volume expert centers, stratified by aneurysm location, morphology, and complexity factors to better inform individual risk/benefit analyses.

METHODS A cohort study among 20 participating expert centers from 9 countries was established. Patients treated microsurgically for UIAs were included. The authors describe the epidemiology of treated patients and UIAs and a comprehensive adverse event profile using 3 outcomes measured at hospital discharge: 1) poor neurological outcome (modified Rankin Scale score ≥ 3), 2) new sensorimotor neurological deficits, and 3) all-cause adverse events (Clavien-Dindo grade ≥ 1). Subgroup reports were given for aneurysm location, morphology, and complexity factors (prior aneurysm

ABBREVIATIONS ACA = anterior cerebral artery; ACom = anterior communicating artery; CDG = Clavien-Dindo grade; ICA = internal carotid artery; MCA = middle cerebral artery; mRS = modified Rankin Scale; PCom = posterior communicating artery; PHASES = population, hypertension, age, size of aneurysm, earlier subarachnoid hemorrhage, site of aneurysm; SAH = subarachnoid hemorrhage; UIA = unruptured intracranial aneurysm.

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treatment, calcifications, complex angioanatomy involving critical branch vessels or perforators, and thrombosis). The authors purposely chose discharge as the time point to capture early postoperative risks and complications in patients with asymptomatic UIAs, for whom preserving neurological function is paramount.

RESULTS The cohort included 3705 patients (mean age 56 [SD 12] years, 28% male). Overall, at discharge 13.9% of patients (95% CI 12.8%–15.0%) had poor neurological functional outcomes, 14.4% (95% CI 13.3%–15.5%) had new sensorimotor deficits, and 24.1% (95% CI 22.8%–25.5%) experienced all-cause adverse events. Poor neurological outcomes ranged from 8.5% (M1 aneurysms) to 37.4% (posterior circulation aneurysms), neurological deficits from 9.3% (distal anterior cerebral artery [ACA] aneurysms) to 34.2% (posterior circulation aneurysms), and all-cause adverse events from 21.2% (distal ACA aneurysms) to 31.3% (posterior circulation aneurysms). Dissecting and fusiform aneurysms showed notably high rates of poor neurological outcomes (22.0%–33.3%), new deficits (25.4%–26.7%), and adverse events (26.7%–37.0%). Complexity factors significantly influenced outcomes, with prior treatment (22.9%, 19.7%, and 30.1%), calcification (16.3%, 18.1%, and 30.5%), complex angioanatomy (13.1%, 15.9%, and 26.9%), and thrombosis (19.6%, 23.9%, and 39.6%) notably increasing the risks for poor neurological outcomes, deficits, and adverse events, respectively.

CONCLUSIONS This large international cohort provides contemporary benchmarks for microsurgical treatment of UIAs, emphasizing variability in outcomes based on aneurysm location, morphology, and complexity. The presented granular and quotable adverse event rates support informed patient counseling and individualized risk/benefit assessments in comparable high-volume centers.

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KEYWORDS risk profile; adverse events; unruptured intracranial aneurysm; microsurgery; neurosurgery

THE diagnosed incidence of unruptured intracranial aneurysms (UIAs) has increased markedly over the past decade, primarily due to improved accessibility and use of intracranial imaging techniques, such as CT angiography and MR angiography.¹ Consequently, several refinements in the preventive treatment of these UIAs have occurred, especially regarding endovascular techniques, which have greatly increased in use since the International Subarachnoid Aneurysm Trial, as well as improvements in microsurgical techniques, including the regular use of intraoperative neuromonitoring.^{2,3} Through the study of aneurysm epidemiology, we have identified key risk factors that have driven the development and validation of scoring systems for rupture risk, such as the PHASES (population, hypertension, age, size of aneurysm, earlier subarachnoid hemorrhage [SAH], and site of aneurysm) score.⁴ Such tools help clinicians more objectively assess the likelihood of rupture and the necessity of treatment, leading to better patient counseling through a more refined benefit analysis of preventive treatment.⁵

However, the decision to preventively treat UIAs requires not only a solid assessment of their expected natural history, and thus the potential benefit of treatment, but also a careful consideration of the risks inherent to each treatment option. As previously noted, a significant volume of research has focused on predicting the natural history of UIAs, while historically, there has been less interest and effort directed at understanding the inherent risks of treatment.^{4,6} Recent studies have focused more on treatment results in terms of long-term occlusion rates (treatment efficacy) rather than on the risks of treatment (safety).⁷ While numerous published cohort studies and case series have historically documented the adverse events following microsurgical treatment of UIAs, these reports have become less frequent over the past decade.^{8–17} This is significant because, since the 2010s, there has been a shift in the types of UIAs being treated microsurgically versus endovascularly, alongside continuous improvements in open neurosurgical techniques.^{18,19} Additionally, due to the rapid evolution of

treatment methods over the past decade, the risks associated with these treatments have undoubtedly changed.

Evidence indicates that case volume per surgeon and center is crucial, and that microsurgical treatment in the hands of experienced neurosurgeons is both a safe and highly effective technique for selected aneurysms and should not be performed by low-volume centers.^{3,13,20–22} The Prediction of Adverse Events After Microsurgery For Intracranial Unruptured Aneurysms (PRAEMIUM) study is an international effort aimed at better characterizing the adverse event profiles of microsurgical treatment among a group of expert centers that treat a high volume of UIAs annually using microsurgical techniques. This multinational effort aims to report adverse event rates both overall and stratified by aneurysm location, morphology, and markers of microsurgical complexity, with the ultimate goal of closing the knowledge gap on the contemporary risk profile of microsurgical treatment for these lesions.

Methods

Overview

Our international consortium (the PRAEMIUM study) was queried, providing a representative sample of patients who underwent microsurgical treatment for UIAs. This study adhered to the STROBE checklist,²³ and was registered with the ClinicalTrials.gov database (<http://clinicaltrials.gov>; registration no.: NCT04819074). The use of patient data for research purposes was approved by each local IRB, and patients provided informed consent or informed consent was waived, depending on the demands of the local IRB.

Inclusion and Exclusion Criteria

We included patients who underwent microsurgical procedures for UIAs from January 1, 2010, forward. These patients were included to represent the contemporary treatment paradigm in the last 10–15 years. Patients undergoing endovascular treatment were excluded, except

those patients who underwent microsurgery specifically for a previously endovascularly treated aneurysm. Patients with a history of SAH who were undergoing microsurgical treatment of an unruptured, different aneurysm were included, but only if microsurgery was performed more than 1 month after ictus. Only microvascular centers with a high caseload (at least 100 UIAs treated microsurgically since January 1, 2010) were included.

Data Collection and Endpoints

We collected data from participating centers, constituting a mix of prospective and retrospective data. A broad range of preoperative demographic, morphological, anatomical, and surgical complexity data were collected on each patient and their aneurysms. Concerning adverse events, 3 endpoints were defined to comprehensively capture surgical risk: 1) neurological outcome, with a favorable result defined as modified Rankin Scale (mRS) score 0–2;²⁴ 2) new sensorimotor neurological deficits; and 3) all-cause adverse events, defined as any event with a Clavien-Dindo grade (CDG) ≥ 1, with only the highest grade event per patient considered, including both surgery- and nonsurgery-related complications.^{25,26} These outcomes were all measured at hospital discharge (from the hospital stay in which index microsurgery was performed).

For patients with multiple aneurysms treated in a single surgical session, 1 set of discharge endpoints was recorded, based solely on the aneurysms that were treated. Morphological characteristics were attributed to the most complex treated aneurysm. If multiple aneurysms were treated across separate surgical sessions, endpoints were assessed independently at each hospital discharge.

Statistical Analysis

Continuous data are reported as means and standard deviations, and categorical data as values and percentages. All analyses were performed in R (version 4.4.2, The R Foundation for Statistical Computing).²⁷ Descriptive measures focusing on the 3 main outcomes (neurological functional outcome at discharge, new sensorimotor neurological deficits at discharge, and all-cause adverse events at discharge) were provided as unadjusted proportions, along with 95% CIs of the proportion calculated using Wald (normal-approximation) intervals. Subgroup analyses for anatomical localization, morphology, and surgical complexity factors were conducted. Stratified Cleveland dot-and-whisker plots are also provided.

Results

Patient Cohort

From a total of 20 centers, data on 3705 patients were available, with a mean age of 56 (SD 12) years that included 1049 (28%) male patients. Detailed demographics as well as patient and aneurysm data are provided in Table 1. Most aneurysms were middle cerebral artery (MCA) bifurcation or distal aneurysms (n = 1903 patients, 51%). The second most common localization was the proximal anterior cerebral artery (ACA) or anterior communicating artery (ACoM; n = 673 patients, 18%). The vast majority of aneurysms had a saccular morphology (n = 3506 pa-

TABLE 1. Baseline and follow-up characteristics over the entire PRAEMIUM cohort

Parameter	Overall
No. of patients, n (%)	3705 (100)
Mean age (SD), yrs	56.21 (11.56)
Males, n (%)	1049 (28.3)
mRS score at admission, n (%)	
0	2161 (58.3)
1	977 (26.4)
2	361 (9.7)
3	144 (3.9)
4	41 (1.1)
5	10 (0.3)
Missing	11 (0.3)
mRS score at discharge, n (%)	
0	1850 (49.9)
1	855 (23.1)
2	480 (13.0)
3	357 (9.6)
4	118 (3.2)
5	29 (0.8)
6	10 (0.3)
Missing	6 (0.2)
Arterial hypertension, n (%)	2071 (55.9)
Anticoagulation/antiplatelet therapy, n (%)	887 (23.9)
Missing	1 (0.0)
ASA Scale score, n (%)	
1	646 (17.4)
2	1531 (41.3)
3	1190 (32.1)
4	148 (4.0)
5	1 (0.0)
Missing	189 (5.1)
Prior SAH, n (%)	474 (12.8)
Mean total no. of aneurysms (SD)	1.68 (1.11)
Multiple aneurysms treated during session, n (%)	738 (19.9)
Missing	3 (0.1)
Mean max aneurysm diameter (SD), mm	7.05 (4.88)
Anatomical location, n (%)	
Paraophthalmic ICA	316 (8.5)
ICA, PCom	261 (7.0)
ICA, other	323 (8.7)
ACA, proximal & ACom	673 (18.2)
ACA, distal	151 (4.1)
MCA, M1	130 (3.5)
MCA, bifurcation & distal	1903 (51.4)
Posterior circulation	115 (3.1)
Other location	53 (1.4)
Calcification of wall or neck, n (%)	410 (11.1)
Missing	235 (6.3)

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TABLE 1. Baseline and follow-up characteristics over the entire PRAEMIUM cohort

Parameter	Overall
Aneurysm morphology, n (%)	
Saccular	3506 (94.6)
Dissecting	15 (0.4)
Fusiform	127 (3.4)
Other	54 (1.5)
Missing	3 (0.1)
Involvement of critical perforating or branch vessels, n (%)	1240 (33.5)
Missing	11 (0.3)
Intraluminal thrombosis, n (%)	331 (8.9)
Missing	181 (4.9)
Prior aneurysm treatment, n (%)	319 (8.6)
Missing	1 (0.0)
Bypass necessary, n (%)	88 (2.4)
Missing	1 (0.0)
Mean PHASES score (SD)	4.95 (3.03)
Mean ELAPSS score (SD)	15.55 (7.68)
Mean UIATS for treatment (SD)	11.67 (4.53)
Mean UIATS for conservative management (SD)	9.71 (2.79)
New sensorimotor neurological deficit, n (%)	534 (14.4)
Missing	1 (0.0)
Poor neurological outcome, n (%)*	514 (13.9)
Missing	6 (0.2)
All-cause adverse events, n (%)†	894 (24.1)
Missing	1 (0.0)

ASA = American Society of Anesthesiologists; ELAPSS = earlier SAH, location of aneurysm, age, population, size of aneurysm, shape of aneurysm; UIATS = Unruptured Intracranial Aneurysm Treatment Score.

* mRS score ≥ 3 .

† CDG ≥ 1 .

tients, 95%). More than 1 aneurysm was treated in a single session in 738 patients (20%), and prior treatment was recorded for 319 aneurysms (8.6%).

Poor Neurological Outcome at Discharge

Figure 1 provides a stratified overview of poor neurological outcome (mRS score ≥ 3) rates in different subpopulations. Overall, 5.3% (95% CI 4.6%–6.0%, n = 195) of patients at admission and 13.9% (95% CI 12.8%–15.0%, n = 514) at discharge had an mRS score ≥ 3 . Figures 2 (anatomical location) and 3 (morphology and complexity) provide Grotta bar charts showing the change in mRS scores from admission to discharge for each subcategory.

In terms of anatomical localization, the lowest rates were seen for M1 aneurysms (8.5%, 95% CI 3.7%–13.3%), distal ACA aneurysms (11.3%, 95% CI 6.2%–16.3%), and MCA bifurcation or distal aneurysms (11.4%, 95% CI 9.9%–12.8%). The highest rates of poor neurological outcome were noted for posterior circulation aneurysms (37.4%, 95% CI 28.5%–46.2%) and posterior communi-

cating artery (PCom) aneurysms (18.5%, 95% CI 13.8%–23.2%).

Regarding aneurysm morphology, dissecting (33.3%, 95% CI 9.5%–57.2%) and fusiform (22%, 95% CI 14.8%–29.3%) morphologies carried a higher rate of poor neurological outcome.

While aneurysms with complex angioanatomy (i.e., involvement of perforators or critical branch vessels) did not exhibit higher rates of poor outcome (13.1%, 95% CI 11.2%–15.0%), all other markers of complexity did. This was true for previously treated aneurysms (22.9%, 95% CI 18.3%–27.5%), calcified aneurysms (16.3%, 95% CI 12.8%–19.9%), and thrombosed aneurysms (19.6%, 95% CI 15.4–23.9%).

New Sensorimotor Neurological Deficits at Discharge

Figure 4 provides a stratified overview of new neurological deficit rates at discharge, in different subpopulations. Overall, we observed a 14.4% (95% CI 13.3%–15.5%, n = 534 patients) rate of sensorimotor neurological deficits at discharge.

Again, MCA aneurysms—both M1 (13.8%, 95% CI 7.9%–19.8%) and bifurcation/distal aneurysms (12.0%, 95% CI 10.6%–13.5%)—as well as distal ACA aneurysms (9.3%, 95% CI 4.6%–13.9%) exhibited the lowest rates of new sensorimotor deficits at discharge. Posterior circulation aneurysms (34.2%, 95% CI 25.5%–42.9%) as well as PCom aneurysms (19.2%, 95% CI 14.4%–23.9%) had somewhat increased rates. Dissecting (26.7%, 95% CI 4.3%–49.0%) and fusiform (25.4%, 95% CI 17.8%–33.0%) aneurysms again had markedly increased rates of new deficits at discharge.

All markers of complexity led to somewhat increased neurological deficits: prior treatment (19.7%, 95% CI 15.4%–24.1%), calcification (18.1%, 95% CI 14.4%–21.8%), complex angioanatomy (15.9%, 95% CI 13.9%–17.9%), as well as thrombosis (23.9%, 95% CI 19.3%–28.5%).

All-Cause Adverse Events up to Discharge

Figure 5 reports stratified results for all-cause adverse events (CDG ≥ 1). A total of 894 patients (24.1%, 95% CI 22.8%–25.5%) experienced adverse events up to discharge. Regarding localization, there was a decreased variance in adverse event rates compared to neurological function and deficits; however, slightly increased rates of all-cause adverse events were observed for posterior circulation (31.3%, 95% CI 22.8%–39.8%) and proximal ACA/ACom aneurysms (27.8%, 95% CI 24.4%–31.2%).

Regarding morphology, both saccular (23.6%, 95% CI 22.2%–25.0%) and dissecting aneurysms (26.7%, 95% CI 4.3%–49.0%) exhibited rates close to the average rate, but fusiform aneurysms (37.0%, 95% CI 28.6%–45.4%) were associated with an importantly higher number of adverse events. In terms of complexity, thrombosed aneurysms carried a relevantly higher rate of all-cause adverse events (39.6%, 95% CI 34.3%–44.8%).

Discussion

In our international multicenter consortium among expert open microsurgical centers, we provide evidence-

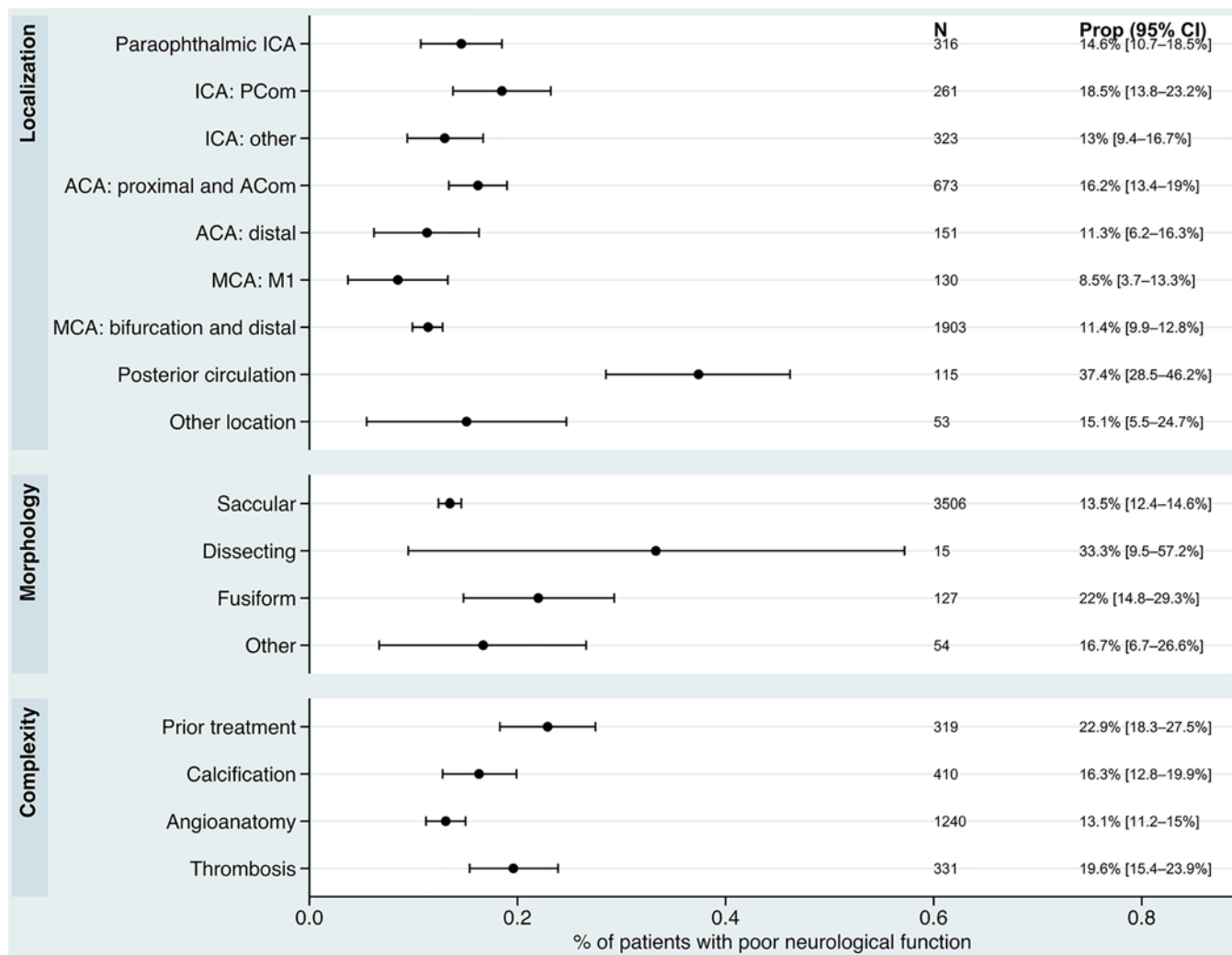


FIG. 1. Cleveland dot-and-whisker plot showing the proportion of patients with poor neurological functional outcome (mRS score \geq 3) at discharge. Stratifications for important subgroups are provided. On the *right*, the proportions are given with Wald 95% CIs.

based risk profiles for various strata of UIAs, emphasizing the significance of aneurysm location, morphology, and complexity in clinical outcomes. Anatomical localization emerged as an important factor influencing neurological outcomes and postoperative deficits, underscoring its relevance in surgical decision-making. Regarding aneurysm morphology, dissecting, fusiform, and saccular aneurysms exhibited distinct risk profiles, with dissecting and fusiform types consistently linked to poorer neurological outcomes and higher rates of new deficits. Additionally, complexity markers—including previously treated aneurysms, calcifications, thrombosis, and complex angioanatomy—were associated with increased risks of adverse outcomes. These findings highlight the critical role of aneurysm-specific characteristics in risk stratification, facilitating informed surgical decision-making in the microsurgical management of UIAs.

Establishing benchmarks for informed and objective risk stratification is important for any surgical procedure, irrespective of the procedure’s magnitude.³ Traditionally,

case series by experts in the field or data from large prospective studies are relied upon, and their values are quoted during consultations when informing patients about expected benefits and risks. However, these values often lack granularity and do not account for the significant variability in patient and disease characteristics, neither in surgeon nor center experience. Consequently, recent decades have seen an evolution toward more individualized risk assessment, either by stratifying patients into relevant subgroups based on specific characteristics, or through model-based approaches such as machine learning techniques, to provide more precise and individualized risk predictions.^{18,28}

While machine learning-based outcome prediction can be a powerful tool, its philosophy differs distinctly from quoting evidence-based values derived from large cohorts. Clinical prediction models suitable for daily clinical practice are rigorously validated to ensure they meet standards in terms of calibration and discrimination for which they were trained, even when applied to new popu-

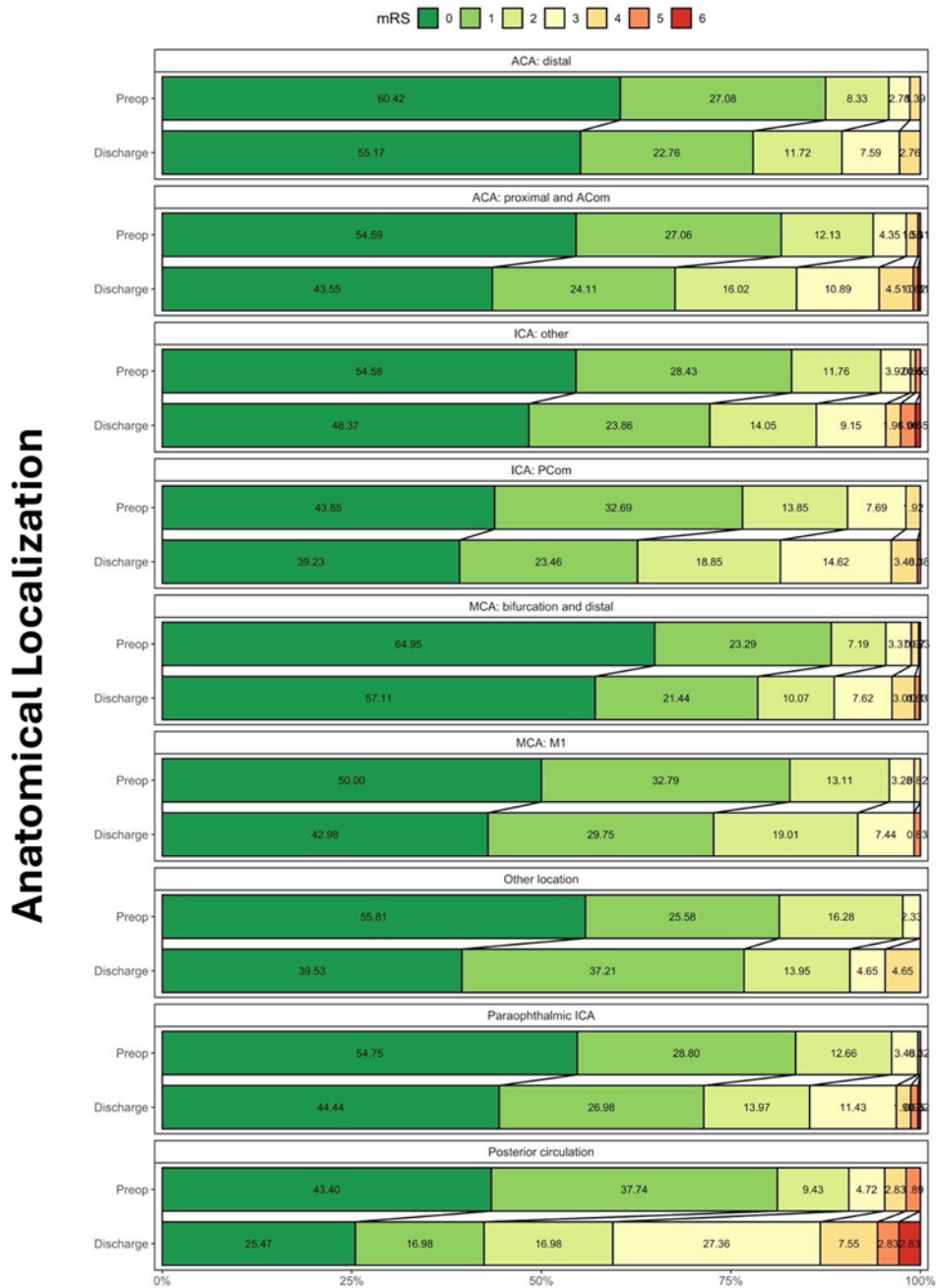


FIG. 2. Gotta bar charts show the evolution of mRS subscores from admission (preop) to discharge for the different anatomical locations of the UIAs. Values within the bars are shown as percentages. Stratified numbers are given for each subcategory of anatomical localization.

lations.²⁹ Developing such clinical prediction models for adverse events is a core objective of the PRAEMIUM consortium. Nevertheless, using clinical prediction models in practice involves a challenge that is only partially resolved: implementation requires neurosurgeons to enter numerous scores and measurements into a web application to calculate individualized risks. The practical burden of this implementation should not be underestimated.^{30,31}

Moreover, the philosophies of prediction (model-based approaches) and inference (descriptive heuristics from co-

horts) are fundamentally different: the former philosophy introduces an additional layer of bias—the model itself—with the “thickness” of this layer increasing alongside model complexity, aiming to achieve individually targeted predictions.^{32,33} In contrast, the latter philosophy involves a simpler, more direct inferential averaging of risks across defined patient subgroups. While both approaches are evidence-based due to validation, citing a published risk directly is often more tangible for patients and clinicians alike. Therefore, we highly value heuristic approaches, as

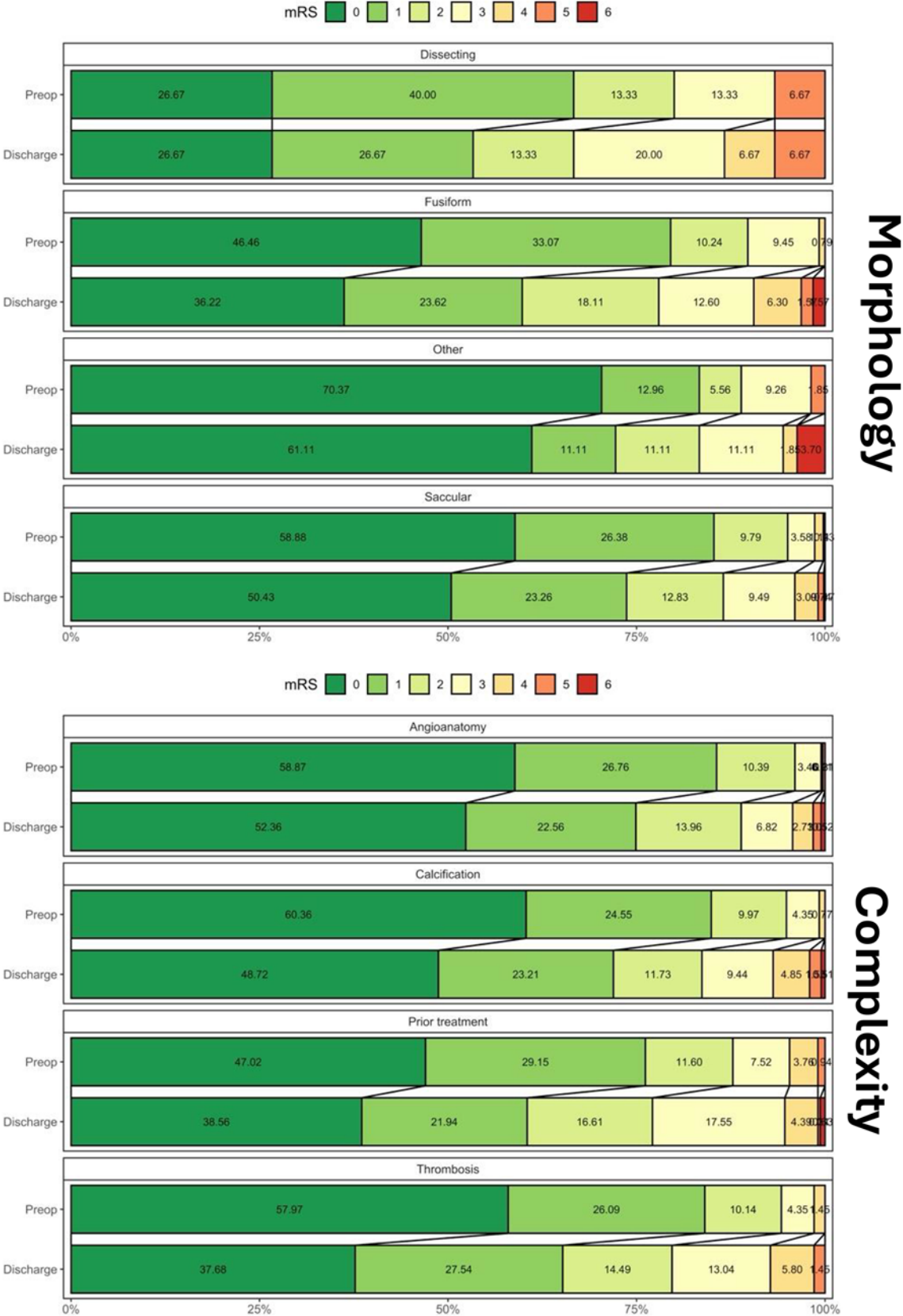


FIG. 3. Gotta bar charts show the evolution of mRS subscores from admission (preop) to discharge for the different subgroups of morphology (**upper**) and complexity (**lower**). Values within the bars are shown as percentages. Stratified numbers are given for each subcategory of morphology and complexity markers.

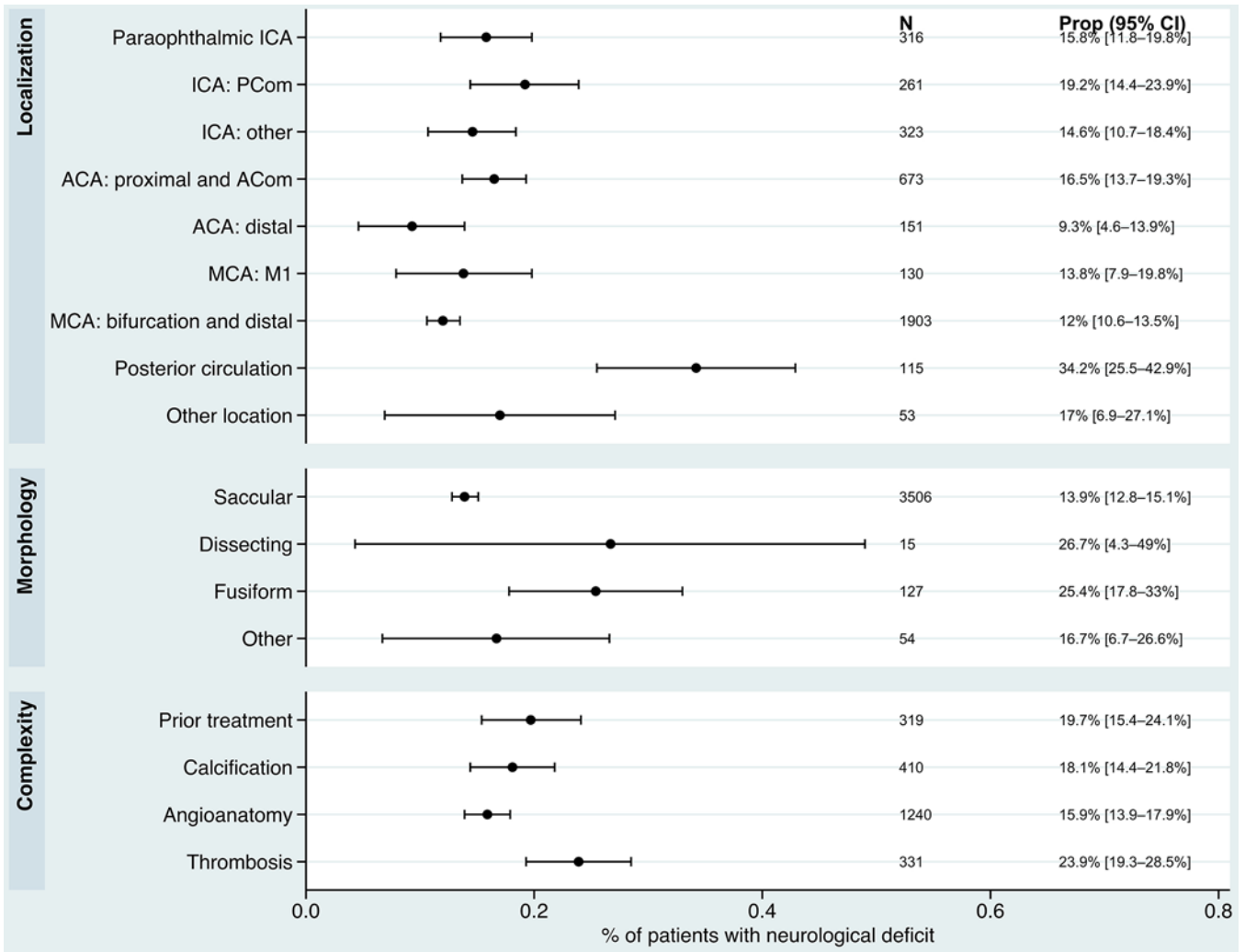


FIG. 4. Cleveland dot-and-whisker plot showing the proportion of patients with any new sensorimotor neurological deficit at discharge. Stratifications for important subgroups are provided. On the *right*, the proportions are given with Wald 95% CIs.

presented in this analysis, offering direct, clearly “quotable” figures for the critical subgroups of aneurysm localization, morphology, and complexity markers relevant to microsurgical treatment.

In this study, we present such heuristics focused on adverse events with a considerable granularity, enabling neurosurgeons to rely on evidence-based but still relatively tailored risk profiles for their patients, all without relying on model-based approaches with the abovementioned added layers of biases. Access to such information is crucial when discussing the decision of whether to preventively treat UIAs. Tools such as the PHASES score are robust in stratifying risk of rupture, but it is difficult to obtain figures of operative risk in specific subgroups. Because both sides of the risk/benefit equation are equally relevant, and considering that the spectrum and frequency of microsurgically treated UIAs has evolved significantly throughout the past two decades, our objective was to report results in a stratified and direct way from an international and diverse consortium of high-volume microvascular centers of excellence. For example, we decidedly did not report model-adjusted rates

(i.e., adverse events rates for different anatomical localizations that are normalized for complexity and morphology) but instead report directly citable, unadjusted (crude) group averages. We also decided to stratify risks according to the 3 factors (anatomy, morphology, and complexity) deemed most relevant in discussion within multidisciplinary team meetings or patient conversations regarding risk.

Notably, our reported rates are measured at discharge. This timing ensured data completeness, as measuring adverse events at discharge is the most accurate method in multicenter studies, although this time point incurs much higher rates of adverse events than at follow-up, because most deficits recover.^{3,34,35} Yet, any new deficit in patients with UIAs is especially serious, as these patients are prophylactically treated, in a usually perfect functional state, to prevent future risk for SAH and catastrophic neurological decline or death. The rates for our 3 outcomes compare with those reported in the literature, although it is hard to find comparable subgroups, especially for more rare subsets of aneurysms or when investigating microsurgical complexity factors.^{19,34–40} Additionally, the definition of

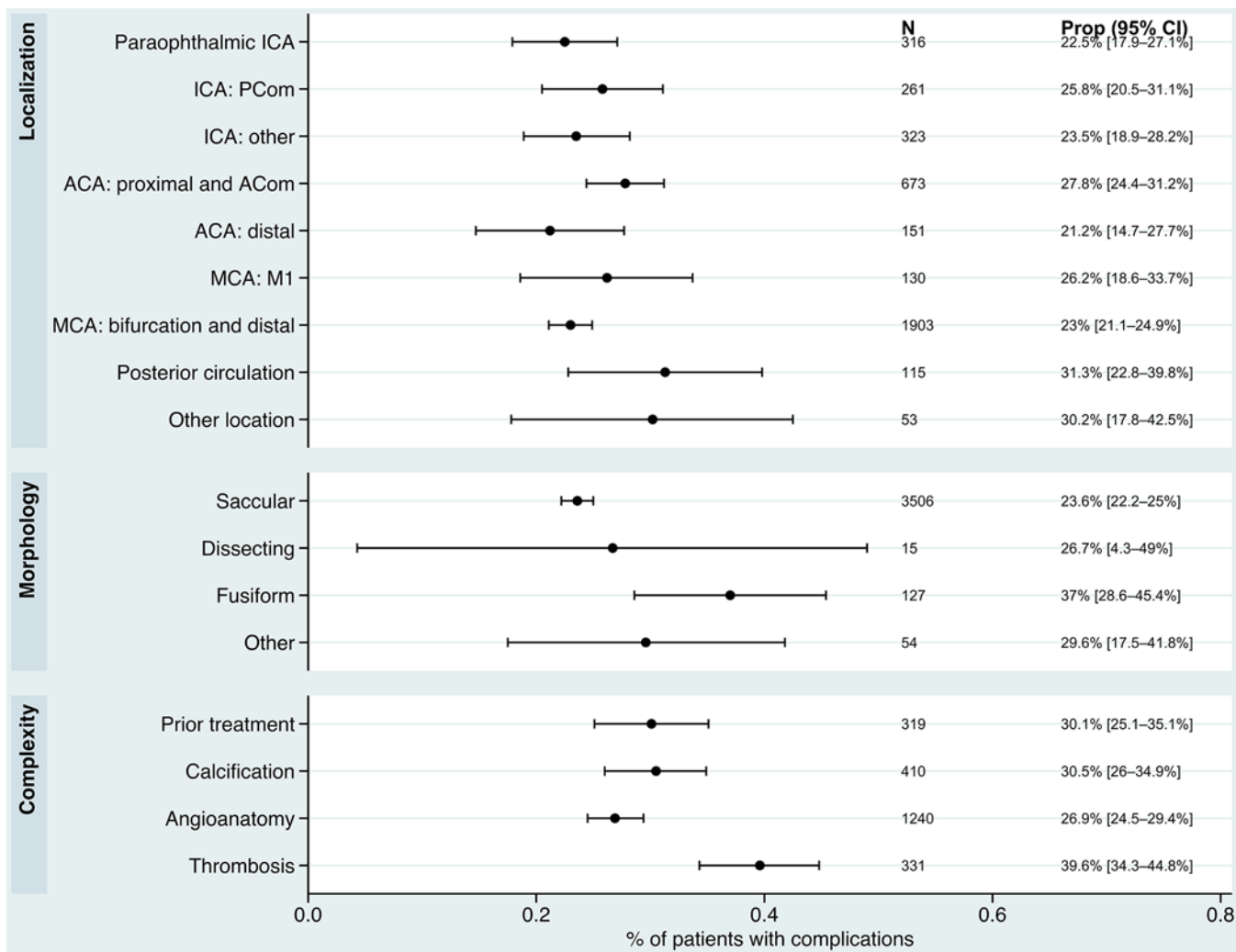


FIG. 5. Cleveland dot-and-whisker plot showing the proportion of patients with any (all-cause) adverse event, according to Clavien-Dindo grading of surgical complications. Any patient with a CDG ≥ 1 (i.e., any deviation from the normal postoperative course) was considered as having experienced an adverse event. Stratifications for important subgroups are provided. On the right, the proportions are given with Wald 95% CIs.

what specifically constitutes an adverse event has an obvious massive influence on its detection rate. In our study, we applied the validated Clavien-Dindo grading, which considers “any deviation from the normal postoperative course” as an adverse event of CDG grade ≥ 1 , including electrolyte disturbances, delirium, or nonsurgery-related infections such as urinary tract infections.^{25,26}

Finally, the cohort itself represents the largest cohort of microsurgical UIA data with granular adverse event data and includes 20 different centers, ensuring generalizability among similar centers. The inclusion of reference centers for complex vascular surgery involves other relevant consequences to be considered. First, there is a certain international and institutional variation in practice (from decision-making to surgical approach and postoperative regimens), which is well-represented in our multi-center cohort. The represented heterogeneity is important for generalizability. Second, the inclusion of referral centers also means an overrepresentation of complex cases.

And third, the cohort represents the patient selection and current practice within the 2nd decade of the 21st century with a strong endovascular presence.

The consequences of including reference centers for complex vascular surgery are reflected within the data: MCA bifurcation aneurysms did not have a significantly lower rate of adverse events as might be expected, likely because the spectrum of MCA bifurcation aneurysms treated microsurgically in the participating centers included a high proportion of more complex aneurysms. Conversely, paraophthalmic internal carotid artery (ICA) aneurysms did not exhibit a much higher rate of adverse events, probably because of careful patient selection in microsurgically eligible versus endovascularly treated patients.

Limitations of the Study

Our analysis has several limitations. First, the dataset comprises a combination of prospectively and retrospectively gathered information, potentially introducing bias

related to the data collection methods. Additionally, the included patients originate exclusively from experienced microsurgical centers in Europe, North America, and Australia, all of which maintain a high and consistent annual caseload of UIA clip procedures. This selection inherently restricts the generalizability of our findings to settings with similar expertise and surgical volume. We intentionally reported unadjusted averages instead of using model-adjusted rates, which would normalize outcomes for complexity or aneurysm morphology. While this approach allows for straightforward, quotable values, it may not fully account for the nuanced variability inherent in individual aneurysm characteristics and clinical scenarios. Manual data entry and expert-dependent classification introduce additional variability. Subjective assessments, such as differentiating calcified from noncalcified aneurysms, and manual measurements like aneurysm dimensions, are subject to interrater discrepancies. This limitation also applies to morphological classifications (i.e., fusiform aneurysms), which can be rater-dependent. Although our definitions for both aneurysm characteristics and clinical endpoints were standardized, the absence of standardized intraoperative procedures across centers—such as electrophysiological monitoring or fluorescence video angiography—could further impact data consistency and interpretation. Our cohort predominantly consisted of patients with more frequently encountered aneurysm types, particularly those located at the MCA or ACom. Complex aneurysms involving the posterior circulation and procedures requiring trapping with bypass surgery were underrepresented, limiting the applicability of our results to these specific patient subgroups. Finally, the clinical endpoints reported reflect patient status at discharge. While neurological deficits and clinical outcomes may improve considerably in the long term, we deliberately selected discharge status to capture immediate postoperative risks and complications relevant for patients with asymptomatic UIAs, with the same goal of maintaining neurological function in these patients.

Conclusions

In this large international multicenter cohort, we provide contemporary benchmarks for microsurgical treatment of UIAs, detailing outcomes with granular data on all-cause adverse events, neurological deficits, and functional outcomes at discharge. Our findings underscore that microsurgical treatment remains highly effective and generally safe in experienced, high-volume centers, but also highlight significant variability in surgical risks depending on aneurysm location, morphology, and complexity. The detailed subgroup analyses presented here offer neurosurgeons evidence-based, quotable values that are directly applicable for patient counseling and multidisciplinary decision-making. These insights are particularly valuable for refining individual risk assessments and supporting informed clinical decisions regarding preventive microsurgical treatment of UIAs in asymptomatic patients.

Appendix

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References

1. Etminan N, de Sousa DA, Tiseo C, et al. European Stroke

- Organisation (ESO) guidelines on management of unruptured intracranial aneurysms. *Eur Stroke J*. 2022;7(3):V. doi:10.1177/23969873221099736
2. Molyneux AJ, Kerr RSC, Yu LM, et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *Lancet*. 2005;366(9488):809-817. doi:10.1016/S0140-6736(05)67214-5
 3. Drexler R, Sauvigny T, Pantel TF, et al. Global outcomes for microsurgical clipping of unruptured intracranial aneurysms: a benchmark analysis of 2245 cases. *Neurosurgery*. 2024;94(2):369-378. doi:10.1227/neu.0000000000002689
 4. Greving JP, Wermer MJH, Brown RD, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. *Lancet Neurol*. 2014;13(1):59-66. doi:10.1016/S1474-4422(13)70263-1
 5. Sacks GD, Dawes AJ, Ettner SL, et al. Surgeon perception of risk and benefit in the decision to operate. *Ann Surg*. 2016;264(6):896-903. doi:10.1097/SLA.0000000000001784
 6. Backes D, Rinkel GJE, Greving JP, et al. ELAPSS score for prediction of risk of growth of unruptured intracranial aneurysms. *Neurology*. 2017;88(17):1600-1606. doi:10.1212/WNL.0000000000003865
 7. Darsaut TE, Findlay JM, Bojanowski MW, et al. A pragmatic randomized trial comparing surgical clipping and endovascular treatment of unruptured intracranial aneurysms. *AJNR Am J Neuroradiol*. 2023;44(6):634-640. doi:10.3174/ajnr.A7865
 8. Hauck EF, Wohlfeld B, Welch BG, White JA, Samson D. Clipping of very large or giant unruptured intracranial aneurysms in the anterior circulation: an outcome study. *J Neurosurg*. 2008;109(6):1012-1018. doi:10.3171/JNS.2008.109.12.1012
 9. Kotowski M, Naggara O, Darsaut TE, et al. Safety and occlusion rates of surgical treatment of unruptured intracranial aneurysms: a systematic review and meta-analysis of the literature from 1990 to 2011. *J Neurol Neurosurg Psychiatry*. 2013;84(1):42-48. doi:10.1136/jnnp-2011-302068
 10. Lai LT, Gragnaniello C, Morgan MK. Outcomes for a case series of unruptured anterior communicating artery aneurysm surgery. *J Clin Neurosci*. 2013;20(12):1688-1692. doi:10.1016/j.jocn.2013.02.015
 11. Yasunaga H, Matsuyama Y, Ohe K. Risk-adjusted analyses of the effects of hospital and surgeon volumes on postoperative complications and the modified Rankin scale after clipping of unruptured intracranial aneurysms in Japan. *Neurol Med Chir (Tokyo)*. 2008;48(12):531-538. doi:10.2176/nmc.48.531
 12. Krisht AF, Gomez J, Partington S. Outcome of surgical clipping of unruptured aneurysms as it compares with a 10-year nonclipping survival period. *Neurosurgery*. 2006;58(2):207-216. doi:10.1227/01.NEU.0000194638.61073.FC
 13. Barker FG, Amin-Hanjani S, Butler WE, Ogilvy CS, Carter BS. In-hospital mortality and morbidity after surgical treatment of unruptured intracranial aneurysms in the United States, 1996-2000: the effect of hospital and surgeon volume. *Neurosurgery*. 2003;52(5):995-1009.
 14. Solomon RA, Fink ME, Pile-Spellman J. Surgical management of unruptured intracranial aneurysms. *J Neurosurg*. 1994;80(3):440-446. doi:10.3171/jns.1994.80.3.0440
 15. Wiebers DO. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet*. 2003;362(9378):103-110.
 16. Krayenbühl HA, Yaşargil MG, Flamm ES, Tew JM. Microsurgical treatment of intracranial saccular aneurysms. *J Neurosurg*. 1972;37(6):678-686. doi:10.3171/jns.1972.37.6.0678
 17. Steinberg GK, Drake CG, Peerless SJ. Deliberate basilar or vertebral artery occlusion in the treatment of intracranial aneurysms. Immediate results and long-term outcome in 201 patients. *J Neurosurg*. 1993;79(2):161-173. doi:10.3171/jns.1993.79.2.0161
 18. Algra AM, Greving JP, de Winkel J, et al. Development of the SAFETEA scores for predicting risks of complications of preventive endovascular or microneurosurgical intracranial aneurysm occlusion. *Neurology*. 2022;99(16):e1725-e1737. doi:10.1212/WNL.000000000000200978
 19. Algra AM, Lindgren A, Vergouwen MDI, et al. Procedural clinical complications, case-fatality risks, and risk factors in endovascular and neurosurgical treatment of unruptured intracranial aneurysms: a systematic review and meta-analysis. *JAMA Neurol*. 2019;76(3):282-293. doi:10.1001/jamaneurol.2018.4165
 20. Berman MF, Solomon RA, Mayer SA, Johnston SC, Yung PP. Impact of hospital-related factors on outcome after treatment of cerebral aneurysms. *Stroke*. 2003;34(9):2200-2207. doi:10.1161/01.STR.0000086528.32334.06
 21. Jabbarli R, Wrede KH, Pierscianek D, et al. Outcome after clipping of unruptured intracranial aneurysms depends on caseload. *World Neurosurg*. 2016;89:666-671.e1. doi:10.1016/j.wneu.2015.12.043
 22. Bekelis K, Gottlieb D, Bovis G, et al. Unruptured cerebral aneurysm clipping: association of combined open and endovascular expertise with outcomes. *J Neurointerv Surg*. 2016;8(9):977-981. doi:10.1136/neurintsurg-2015-011986
 23. Elm E V, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*. 2007;335(7624):806-808.
 24. Broderick JP, Adeoye O, Elm J. Evolution of the modified Rankin Scale and its use in future stroke trials. *Stroke*. 2017;48(7):2007-2012. doi:10.1161/STROKEAHA.117.017866
 25. Sebök M, Blum P, Sarnthein J, et al. Validation of the Clavien-Dindo grading system of complications for microsurgical treatment of unruptured intracranial aneurysms. *Neurosurg Focus*. 2021;51(5):E10. doi:10.3171/2021.8.FOCUS20892
 26. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg*. 2009;250(2):187-196. doi:10.1097/SLA.0b013e3181b13ca2
 27. R Core Team R: A Language and Environment for Statistical Computing. Accessed October 21, 2025. <https://www.R-project.org/>
 28. Staatjes VE, Sebök M, Blum PG, et al. Development of machine learning-based preoperative predictive analytics for unruptured intracranial aneurysm surgery: a pilot study. *Acta Neurochir (Wien)*. 2020;162(11):2759-2765. doi:10.1007/s00701-020-04355-0
 29. Kernbach JM, Staatjes VE. Foundations of machine learning-based clinical prediction modeling: part ii-generalization and overfitting. *Acta Neurochir Suppl*. 2022;134:15-21. doi:10.1007/978-3-030-85292-4_3
 30. Staatjes VE. Evolving applications of machine intelligence in neurosurgery. Dissertation. University of Zurich; 2022. doi:10.5167/uzh-229109
 31. Staatjes VE, Stienen MN. Data mining in spine surgery: leveraging electronic health records for machine learning and clinical research. *Neurospine*. 2019;16(4):654-656. doi:10.14245/ns.1938434.217
 32. Marewski JN, Gigerenzer G. Heuristic decision making in medicine. *Dialogues Clin Neurosci*. 2012;14(1):77-89. doi:10.31887/DCNS.2012.14.1/jmarewski
 33. Whelehan DF, Conlon KC, Ridgway PF. Medicine and heuristics: cognitive biases and medical decision-making. *Ir J Med Sci*. 2020;189(4):1477-1484. doi:10.1007/s11845-020-02235-1

34. Sauvigny J, Drexler R, Pantel TF, et al. Microsurgical clipping of unruptured anterior circulation aneurysms—a global multicenter investigation of perioperative outcomes. *Neurosurgery*. 2024;94(6):1218-1226. doi:10.1227/NEU.0000000000002829
35. Stroh-Holly N, Rauch P, Stefanits H, et al. Microsurgical clipping of unruptured middle cerebral artery bifurcation aneurysms: a single-center experience. *Brain Sci*. 2024;14(11):1068. doi:10.3390/brainsci14111068
36. Chung J, Hong CK, Shim YS, et al. Microsurgical clipping of unruptured middle cerebral artery bifurcation aneurysms: incidence of and risk factors for procedure-related complications. *World Neurosurg*. 2015;83(5):666-672. doi:10.1016/j.wneu.2015.01.023
37. Yang K, Begley SL, Lynch D, et al. Long-term outcomes of surgical clipping of saccular middle cerebral artery aneurysms: a consecutive series of 92 patients. *Neurosurg Rev*. 2023;46(1):271. doi:10.1007/s10143-023-02167-1
38. Dashti R, Hernesniemi J, Niemelä M, et al. Microsurgical management of middle cerebral artery bifurcation aneurysms. *Surg Neurol*. 2007;67(5):441-456. doi:10.1016/j.surneu.2006.11.056
39. Jang CK, Park KY, Lee JW, et al. Microsurgical treatment of unruptured anterior choroidal artery aneurysms: incidence of and risk factors for procedure-related complications. *World Neurosurg*. 2018;119:e679-e685. doi:10.1016/j.wneu.2018.07.241
40. Byoun HS, Bang JS, Oh CW, et al. The incidence of and risk factors for ischemic complications after microsurgical clipping of unruptured middle cerebral artery aneurysms and the efficacy of intraoperative monitoring of somatosensory evoked potentials: a retrospective study. *Clin Neurol Neurosurg*. 2016;151:128-135. doi:10.1016/j.clineuro.2016.10.008

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