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TREATMENT OF UNRUPTURED INTRACRANIAL ANEURYSMS

A surgical long-term evaluation for preoperative predictive analytics.

Doctoral Thesis
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in the Doctoral Program

Medical Sciences

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1. Disclosure / Declaration

Statement of originality:

I hereby declare that I have authored this thesis independently. I certify that the intellectual content of this thesis is the product of my own work, with no falsified or fabricated information, and all sources have been appropriately acknowledged.

This thesis has not been previously submitted for any degree or other academic purposes.

The author, Nico Stroh-Holly, declares no conflict of interest concerning this study. Permission was granted by the respective publishers for publication of the inherited journal articles.

2. Table of contents

3. Abbreviations

3DRA	3D-rotational angiography
ACA	Anterior cerebral artery
AChA	Anterior choroidal artery
AComA /ACOM	Anterior communicating artery
ADPKD	Autosomal dominant polycystic kidney disease
AI	Artificial intelligence
AP	Average precision
ASA	American Society of Anesthesiologists
aSAH	Aneurysmal subarachnoid hemorrhage
AUC	Area under the curve
BMI	Body mass index
CAD	Computer-aided diagnosis
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CSF	Cerebrospinal fluid
CT	Computed tomography
Diff.	Difference
DM	Diabetes mellitus
DSA	Digital subtraction angiography
ET	Extremely randomized trees
FD	Flow-diversion
GAM	Generalized additive model
GDC	Guglielmi detachable coils
GOS	Glasgow Outcome Scale
IA	Intracranial Aneurysm
ICA	Internal carotid artery
ICH	Intracerebral hemorrhage
ICU	Intensive care unit
KNN	k-nearest neighbor classifiers

LDA	Linear discriminant analysis
LR	Logistic regression
MCA	Middle cerebral artery
ML	Machine learning
MLP	Multilayer perceptron
Mm	Millimetre
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NND	New neurological deficit
No.	Number
NPV	Negative predictive value
OR	Odds ratio
PComA /PCOM	Posterior communicating artery
pNND	Permanent new neurological deficit
PPV	Positive predictive value
QDA	Quadratic discriminant analysis
RF	Random forest
ROC-AUC	Area under receiver operating characteristic curve
SAH	Subarachnoid Hemorrhage
SHAP	Shapely additive explanations
SSI	Surgical site infection
std.dev.	Standard deviation
SVM	Support vector machines
tNND	Transient new neurological deficit
UIA	Unruptured intracranial aneurysms
UIATS	Unruptured intracranial aneurysm treatment score
US	United States of America
XGB	Extreme gradient boosting estimators

4. List of figures

5. List of tables

6. Abstract in English

Background:

Intracranial aneurysms (IAs) are pathological dilatations of cerebral arteries that pose a significant risk due to potential rupture, leading to subarachnoid hemorrhage (SAH). The management of unruptured intracranial aneurysms (UIAs) requires a careful balance between the natural history and procedural risks.

This cumulative dissertation explores critical aspects of UIA treatment, including predictive modeling using machine learning (ML), the development of international benchmarking standards for quality assessment, and the analysis of surgical outcomes in a global, multicenter setting.

Methods:

Three scientific studies were conducted using retrospective multicenter data on microsurgical UIA treatment. These studies (1) developed and externally validated ML models to predict functional and neurological outcomes after aneurysm clipping, (2) established benchmark values for perioperative and long-term results, and (3) analyzed clinical risk factors for postoperative complications and outcomes.

Results:

ML models demonstrated high internal accuracy in predicting postoperative neurological deficits (ROC-AUC up to 0.87) but had limited generalizability in external cohorts. Benchmark analysis defined optimal outcome thresholds for mortality (≤0.6%), intraoperative rupture (≤3.8%), and unfavorable neurological outcome (mRS ≥3, ≤2.03%). The multicenter analysis confirmed high complete occlusion rates (up to 99%) following microsurgical clipping, particularly for anterior circulation aneurysms.

Conclusion:

The findings of this dissertation provide insights into optimizing UIA management through data-driven decision-making. ML-based outcome prediction shows promise but requires further validation and adaptation. Benchmarking enables objective quality assessment,

while the multicenter analysis supports the continued role of microsurgical treatment. The integration of these methodologies can contribute to improved patient safety and treatment quality in the long term.

7. Abstract in German

Hintergrund:

Intrakranielle Aneurysmen (IA) sind pathologische Gefäßaussackungen, die potenziell rupturieren können und somit ein erhebliches Risiko für eine Subarachnoidalblutung (SAB) darstellen. Die Entscheidung über die optimale Therapie von unrupturierten intrakraniellen Aneurysmen (UIAs) erfordert eine präzise Risikoabwägung zwischen dem natürlichen Verlauf und dem Eingriffsrisiko.

Diese kumulative Dissertation untersucht verschiedene Aspekte der Behandlung von UIAs, einschließlich der Vorhersage von klinischen Ergebnissen mittels maschinellen Lernens (ML), der Entwicklung internationaler Benchmarking-Standards zur Qualitätssicherung sowie der Analyse von chirurgischen Ergebnissen in einem globalen multizentrischen Kontext.

Methodik:

In drei wissenschaftlichen Publikationen wurden retrospektive multizentrische Daten zur operativen Behandlung von UIAs analysiert. Dabei wurden (Studie 1) ML-Modelle zur Vorhersage funktioneller und neurologischer Ergebnisse nach mikrochirurgischer Clipping-Operation entwickelt und extern validiert, (Studie 2) Benchmark-Werte für perioperative und Langzeitergebnisse etabliert und (Studie 3) klinische Risikofaktoren für postoperative Komplikationen und Outcome untersucht.

Resultate:

Die ML-Modelle zeigten eine hohe interne Vorhersagegenauigkeit für postoperative neue neurologische Defizite (ROC-AUC bis 0,87), jedoch eine eingeschränkte Generalisierbarkeit in externen Kohorten. Die Benchmark-Analyse ergab optimale Outcome-Grenzwerte für Mortalität (≤0,6%), intraoperative Ruptur (≤3,8%) und ungünstige neurologische Ergebnisse (mRS ≥3, ≤2,03%). Zudem bestätigte die multizentrische Analyse eine hohe vollständige Verschlussrate (bis zu 99%) nach mikrochirurgischem Clipping, insbesondere für Aneurysmen der vorderen Zirkulation.

Conclusio:

Die Ergebnisse dieser Dissertation bieten neue Erkenntnisse zur Optimierung der Behandlung von UIAs durch datenbasierte Entscheidungsfindung. ML-gestützte Outcome-Vorhersagen haben Potenzial, müssen jedoch weiter validiert und angepasst werden. Benchmarking ermöglicht eine objektive Qualitätsbewertung, während die multizentrische Analyse die Rolle der mikrochirurgischen Therapie bestätigt.

8. Introduction

8.1. Intracranial Aneurysms

Intracranial aneurysms (IA) are pathological dilatations of the cerebral arteries supplying the brain, and most of the cases arise because of a vessel wall defect acquired during life. The medical condition is the potential rupture risk of IAs, and the clinical challenge is the estimation of the rupture risk, which is hardly predictable but has fatal consequences, causing subarachnoid hemorrhage (SAH).

Around 3% of the population is estimated to have an IA.[1] The development of IAs remains not entirely understood. While various risk factors have been identified and validated, a multifactorial pathomechanism likely underlies their formation, involving multiple risk factors that may interact and even amplify their effects.[1,2]

This introduction should provide an overview of the epidemiology, pathophysiology, risk factors, clinical presentation depending on rupture state, and treatment strategies for IAs.

8.1.1. Epidemiology

The prevalence of IAs depends on several demographic factors, like age, sex, or geography. Women are more commonly affected than men, particularly after menopause, with hormonal changes potentially playing a significant role in aneurysm formation and rupture risk.[3]

The factor of age is another critical one, with the majority of aneurysms being diagnosed between the ages of 40 and 60.[4]

Geographically, higher prevalence rates have been observed in particular populations, including those in Japan and Finland, suggesting potential genetic or environmental

influences.[5] Recent studies have shown that the higher incidence in Finland is probably associated with higher smoking rates. Therefore, a decrease in smoking rates goes along with a decreasing incidence of SAH. Nowadays, the incidence of SAH in Finland is similar to other Nordic countries.[6]

However, Japanese and Finns are considered to have a higher risk of rupture and, therefore, a higher recommendation for treatment is needed according to current risk scores.[7,8]

8.1.2. Pathophysiology

The development of IAs is a multifactorial pathogenesis involving structural, hemodynamic, genetic, and environmental factors. The arterial wall comprises three layers: the intima, media, and adventitia. In IAs, the media layer often exhibits a loss of smooth muscle cells and elastin fibers, leading to a thinning of the vessel wall.[9]

Hemodynamic factors also play a significant role in the development of IAs. In particular, arterial bifurcations, where blood flow is turbulent, are critical locations in aneurysm initiation and progression.[10] Shear stress can damage endothelial cells, triggering an inflammatory cascade that weakens the vessel wall.[10]

Genetic predisposition also plays a role, with mutations in genes involved in vascular integrity and inflammatory pathways implicated in aneurysm susceptibility.[11] Patients with connective tissue diseases such as autosomal dominant polycystic kidney disease, Marfan syndrome, neurofibromatosis type I, Ehlers-Danlos syndrome, or Loeys-Dietz syndrome have a higher risk for developing intracranial aneurysms.[12,13]

8.1.3. Risk factors

Risk factors for IAs can be divided into modifiable and non-modifiable risk factors. Non-modifiable risk factors include age, sex, geography, genetic predisposition, or family history.

Modifiable risk factors for developing IAs, the growth of IAs, and the rupture of an IA have been identified in the published literature.[14-16] Although the exact biological effect of smoking on the pathogenesis of intracranial aneurysms is unknown, many studies have already shown that current smoking is a very influential risk factor for IAs, as it promotes endothelial dysfunction and inflammation.[17] Also, excessive alcohol consumption is not only associated with an increased risk of the development of intracranial aneurysms but also increases the risk of aneurysm rupture.[18]

8.1.4. Classification

There are several methods of categorizing IAs. One possibility is to categorize IAs according to their localization. IAs most frequently occur in the anterior circulation of the Circle of Willis, particularly in the area of the anterior communicating artery (AComA) and the middle cerebral artery (MCA) bifurcation.[19] However, aneurysms can also occur in other vessels like in the area of the internal carotid artery (ICA) and its leaving vessels, other segments of the MCA or anterior cerebral artery (ACA), and the posterior communicating artery (PComA).[19] Second, IAs can be categorized according to their size. Aneurysms with a more than 25 mm diameter are called giant aneurysms, but these only account for around 3-5 % of IAs.[20] Third, IAs can also be categorized according to their shape. For example, a distinction can be made between saccular and fusiform or dissecting aneurysms.

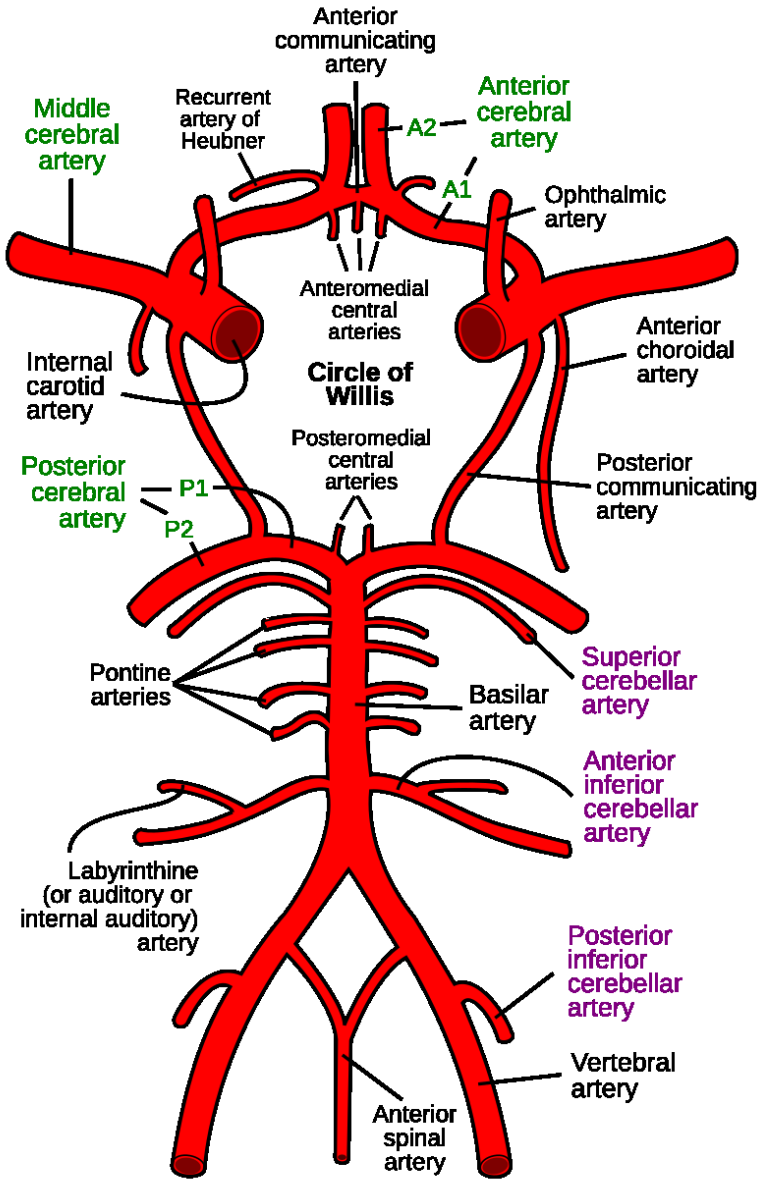

Figure 1: *Schematic representation of the circle of Willis, arteries of the brain and brain stem.* (*Source: Rhcastilhos, Wikimedia Commons, License: Public Domain)*

8.1.5. Clinical presentation

The clinical presentation depends mainly on the rupture state of the aneurysm. Most unruptured aneurysms are asymptomatic and are discovered incidentally during imaging for

other medical conditions. However, certain unruptured aneurysms, particularly those that are large, partially thrombosed or located in critical areas of the brain, may present with neurological symptoms, including cranial nerve palsies, headache, nausea, vomiting, and visual disturbances. Depending on the individual risk profile, there is not always a need for urgent treatment in the presentation of unruptured aneurysms.

In contrast, the rupture of an aneurysm is always an emergency scenario with a life-threatening medical condition. Sudden onset of severe headache, often described as the "thunderclap" headache, accompanied by nausea, vomiting, photophobia, and altered mental status are pathognomonic symptoms for ruptured aneurysms, causing SAH. Focal neurological deficits may occur, depending on the location and extent of the hemorrhage. An early recognition of these symptoms is critical, and immediate medical attention can significantly improve outcomes.

8.2. Ruptured intracranial aneurysms / Subarachnoid Hemorrhage

IAs have a significant health risk due to their potential to rupture, which leads, in most cases, to a life-threatening SAH. Rupture of IAs is the cause of approximately 80% of all spontaneous SAH. SAH is often associated with a fatal outcome[21], and the median mortality in Europe is approximately 44%.[22]

SAH typically presents clinically with sudden, severe "thunderclap" headaches. Depending on severity, headache may be accompanied by autonomic dysregulation, such as nausea and vomiting. Due to the localization of the bleeding within the subarachnoid space, additional symptoms such as paresis, epileptic seizures, or cranial nerve deficits like double vision may occur. Altered mental states, ranging from confusion to reduced vigilance and even coma, can be the consequence. These manifestations may result from the extent of the SAH, mass effect, brain edema, or complications such as consecutive hydrocephalus. Hydrocephalus may arise from impaired cerebrospinal fluid (CSF) resorption due to subarachnoid blood deposits (Hydrocephalus malresorptivus) or from obstruction of CSF

flow (Hydrocephalus occlusus). In the acute phase, external ventricular drainage is often indicated as an initial treatment for hydrocephalus.

The Hunt and Hess scale can classify the severity of the SAH.[23] It categorizes patients based on the clinical presentation and symptom severity from Grade I (asymptomatic or minimal headache) to Grade V (deep coma). It can be used as a predictor of survival.[23]

In the subacute phase following an SAH, with a peak between days 4 and 7, there is an increased risk of cerebral vasospasm. This complication occurs because of blood breakdown products within the subarachnoid space that have a narrowing effect on the cerebral vessels. As a result of vasospasm, delayed cerebral ischemia can occur.[24] This is a leading cause of secondary neurological deterioration following SAH, contributing to significant secondary morbidity and mortality over time.[25] Assessing the risk of vasospasm remains challenging. The Fisher Scale estimates the likelihood of vasospasm based on the initial distribution of the SAH, using a four-grade classification system.[26]

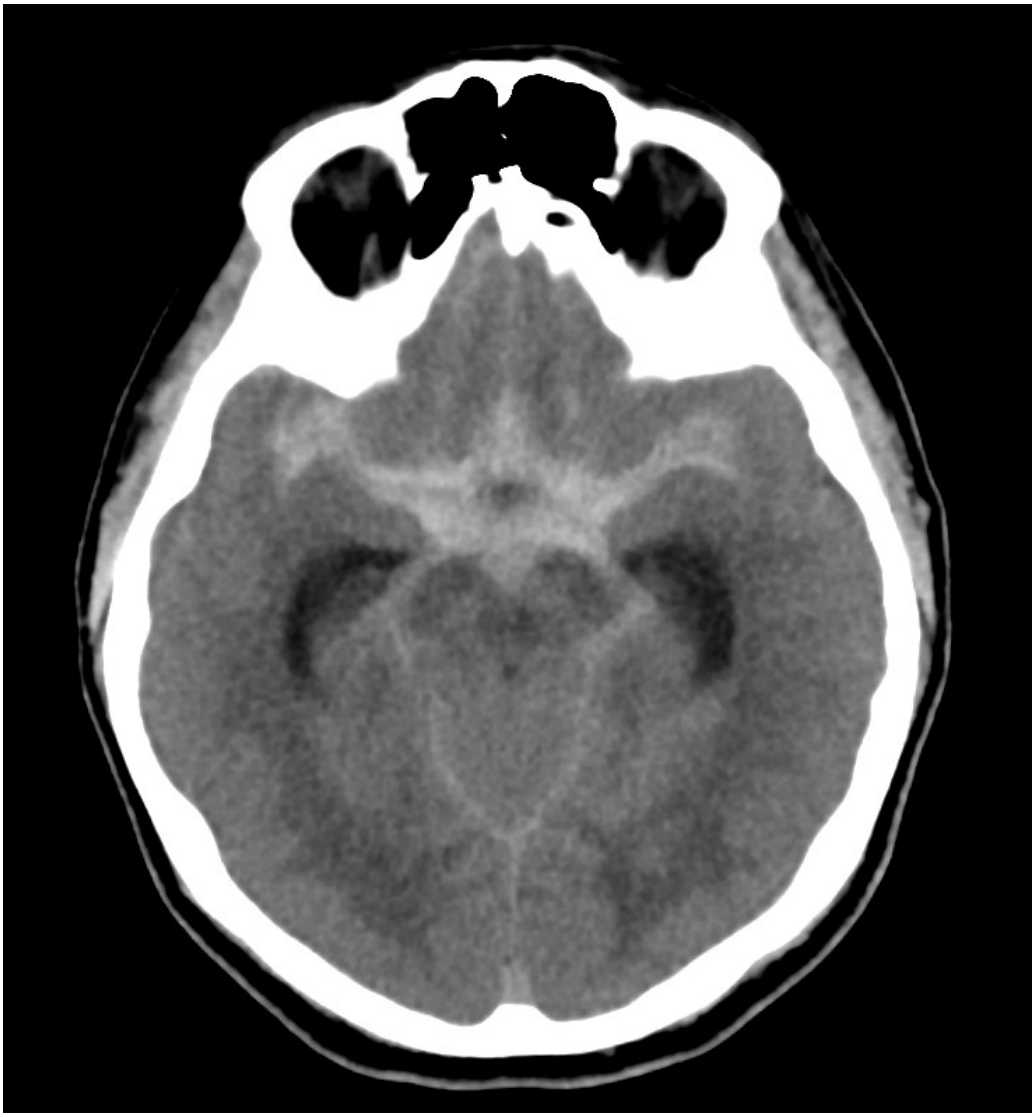

Figure 2: *A non-contrast cranial CT shows an extensive SAH. (Source: James Heilman, MD, A subarachnoid hemorrhage, Wikimedia Commons, License: CC BY-SA 3.0, https://commons.wikimedia.org/wiki/File:SubarachnoidP.png)*

8.3. Unruptured intracranial aneurysms

Neuroradiological imaging plays an essential role in the diagnosis and prognostic evaluation during the acute phase of a ruptured aneurysm but also increasingly in the incidental detection of unruptured intracranial aneurysms (UIA).

Advances in neuroradiological imaging have led to an increasing detection rate of UIAs. Magnetic resonance imaging (MRI) and incredibly magnetic resonance angiography (MRA) or computed tomography (CT) angiographies are indicated at a much lower threshold, which has resulted in a higher detection rate in recent years - regardless of the question of what therapeutic consequences result from this. Each of the imaging modalities has advantages and disadvantages. For years, state-of-the-art aneurysm diagnostics, particularly in geometric and hemodynamic parameters, have been using digital subtraction angiography (DSA).[27] However, in recent years, 3D rotational angiography (3DRA) has emerged as the new gold standard.[28]

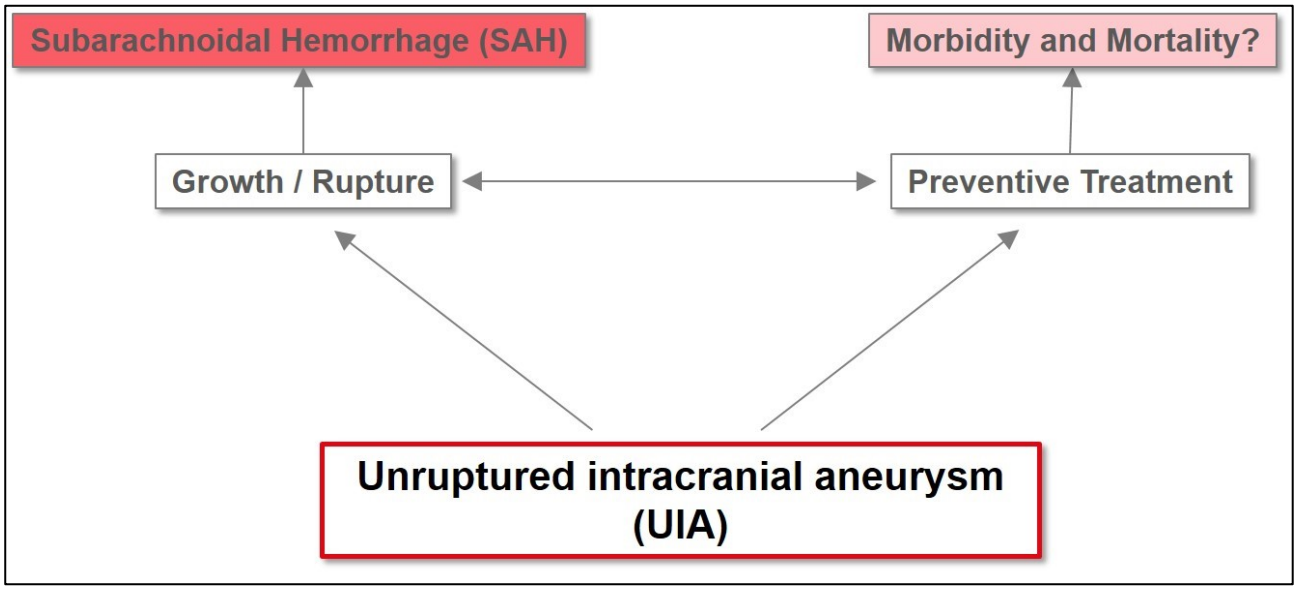

Figure 3: *Schematic representation of the natural course and management of UIAs, highlighting the risk of SAH through growth or rupture and the potential impact of preventive treatment on morbidity and mortality. UIA = unruptured intracranial aneurysm, SAH = subarachnoidal hemorrhage.*

8.3.1. Aneurysm Treatment

The goal of treating UIAs must be to reduce the risk of aneurysm rupture and to prevent potentially fatal SAH. As such, it is a prophylactic intervention that necessitates a comprehensive benefit-risk assessment, contrasting with a conservative observation approach and ongoing neuroradiologic monitoring.

8.3.1.1. Microsurgical Treatment

The first microsurgical treatment of an IA was published by Norman Dott in 1933, performing a wrapping of the aneurysms.[29] The first published clipping of an IA was performed in 1938 by Walter Dandy.[30] In 1975, Yasargil published the classic microscopic assisted open approaches for clipping like pterional craniotomy, which afforded safe and adequate exposure of the circle of Willis through the Sylvian fissure with minimal retraction on the frontal and temporal lobes.[31,32]

For many years, the terms aneurysm and microsurgical treatment could be used synonymously. Microsurgical treatment, like clipping, has been regarded as the primary treatment method for an extended period. Different techniques in the microsurgical treatment of aneurysms depend on the size, localization, or configuration of the aneurysm. Microsurgical treatment has been refined in various approach options and tailored craniotomies and microsurgical techniques like retractorless surgery or bypass techniques.[33] Clipping is the most common technique for microsurgical aneurysm occlusion. Still, in cases of more fusiform or giant aneurysms and, therefore, potentially unclippable aneurysms, alternative techniques like circumferential wrapping of the aneurysm with or without clip reinforcement,[34] or proximal occlusion of the parent artery (trapping) with or without bypass can be used for aneurysm treatment.[35]

In addition to the wide range of available microsurgical treatment options, endovascular treatment strategies have significantly improved in recent decades.

8.3.1.2. Endovascular Treatment

There have been various endovascular approaches to aneurysm treatment since 1965.[36] However, Guido Guglielmi laid the foundation stone for endovascular treatment in 1990. He demonstrated the potential of endovascular aneurysm embolization by developing electrically detachable platinum coils, known as Guglielmi detachable coils (GDC), inserted intraluminally using the microcatheter.[37] Even though the closure of a direct carotid-cavernous fistula initially was the cause of sensation at the University of California at Los Angeles, it quickly became apparent that GDC coils would result in an excellent endovascular treatment strategy for intracranial aneurysms. [38]

In the years that followed, endovascular treatment options continued to develop. Modified coiling techniques were published, such as balloon-assisted coiling of broad-based aneurysms.[39] Another milestone was flow diversion. This technique represented a novel approach in which a low porosity, low profile stent is situated within the parent artery, extrinsic to the aneurysm, leading to vessel wall remodeling and aneurysm occlusion.[40,41]. Various manufacturers further developed these semi-permeable stents.[42] Furthermore, intrasaccular flow diverters are now also available, whereby the device is placed in the aneurysm and not in the parent vessel as with the flow diverter.[43] Bioactive devices intended to promote an aneurysm's healing process are still the subject of scientific debate and do not yet show any superiority over conventional non-bioactive stents and coils.[44,45]

Despite numerous endovascular and microsurgical opportunities, some complex aneurysms often cannot be treated entirely with a single approach. Therefore, a combination of microsurgical and endovascular techniques in a hybrid angiographic operation room setting is sometimes needed for sufficient treatment, and modalities should be seen as complementary rather than competitive.[46]

Due to the numerous microsurgical and endovascular treatment options and different modalities, it makes sense to discuss each corresponding case in an interdisciplinary

cerebrovascular board attended by all treatment partners (endovascular and microsurgical) to determine the ideal treatment modality.[47]

8.3.1.3. Decision-Making in Aneurysm Treatment

An important consideration in treatment decisions is the type of treatment itself and, eventually, even more critical, whether incidentally detected UIAs require treatment.

The increasing accessibility of neuroradiological imaging has led to a growing number of incidentally diagnosed UIAs that have been subsequently evaluated for potential treatment. However, the incidence of ruptured aneurysms and, consequently, SAH has not shown a significant increase over the past decades.[48]

Decision-making for the management of UIAs is inherently complex. It involves balancing the benefits and risks of treatment versus observation by considering numerous risk factors for aneurysm growth and rupture. When the likelihood of postoperative complications or adverse outcomes is high, conservative management, which includes clinical and radiological follow-up, lifestyle modifications, and treatment of known risk factors, may be more advantageous.[47] Deciding on treatment involves carefully weighing the natural progression of the intracranial aneurysm against the procedural risks, considering both aneurysm-specific and patient-specific risk factors. These factors can also be key in selecting the appropriate treatment modality.

Risk scores aid in objectively assessing rupture risk for UIAs. For example, the PHASES score helps estimate the 5-year rupture risk based on six patient- and aneurysm-specific parameters (population, hypertension, age, size, location, and previous SAH.[49] However, studies have also demonstrated significant limitations of the PHASES score in guiding decision-making for small UIAs. The PHASES score tends to underperform in assessing the risk of small intracranial aneurysms.[7]

Furthermore, the PHASES score considers only the above-mentioned aneurysm- and patient-specific parameters in risk stratification without accounting for the potential

complications associated with the treatment. Morbidity and mortality are critical factors in elective preventive therapies, such as treating UIAs. In contrast, the unruptured intracranial aneurysm treatment score (UIATS), developed through multidisciplinary consensus, incorporates a few treatment-related risk factors, like age-related risk, aneurysm size-related risk, aneurysms complexity-related risk, and constant intervention-related risk. The UIATS provides a comprehensive recommendation of how a large group of specialists might manage an individual patient with a UIA.[8] A limitation of the UIATS is the lack of differentiation between treatment modalities, even though endovascular coiling, for example, has a different procedural risk profile than microsurgical clipping.

Despite all efforts to evaluate the risk as accurately as possible, the treatment decision for UIAs remains challenging. Another difficulty is that the rupture risk represents a long-term risk over time, and the treatment risk represents the risk of a specific event. Consequently, these risks cannot be validly compared, even though such comparisons are made in clinical practice.[8,50]

Risk scores provide a solid basis for discussion, but the individualized treatment decision for UIAs remains highly complex. It must account for numerous aneurysm-specific risk factors, patient-specific risk factors for rupture- and treatment-related complications, and complications associated with the chosen treatment modality. An interdisciplinary case-by-case discussion of the radiological and clinical parameters is likely the most effective way to comprehensively evaluate these factors and arrive at an appropriate treatment decision.[47]

In the future, artificial intelligence could offer a way of processing the numerous influencing risk factors that need to be considered in treatment decision-making and the associated data volumes big-data studies will have to deal with and identify patterns and correlations, which ordinary classifications or logistic regression analyses might not achieve.

8.3.2. Outcome and Complications

In the context of prophylactic treatments, such as elective clipping of UIAs, the potential benefits must outweigh the associated risks of the treatment. Achieving this balance requires an evaluation of the expected postoperative outcomes and possible postoperative complications. Moreover, it is essential to identify risk factors that may contribute to unfavorable postoperative results, enabling a more informed and individualized treatment strategy.

The primary goal of clipping surgery is to achieve complete occlusion of the aneurysm. This outcome can be objectively assessed intraoperatively or postoperatively using conventional DSA or 3DRA, considered the gold standard. Clipping of MCA aneurysms, for example, demonstrates occlusion rates as high as 99% in the literature.[51-54] In cases of incomplete aneurysm occlusion, the residual aneurysm can be categorized using the Raymond-Roy Classification, providing a standardized framework for evaluation (Class I: Complete occlusion, Class II: Residual neck, Class III: Residual aneurysm).[55] The classification was initially designed to grade the occlusion grade after coiling but is also used for post-clipping assessment. It is a possible standardized classification for comparison between several treatment methods.

Postoperative clinical outcomes can be evaluated based on the presence or absence of complications and by applying established clinical scoring systems, such as the modified Rankin Scale (mRS) or the Glasgow Outcome Scale (GOS). Although these scores were not designed explicitly for postoperative assessment after aneurysm clipping, both are frequently used to compare outcomes between studies objectively.[51,53,56-58]

The mRS was initially developed to classify the degree of disability following a stroke.[59] Over the years, it has undergone several modifications and now includes gradations ranging from 0 (healthy) to 6 (death). The simplicity and comparability have made it a widely used tool in cerebrovascular research and can, therefore, also be used to classify the degree of disability after neurosurgical interventions.[60-62] The same applies to the GOS, which was initially developed to assess functional outcomes after brain injury but is also applied as a

postoperative classification tool. The GOS categorizes outcomes on a scale from 1 to 5, following a structure similar to the mRS.

Mortality is already included in these two outcome scores but can also be considered a separate clinical outcome parameter. In surgical procedures, mortality refers to the death rate occurring postoperatively, directly attributed to the surgery.

As with any surgical procedure, undesirable postoperative complications may occur, generally defined as any deviation from the expected course of recovery. Following neurosurgical procedures, postoperative complications may manifest in various parameters. Intracerebral hemorrhage (ICH) is a possible complication, often requiring immediate attention. Meningitis, though less common, can also occur and represents a serious postoperative challenge and a prolonged recovery. Seizures are another potential complication after any craniotomy and are typically classified as focal or generalized, depending on their presentation. Strokes are another possible complication and can be categorized as minor or major depending on severity. Therefore, new neurological deficits (NND) are among the more concerning complications. These deficits can be transient (tNND) or permanent (pNND) and may occur with or without associated infarction. Subdural hematomas, which may or may not require surgical evacuation, also present a significant risk. Surgical site infections (SSI) remain a critical concern, as they can delay recovery and increase morbidity.

Postoperative complications are not limited to those directly associated with the surgical procedure. Internal medical complications, such as cardiac issues, may also be a direct or indirect consequence of surgery. Pulmonary complications, including infections or pulmonary embolism, can also occur during recovery.

Lastly, the duration of stay in the intensive care unit (ICU) and the length of postoperative hospitalization are essential for evaluating recovery and surgical success. These parameters and the management of complications play a significant role in determining patient outcomes.

8.3.2.1. Outcome Prediction

Postoperative complications are generally associated with poorer patient outcomes and are therefore avoidable. The patient's preoperative constitution is essential for avoiding postoperative complications and results in a better postoperative outcome.

Furthermore, the preoperative condition of patients represents a potentially modifiable risk factor in the context of elective treatments for UIAs. Several risk factors associated with postoperative complications and unfavorable outcomes have been identified.

Advanced age, particularly beyond 65 years, is an independent risk factor for unfavorable outcomes, owing to the natural decline in physiological reserves and the increased likelihood of comorbidities in this population.[63] Additional factors contributing to higher risks include chronic obstructive pulmonary disease (COPD), which can compromise respiratory function, as well as coagulation disorders or bleeding tendencies, which may complicate both the surgical procedure and recovery.[64]

A history of congestive heart failure or prior stroke further underscores the vulnerability of these patients due to preexisting vascular or neurological impairments. Patients with an American Society of Anesthesiologists (ASA) physical status of IV or higher face particularly elevated risks, as this classification reflects severe systemic disease that may limit the patient’s ability to withstand surgical stress.[65] Obesity, defined by a body mass index (BMI) exceeding 40 kg/m², introduces additional challenges, including difficulties in perioperative management and increased risk of wound healing complications.[66]

In addition, aneurysm-specific risk factors significantly contribute to the complexity of complications, especially the anatomical and morphological characteristics of UIAs, which play a critical role. Aneurysms located in the posterior circulation are associated with exceptionally high risks, as well as aneurysms with a size that exceeds 10 mm.[67] Furthermore, aneurysms with calcifications or irregular morphologies increase the technical difficulty of the surgical procedure and contribute to a higher likelihood of adverse events during or after the procedure.

8.3.2.2. Machine Learning

Determining correlations between preoperative patient- and aneurysm-specific parameters and postoperative complications or outcomes remains a complex challenge. Traditional statistical methods, such as logistic regression (LR) models, are commonly used to examine such relationships. However, incorporating artificial intelligence (AI), particularly Machine learning (ML) techniques, has shown the potential to outperform conventional statistical approaches in specific scenarios.

ML-algorithms offer considerable advantages in processing and predictive tasks, as they can analyze extensive datasets and detect patterns that traditional classifications or LR models might miss. Various ML approaches have been employed to develop predictive analytics tailored to individual patients, particularly in neurosurgery.[68-70] Several studies have reported exceptional performance in predicting outcomes for cerebrovascular neurosurgical conditions.[71-73]

For example, numerous ML-based tools have been designed to predict the complication risk and the treatment outcomes for patients with aneurysmal SAH.[74,75] Despite these advancements, the application of ML to predict outcomes in cases of UIAs has been relatively limited, with not even a handful of studies addressing this specific area.[76,77]

ML has proven to be helpful for these predictive purposes. Whether machine learning models could assist in the future preoperative risk evaluation of specific surgical procedures arises.

8.3.2.3. Quality Assessment / Benchmarking

In addition to the growing interest in preoperative outcome prediction and the corresponding pre- and postoperative correlation of various parameters, performance monitoring and quality assessment have gained significant importance in recent years. These aspects are essential for evaluating postoperative outcomes and, ultimately, for enhancing long-term

results and ensuring patient safety. As with many other medical specialties, quality assessment has become increasingly crucial in surgical medical fields, particularly neurosurgery.

One commonly used tool in economic fields is benchmarking for quality assessment and further quality improvement. The concept of benchmarking involves continuously improving specific processes, such as surgical procedures, by constantly comparing them to the best achievable standards.[78,79] The idea has already been applied to medical fields,[80,81] including surgical specialties[82]. Benchmarking represents the optimal achievable outcome for a given procedure and is the desirable goal.[82]. Using benchmarks allows for continuous comparison with the optimal outcome. It facilitates comparability between centers or modalities, like microsurgical and endovascular treatment.

9. Aims of the thesis

In this cumulative dissertation thesis, the overarching aim is to address critical challenges in treating UIAs through a comprehensive, multidisciplinary approach. This thesis shows the utilization of ML, international benchmarking standards, and global multicenter data to improve clinical decision-making, optimize surgical outcomes, and, most importantly, enhance patient safety in treating UIAs.

In times of an increasing role of ML in medical fields like neurosurgery, this thesis aims to show the application of machine learning in microsurgical treatment for UIAs, aiming to predict functional and clinical outcomes based on preoperative parameters. Therefore, it is essential to identify robust algorithms capable of generalizing across patient populations while addressing domain shifts in clinical data with a temporal train-test split. Therefore, external validation is necessary to explore the predictive power of ML in risk stratification and outcome prediction on previously unseen external data.

When addressing clinical and functional outcomes prediction using ML models, the question of the best possible outcome is crucial. In this context, establishing benchmarks for UIA treatment is essential as a quality assessment tool. Therefore, a significant focus is placed on defining benchmark cutoffs for perioperative and long-term outcomes of microsurgical clipping. This thesis aims to provide internationally applicable benchmarks from a multicenter dataset that includes diverse healthcare systems. These benchmarks could be a reference for evaluating surgical performance and facilitating comparisons between treatment modalities and different centers.

Further, this thesis investigates patient- and aneurysm-specific factors influencing outcomes in microsurgical clipping. By analyzing risk factors, this thesis aims to refine surgical techniques and identify predictors of postoperative morbidity and neurological deterioration. Furthermore, intraoperative parameters are compared with alternative methods, reinforcing the clinical importance of microsurgical repair. Given the heterogeneity in surgical outcomes across different international centers, this thesis examines the impact of caseload, expertise, and interhospital variability on postoperative results. Analyzing data from high-volume

cerebrovascular centers worldwide aims to provide insights into the volume-outcome relationship, supporting the potential centralization of complex UIA treatments to ensure optimal care.

Through these objectives, this cumulative dissertation contributes advances to the field of cerebrovascular neurosurgery by integrating predictive analytics and standardized outcome assessment. Addressing the complexities of UIA management, this work aims to improve patient outcomes.

10. Results

10.1. Machine learning based outcome prediction of microsurgically treated unruptured intracranial aneurysms

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10.1.1. Abstract

Machine learning (ML) has revolutionized data processing in recent years. This study presents the results of the frst prediction models based on a long-term monocentric data registry of patients with microsurgically treated unruptured intracranial aneurysms (UIAs) using a temporal train-test split. Temporal train-test splits allow to simulate prospective

validation, and therefore provide more accurate estimations of a model's predictive quality when applied to future patients.

ML models for the prediction of the Glasgow outcome scale, modifed Rankin Scale (mRS), and new transient or permanent neurological defcits (output variables) were created from all UIA patients that underwent microsurgery at the Kepler University Hospital Linz (Austria) between 2002 and 2020 (n= 466), based on 18 patient- and 10 aneurysm-specifc preoperative parameters (input variables). Train-test splitting was performed with a temporal split for outcome prediction in microsurgical therapy of UIA. Moreover, an external validation was conducted on an independent external data set (n= 256) of the Department of Neurosurgery, University Medical Centre Hamburg-Eppendorf.

In total, 722 aneurysms were included in this study. A postoperative mRS> 2 was best predicted by a quadratic discriminant analysis (QDA) estimator in the internal test set, with an area under the receiver operating characteristic curve (ROC-AUC) of 0.87 ± 0.03 and a sensitivity and specifcity of 0.83 ± 0.08 and 0.71 ± 0.07, respectively. A Multilayer Perceptron predicted the post- to preoperative mRS diference> 1 with a ROC-AUC of 0.70 ± 0.02 and a sensitivity and specifcity of 0.74 ± 0.07 and 0.50 ± 0.04, respectively. The QDA was the best model for predicting a permanent new neurological defcit with a ROC-AUC of 0.71 ± 0.04 and a sensitivity and specifcity of 0.65 ± 0.24 and 0.60 ± 0.12, respectively. Furthermore, these models performed signifcantly better than the classic logistic regression models (p< 0.0001).

The present results showed good performance in predicting functional and clinical outcomes after microsurgical therapy of UIAs in the internal data set, especially for the main outcome parameters, mRS and permanent neurological defcit. The external validation showed poor discrimination with ROC-AUC values of 0.61, 0.53 and 0.58 respectively for predicting a postoperative mRS> 2, a pre- and postoperative diference in mRS> 1 point and a GOS< 5. Therefore, generalizability of the models could not be demonstrated in the external validation. A SHapley Additive exPlanations (SHAP) analysis revealed that this is due to the most important features being distributed quite diferently in the internal and external data

sets. The implementation of newly available data and the merging of larger databases to form more broad-based predictive models is imperative in the future.

10.1.2. Introduction

Unruptured intracranial aneurysms (UIAs) have an estimated prevalence of 3%[1]. Life-threatening intracranial hemorrhages, usually subarachnoid hemorrhage (SAH), are the consequences of UIA rupture with an associated mortality rate of up to 44%[22].

Owing to the increasing availability and widespread use of neuroradiological imaging, UIAs have been detected more frequently in recent years. The treatment of UIAs aims to minimize or eliminate the risk of rupture. Microsurgical treatment of a UIA should be regarded as a prophylactic intervention, and the indication must be based on an objectifiable benefit-risk assessment. Accordingly, sufficient occlusion of the UIA and the associated elimination of the risk of rupture must prevail over the complication risk of the microsurgical intervention.

However, decision-making in UIAs is complex and many risk factors for aneurysm growth and rupture should be considered to balance the benefits and risks of treatment versus observation. In the case of a high probability of a postoperative complication or a negative outcome, conservative management including clinical and radiological follow-up as well as lifestyle modification or treatment of known risk factors might be more beneficial.[8] Predicting the postoperative outcomes is challenging. There is a large number of potential influencing factors and corresponding data; therefore, the aid of machine learning (ML) algorithms could be helpful in processing and prediction. ML algorithms can analyze large amounts of data and identify complex patterns which might not be achieved by ordinary classifications or logistic regression analysis (LR). A range of ML models have been applied to generate patient-specific predictive analytics for outcomes in neurosurgery, and some studies have demonstrated excellent performance in outcome prediction for a range of neurosurgical conditions[68-70], particularly cerebrovascular neurosurgery[71-73,84].

Several ML-based prediction tools for the complication- and treatment-aware outcomes of patients with aneurysmal subarachnoid hemorrhage (aSAH) have been published[74,75,85,86]. However, very few studies have been published on prediction models for UIAs[76,77].

The aim of this study was to demonstrate that the prediction of early clinical and functional endpoints after microsurgical clipping of UIAs is feasible using advanced ML techniques. As experience and surgical techniques are improving in cerebrovascular centres over time, prediction models need to be continuously adapted. Long-term databases have a clear temporal character, and thus relevant domain shifts must be addressed. This can be accomplished by using temporal train-test splits instead of random splits, to simulate prospective validation on retrospective data. This approach makes it possible to identify those ML algorithms that generalize best from past to future patients. Later, they can be trained on all available data to obtain models for actual clinical use, where a particular focus may even be put on more recent data to account for current and emerging trends in cerebrovascular surgery, and thereby improve the predictive quality of these models. In addition to the prediction model performance on an internal test set, the performance on an independent external data set is of great interest as an external validation of the predictive models.

This study presents the results of the first prediction models based on a long-term monocentric data registry of patients with microsurgically treated UIAs using a temporal train-test split, tested on an internal as well as an external test set.

10.1.3. Methods

Ethics board approval was obtained prior to data acquisition from the local ethics committee (JKU-Ethikkommission, EC-No.: 1255/2019). All patients or their legal representatives gave their legal informed consent to the surgical procedures and the study conducted in accordance with the Declaration of Helsinki.

Every UIA of the anterior circulation that was microsurgically treated between January 2002 and December 2020 at the Department of Neurosurgery, Kepler University Hospital Linz, was added to the retrospectively collected registry.

The microsurgical operations were all performed using standard approaches and a compilation of the technical intraoperative parameters is shown in Table 1.

Preoperative parameters

Preoperative parameters were divided into patient- and aneurysm-specific parameters and constituted the input variables for the ML algorithms. Patient-specific parameters consisted of basic demographic parameters (age and sex), parameters concerning personal medical history (earlier SAH, hypertension, diabetes mellitus, body mass index (BMI), autosomal dominant polycystic kidney disease, chronic obstructive pulmonary disease, previous stroke, psychiatric disorder, smoking, alcohol abuse, familial frequency of aneurysms), and preoperative scores (PHASES-Score[49], ASA-Score[87] (American Society of Anesthesiologists), and modified Rankin Scale (mRS)[60]).

Aneurysm-specific parameters included aneurysm location, calcification, neck diameter, maximum diameter, side, size of the parenteral vessel, morphology, and the occurrence of multiple aneurysms. Preoperative aneurysm-related symptoms such as cranial nerve deficits, epileptic seizures, or aneurysm-related thromboembolic events were also recorded.

Outcome parameters

Prediction models were calculated for the postoperative parameters. Digital subtraction angiography was performed in every patient to assess complete aneurysm occlusion. New postoperative neurological deficits (nND) were surveyed and divided into transient and permanent nND. A permanent nND persisted after hospital discharge. The functional outcome was assessed using the Glasgow Outcome Scale (GOS)[88], mRS[60], and the difference in the mRS preoperatively to postoperatively. An mRS score of >2 or a GOS of <5 was defined as a poor outcome[52,88]. A worsening in mRS of more than one point (postoperatively compared to preoperatively) was regarded as functional deterioration.

Statistical analysis

Statistical analysis included a univariate descriptive analysis of the collected input and output variables. In addition, an unpenalized LR model was trained on all available features as a simple baseline to quantify the benefit of sophisticated hyperparameter tuning and complex model classes[89].

Train-test split

The data were split into training and testing sets. To stimulate prospective validation and obtain reliable estimates of the predictive performance for future patients, we opted for a temporal split, in which the training set consisted of all data until, and including, the year 2018, and the test set consisted of all remaining data from 2019 and 2020.

Intraoperative parameters	**Total**	**mRS>2**	**pnND**	**GOS<5**	**tnND**	**mRS-Diff>1**	**Train Set**	**Test Set**
Number of Aneurysms	466	59	29	63	35	48	380	86
Mean operating duration in minutes (±SD)	250 (±109)	263 (±107)	261 (±108)	291 (±114)	284 (±117)	278 (±115)	226 (±93)	357 (±110)
Blood transfusion	4 (0.9%)	2 (3.4%)	0	3 (4.8%)	1 (2.9%)	1 (2.1%)	4 (1.1%)	0
Use of more than 1 clip	163 (35.1%)	24 (40.7%)	11 (37.9%)	25 (40.3%)	12 (35.3%)	20 (42.6%)	134 (35.3%)	29 (34.1%)
Simultaneous clipping of multiple aneurysms	81 (17.4%)	16 (27.1%)	12 (41.4%)	17 (27.0%)	7 (20.0%)	13 (27.1%)	61 (16.1%)	20 (23.3%)
Simultaneous bypass	2 (0.4%)	1 (1.7%)	1 (3.6%)	2 (3.2%)	1 (2.9%)	1 (2.1%)	0	2 (2.4%)
Temporary vessel occlusion	51 (11.1%)	11 (18.6%)	4 (14.3%)	11 (18.0%)	5 (14.3%)	9 (18.8%)	46 (12.2%)	5 (5.9%)
Repositioning of initial clip	88 (19.1%)	14 (23.7%)	8 (28.6%)	17 (27.9%)	9 (25.7%)	10 (20.8%)	83 (22.1%)	5 (5.9%)
Intraoperative rupture	16 (3.5%)	6 (10.2%)	6 (21.4%)	7 (11.3%)	2 (5.7%)	6 (12.5%)	14 (3.7%)	2 (2.4%)
Wrapping	14 (3.0%)	0	0	0	0	0	11 (2.9%)	3 (3.5%)

Table 1: *Intraoperative parameters; mRS = modified Rankin Scale, pnND = permanent new neurological deficit, GOS = Glasgow Outcome Scale, tnND = transient new neurological deficit, mRS-Diff>1 = mRS difference >1 (preoperative vs. postoperative).*

This led to a train-test ratio of 81:19 or 380 vs. 86 samples. Although a single patient can occur multiple times with different aneurysms in the data, ensuring that all corresponding samples appear in either the training or test set was not considered necessary because these samples can safely be assumed to be independent of each other.

Machine learning algorithms and model selection

A range of ML models was trained on the training set and evaluated on the test set, including extreme gradient boosting estimators (XGB), random forests (RF), extremely randomized trees (ET), support vector machines (SVM), k-nearest neighbor classifiers (KNN), generalized additive models (GAM), multilayer perceptrons (MLP), linear discriminant analysis (LDA), and Quadratic Discriminant Analysis (QDA) models. This diverse set of algorithms was selected to make sure we would find the best-performing algorithm for each outcome. Tree-based algorithms, like random forests, are known to work well on tabular data, but including simpler algorithms as well seemed sensible to avoid overfitting due to the small data set.

The hyperparameters of these models were optimized using recent techniques of Bayesian optimization and meta-learning, as implemented in the auto-sklearn package for Python[90]. Hyperparameter optimization not only included finding an optimal model instance but also selecting the optimal preprocessing steps, particularly the class balancing strategy (balancing with respect to class frequencies, vs. no balancing), imputation strategy (mean vs. median imputation for numerical features, most frequent for categorical features), and feature selection. The area under the receiver operating characteristic curve (ROC-AUC) served as the optimization objective because this metric is widely used to illustrate the discriminative power of a binary classifier. Preliminary experiments suggest that optimizing the average precision (AP) does not lead to better overall results. The ROC-AUC was calculated on five predefined train-validation splits of the original training data, where the validation sets were not pairwise disjoint and were biased towards more recent samples from 2017 and 2018, to account for the temporal train-test split. Preliminary experiments suggested that this form of validation was superior to standard k-fold cross-validation.

In addition to ROC-AUC and AP, we also reported threshold performance metrics (such as accuracy and sensitivity) on the test set. Analogous to Staartjes et al., the decision thresholds were chosen according to the closest-to-(0, 1) criterion on the training set[76,91]. However, we note that these metrics were only included for the sake of completeness. Because of their strong dependence on a particular decision threshold and the fact that many different threshold selection strategies exist, one must be careful when comparing these metrics between different studies. The ROC-AUC is more robust in this respect and was therefore chosen as the main performance metric.

For estimating the variance of the performance metrics, after fixing hyperparameters, we trained models on 100 bootstrap resamples of the original training set and evaluated them on the test set[92]. The decision threshold was calculated for each of these models individually.

Python version 3.9.7[93], with scikit-learn 0.24.2[94], xgboost 1.5.0[95], pandas 1.4.1[96], and auto-sklearn 0.14.6[90] were used for all analyses through the open-source CaTabRa framework[97]. ML models were compared to LR models using the Mann-Whitney U-test.

Feature importance

The SHapely Additive exPlanations (SHAP) framework was used to determine the relevance of individual features to each model and thereby gain insights into the inner workings of otherwise opaque prediction models[98]. In contrast to simpler explanation techniques, such as permutation importance, SHAP also considers interactions between multiple features.

External Validation

We evaluated our models on a retrospectively collected registry from the Department of Neurosurgery of the University Medical Centre Hamburg-Eppendorf, Germany. Apart from new neurological deficits, the registry contained information about the same pre- and postoperative parameters as in our internal data set, and covered the years between 2016 and 2020. A statistical analysis was performed to identify differences in the distribution of the two data sets, focusing on parameters that were deemed important by the SHAP feature

importance analysis. The variance of the performance metrics was estimated using the same models that were used for estimating the variance on the internal test set.

10.1.4. Results

A total of 466 microsurgically treated patients with UIAs were included in the internal data set of this retrospective registry. With a mean age of 55.5 ± 10.5 years, 67.2% of patients were female and 32.8% male. A detailed summary of the 18 preoperative patient-specific parameters is shown in Table 2, and the 10 aneurysm-specific characteristics are listed in Table 3.

Intraoperative parameters were collected as listed in Table 1. For the establishment of the preoperative prediction models, these parameters were not used, with the exception of "simultaneous clipping of multiple aneurysms", because this parameter is actually already preoperatively known and therefore applicable for a preoperative prediction model.

Postoperatively, 35 patients (7.5%) presented with a transient nND, and 29 (6.2%) had a permanent nND. A good functional outcome, corresponding to a GOS of ≥ 5, was identified in 403 patients (86.5%). The postoperative mRS was <2 in 407 patients (87.3%), whereas after subtracting the preoperative baseline mRS, only 48 patients (10.3%) had a worsening in mRS of >1, in the sense of an objectifiable functional deterioration. All the outcome parameters are listed in Table 4.

Patient-specific preoperative parameters		Internal Set	mRS>2	pnND	GOS<5	tnND	mRS-Diff>1	Train Set	Test Set	External Set	p-Value
Number of Aneurysms		466	59	29	63	35	48	380	86	256	
Mean Age in years (±SD)		55.5 (±10.5)	55.9 (±12.2)	59.8 (±10.7)	55.9 (±13.1)	55.2 (±12.9)	58.1 (±11.5)	55.1 (±10.4)	57.3 (±10.7)	57.4 (±9.6)	0.0259
Female Gender		313 (67.2%)	31 (52.5%)	22 (75.9%)	34 (54.0%)	23 (65.7%)	30 (62.5%)	257 (67.6%)	56 (65.1%)	198 (77.3%)	0.0041
ASA Classification											<0.0001
	ASA I	101 (21.7%)	3 (5.1%)	3 (10.3%)	6 (9.5%)	10 (28.6%)	5 (10.4%)	93 (24.5%)	8 (9.3%)	2 (0.8%)	
	ASA II	255 (54.7%)	28 (57.4%)	15 (51.7%)	30 (47.6%)	15 (42.9%)	27 (56.2%)	200 (52.6%)	55 (64.0%)	157 (61.3%)	

	ASA III	101 (21.7%)	24 (40.7%)	10 (34.5%)	23 (36.5%)	8 (22.8%)	14 (29.2%)	80 (21.1%)	21 (24.4%)	95 (37.1%)	
	ASA IV	8 (1.7%)	3 (5.1%)	0	3 (4.8%)	2 (5.7%)	1 (2.1%)	6 (1.6%)	2 (2.3%)	2 (0.8%)	
	ASA V	1 (0.2%)	1 (1.7%)	1 (3.5%)	1 (1.6%)	0	1 (2.1%)	1 (0.2%)	0	0	
mRS preoperative											<0.0001
	0	288 (61.8%)	14 (23.7%)	15 (51.7%)	19 (30.2%)	15 (42.8%)	29 (60.4%)	222 (58.4%)	66 (76.7%)	124 (48.4%)	
	1	107 (23.0%)	14 (23.7%)	8 (27.6%)	17 (27.0%)	13 (37.1%)	14 (29.2%)	89 (23.4%)	18 (20.9%)	102 (39.8%)	
	2	51 (10.9%)	12 (20.4%)	4 (13.9%)	13 (20.6%)	5 (14.3%)	4 (8.3%)	51 (13.4%)	0	28 (10.9%)	
	3	15 (3.2%)	14 (23.7%)	1 (3.4%)	9 (14.3%)	1 (2.9%)	1 (2.1%)	15 (4.0%)	0	2 (0.8%)	
	4	4 (0.9%)	4 (6.8%)	0	4 (6.3%)	1 (2.9%)	0	3 (0.8%)	1 (1.2%)	0	
	5	1 (0.2%)	1 (1.7%)	1 (3.4%)	1 (1.6%)	0	0	0	1 (1.2%)	0	
ADPKD		9 (1.9%)	3 (5.1%)	2 (6.9%)	4 (6.3%)	1 (2.9%)	4 (8.3%)	7 (1.9%)	2 (2.5%)	5 (2.0%)	0.9518
Hypertension		282 (60.5%)	38 (64.4%)	19 (65.6%)	37 (58.7%)	22 (62.9%)	32 (66.7%)	225 (59.4%)	57 (67.9%)	159 (62.1%)	0.7516
COPD		70 (15.0%)	12 (20.3%)	6 (20.1%)	11 (17.5%)	4 (11.4%)	9 (18.8%)	63 (16.6%	7 (8.2%)	20 (7.8%)	0.0049
DM II		20 (4.3%)	3 (5.1%)	1 (3.4%)	6 (9.5%)	4 (11.4%)	3 (6.3%)	11 (2.9%)	9 (10.6%)	19 (7.4%)	0.0778
Previous stroke		43 (9.2%)	9 (15.2%)	4 (13.8%)	9 (14.3%)	7 (20.0%)	5 (10.4%)	36 (9.5%)	7 (8.2%)	42 (16.4%)	0.0044
Psychiatric disorder		72 (15.4%)	10 (16.9%)	5 (17.2%)	8 (12.7%)	4 (11.4%)	6 (12.5%)	61 (16.1%)	11 (13.1%)	19 (7.4%)	0.0018
Earlier SAH (another aneurysm)		78 (16.7%)	12 (20.3%)	1 (3.4%)	8 (12.7%)	6 (17.1%)	3 (6.3%)	69 (18.2%)	9 (10.1%)	14 (5.5%)	<0.0001
Smoking		108 (23.2%)	14 (23.7%)	8 (27.6%)	13 (20.6%)	6 (17.1%)	11 (22.9%)	91 (24.1%)	17 (20.5%)	122 (47.7%)	<0.0001
Alcohol abuse		30 (6.4%)	6 (10.2%)	2 (6.9%)	6 (9.5%)	1 (2.9%)	3 (6.3%)	25 (6.6%)	5 (6.0%)	21 (8.2%)	0.3936
Aneurysm in family history		22 (4.7%)	3 (5.1%)	2 (6.9%)	3 (4.8%)	2 (5.7%)	2 (4.2%)	20 (5.3%)	2 (2.4%)	22 (8.6%)	0.0390

Table 2: *Patient-specific preoperative parameters, with p-values for comparing the external set to the internal set; ASA = American Society of Anesthesiologists Classification, ADPKD = autosomal dominant polycystic kidney disease, COPD = chronic obstructive pulmonary disease, DM = Diabetes mellitus, mRS = modified Rankin Scale, SAH = subarachnoid hemorrhage, SD = standard deviation, mRS = modified Rankin Scale, pnND = permanent new neurological deficit, GOS = Glasgow Outcome Scale, tnND = transient new neurological deficit, mRS-Diff>1 = mRS difference >1 (preoperative vs. postoperative).*

The best model for predicting postoperative mRS >2 was a QDA estimator, which achieved a ROC-AUC of 0.87 ± 0.03. This model significantly outperformed the LR baseline, which achieved only 0.77 ± 0.05 ($p<0.0001$). The ROC-AUC of all models trained to predict this outcome is shown in Figure 4. The sensitivity and specificity of the QDA model were 0.83 ±

0.08 and 0.71 ± 0.07, respectively. SHAP identified preoperative aneurysm-related symptoms, aneurysm location, and preoperative mRS as the most important features; see Figure 5a for details.

The best model for predicting post- to preoperative mRS difference >1 was a MLP, with a ROC-AUC of 0.70 ± 0.02 in the test set. The LR baseline, which achieved 0.65 ± 0.06, was significantly outperformed ($p<0.0001$) by the MLP model. The ROC-AUC of all models trained to predict this outcome is shown in Figure 6. The sensitivity and specificity of the MLP were 0.74 ± 0.07 and 0.50 ± 0.04, respectively. SHAP identified aneurysm location, preoperative aneurysm-related symptoms and dome projection as the most important features; see Figure 5b for details.

The best model for predicting permanent nND was QDA, achieving a ROC-AUC of 0.71 ± 0.04 on the test set and significantly outperforming the LR baseline with 0.49 ± 0.09 ($p<0.0001$). The ROC-AUC of all models trained to predict this outcome is shown in Figure 7. Sensitivity and specificity were 0.65 ± 0.24 and 0.60 ± 0.12, respectively. Aneurysm location was identified as the single most important feature, as shown in Figure 5c.

The best model for predicting transient nND was a SVM estimator, achieving a ROC -AUC of 0.73 ± 0.07 on the test set. The LR baseline performed again significantly worse, with 0.63 ± 0.11 ($p<0.0001$). The ROC-AUC of all models trained to predict this outcome is shown in Figure 8. The sensitivity and specificity of the SVM model were 0.00 ± 0.02 and 0.97 ± 0.03, respectively, indicating a non-optimal threshold selection strategy in this case. The side of the aneurysm, ASA score and aneurysm morphology (regular vs. irregular) were identified as the most important features in this model (Figure 5d).

The best model for predicting GOS <5 was the GAM estimator, achieving a ROC-AUC of 0.79 ± 0.07 on the test set. The LR baseline performed significantly worse, with 0.75 ± 0.04 ($p<0.0001$). The ROC-AUC of all models trained to predict this outcome is shown in Figure 9. The sensitivity and specificity of the GAM were 0.69 ± 0.12 and 0.73 ± 0.06, respectively. Preoperative mRS score, PHASES score, and aneurysm location were identified as the most important features in this model, as shown in Figure 5e.

Aneurysm-specific preoperative parameters		Internal Set	mRS>2	pnND	GOS<5	tnND	mRS-Diff>1	Train Set	Test Set	External Set	p-Value
Number of Aneurysms		466	59	29	63	35	48	380	86	256	
Symptomatic aneurysm		41 (8.8%)	14 (23.7%)	4 (13.8%)	15 (23.8%)	6 (17.1%)	7 (14.6%)	29 (7.6%)	9 (10.5%)	74 (28.9%)	<0.0001
Calcification		31 (6.7%)	8 (13.6%)	4 (13.8%)	9 (14.3%)	3 (8.6%)	6 (12.5%)	18 (4.7%)	13 (15.1%)	67 (26.2%)	<0.0001
Aneurysm location											<0.0001
	MCA	309 (66.3%)	33 (55.9%)	12 (41.4%)	34 (54.0%)	23 (65.7%)	21 (43.8%)	255 (67.1%)	54 (62.6%)	164 (64.1%)	
	ACA	29 (6.2%)	5 (8.5%)	7 (24.1%)	6 (9.5%)	1 (2.9%)	4 (8.3%)	20 (5.3%)	9 (10.5%)	5 (2%)	
	AComA	116 (24.9%)	21 (35.6%)	10 (34.5%)	23 (36.5%)	10 (28.6%)	23 (47.9%)	99 (26.1%)	17 (19.8%)	61 (23.8%)	
	PComA	10 (2.1%)	0	0	0	1 (2.9%)	0	5 (1.3%)	5 (5.8%)	16 (6.3%)	
	AChA	2 (0.4%)	0	0	0	0	0	1 (0.3%)	1 (1.2%)	10 (3.9%)	
Neck diameter; mean (range) in mm		3.9 (1-12)	4.3 (2-12)	4.1 (2-8)	4.6 (2-12)	4.7 (2-12)	4.3 (2-9)	3.9 (1-12)	3.8 (1-10)	3.0 (1-10)	<0.0001
Maximum diameter; mean (range) in mm		5.9 (1-25)	7.2 (2-25)	7.0 (3-20)	8.1 (2-25)	7.9 (3-25)	7.7 (3-21)	5.8 (1-25)	6.3 (1-21)	6.0 (1.7-25)	0.1717
Size of parenteral vessel		2.0 (1-3)	2 (1.6-3)	2 (1.7-2.3)	2.0 (1.6-3)	2.1 (1.9-3)	2.0 (2-3)	2.0 (1.1-3)	2.1 (1.7-3)	2.6 (1-6)	<0.0001
Multiple aneurysms		213 (45.7%)	26 (44.1%)	13 (44.8%)	25 (39.7%)	13 (37.1%)	18 (37.5%)	176 (46.3%)	37 (43.0%)	129 (50.4%)	0.2284
Irregular morphology / Lobulation		172 (36.9%)	30 (50.8%)	17 (58.6%)	32 (50.8%)	12 (34.3%)	27 (56.3%)	145 (38.4)	27 (31.4%)	71 (27.7%)	0.0101

Table 3: *Aneurysm-specific preoperative parameters, with p-values for comparing the external set to the internal set; MCA = middle cerebral artery, ACA = anterior cerebral artery, AComA = anterior communicating artery, PComA = posterior communicating artery, PCA = posterior cerebral artery, AChA = anterior choroidal artery, mRS = modified Rankin Scale, pnND = permanent new neurological deficit, GOS = Glasgow Outcome Scale, tnND = transient new neurological deficit, mRS-Diff>1 = mRS difference >1 (preoperative vs. postoperative).*

Outcome parameters		Internal Set	Train Set	Test Set	External Set	p-Value
New neurological deficit		64 (13.7%)	52 (13.7%)	12 (14.0%)		
	Transient	35 (7.4%)	29 (7.6%)	6 (7.0%)		
	Permanent	29 (6.3%)	23 (6.1%)	6 (7.0%)		
mRS >2		59 (12.8%)	51 (13.4%)	8 (9.3%)	11 (4.3%)	<0.0001
mRS difference >1 (preop vs. postop.)		48 (10.2%)	40 (10.5%)	8 (9.3%)	9 (3.5%)	0.0004
GOS <5		63 (13.6%)	51 (13.4%)	12 (14.0%)	19 (7.4%)	0.0043
Complete angiographical occlusion*		459 (98.5%)	373 (98.2%)	86 (100.0%)	248 (96.9%)	0.1445

Table 4: *Outcome Parameters, with p-values for comparing the external set to the internal set; GOS = Glasgow Outcome Scale, mRS = modified Rankin Scale, preop = preoperative, postop = postoperative; *no prediction models were made for this outcome parameter.*

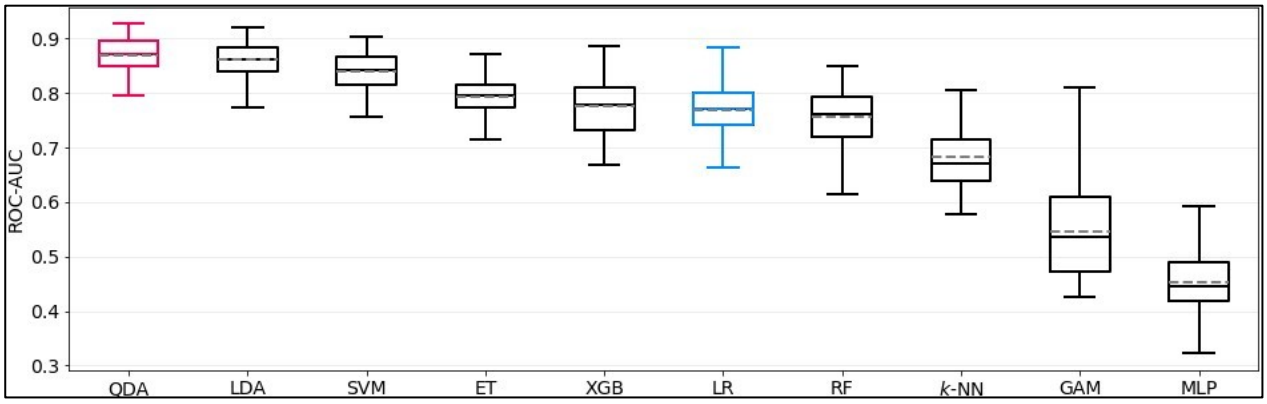

Figure 4: *Bootstrapped test-set ROC-AUC of all models trained to predict postoperative mRS >2, sorted by mean ROC-AUC. QDA is the top-performing model, and LR represents the logistic regression baseline model (both highlighted). mRS = modified Rankin Scale, ROC-AUC = area under Receiver Operating Characteristic curve, QDA = Quadratic Discriminant Analysis, ET = Extremely Randomized Trees, SVM = Support Vector Machine, LDA = Linear Discriminant Analysis, XGB = Extreme Gradient Boosting, RF = Random Forest, KNN = k-Nearest Neighbors, GAM = generalized additive model, MLP =Multilayer Perceptron.*

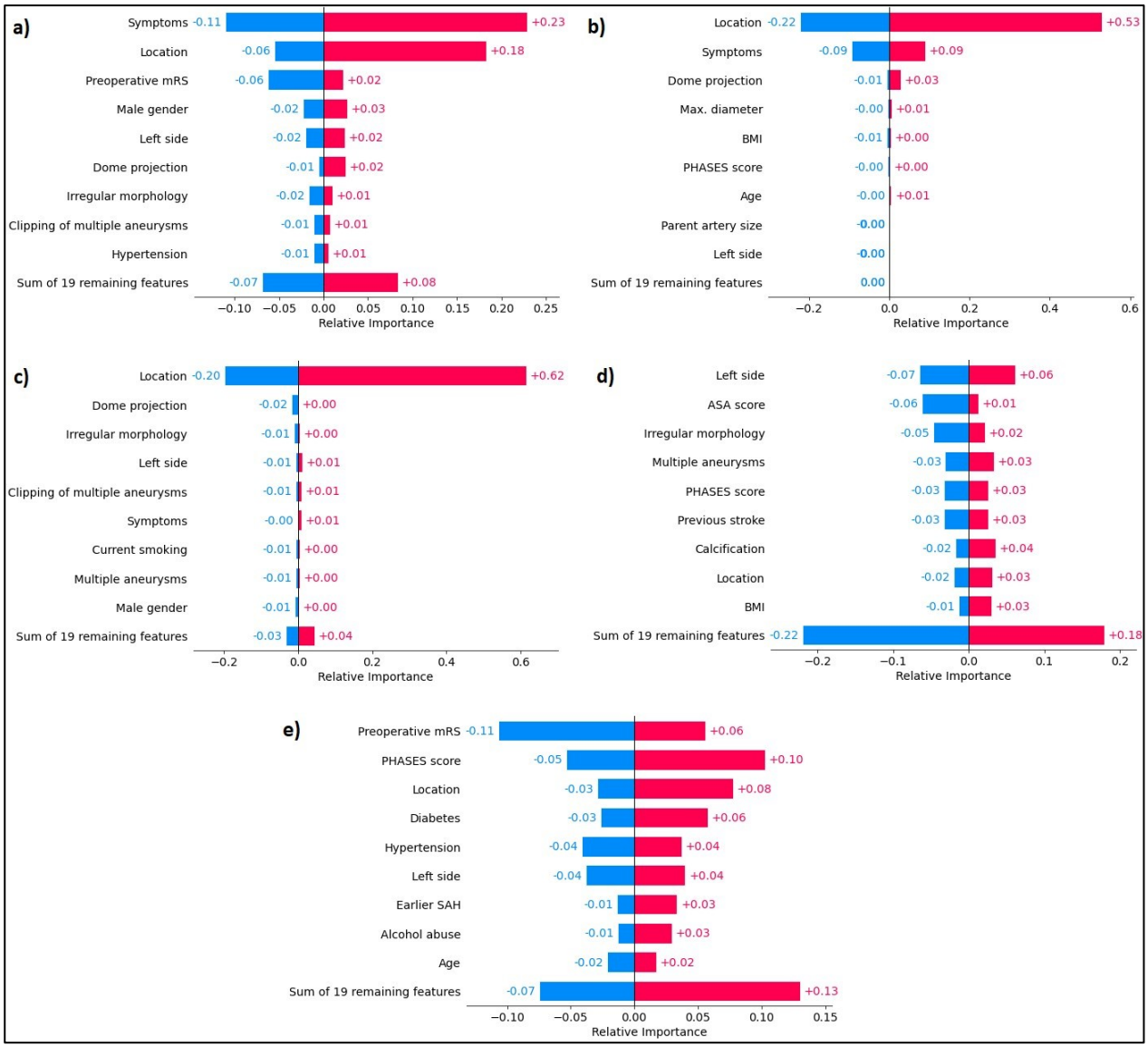

Figure 5: *SHAP feature importance of the best prediction models for each task (a-e). For every feature, negative and positive average contributions are depicted separately, in bluish and reddish hues, respectively. a) mRS >2, b) mRS-difference >1, c) permanent nND, d) transient nND, e) GOS <5. mRS = modified Rankin Scale, BMI = body mass index, nND = new neurological deficit, ADPKD = autosomal dominant polycystic kidney disease, GOS = Glasgow Outcome Scale.*

All the performance metrics are summarized in Table 5.

The external validation set contained 256 patients with a mean age of 57.4 ± 9.6 years. 77.3% of the patients were female and 22.7% male. A detailed summary of the preoperative

patient-specific parameters is shown in Table 2, and the aneurysm-specific characteristics are listed in Table 3. Most of the preoperative parameters differ significantly from the internal data set. In particular, this applies to all parameters that were found most relevant by the SHAP feature importance analysis, namely aneurysm-related symptoms, aneurysm location and preoperative mRS ($p<0.0001$).

A good functional outcome, corresponding to a GOS of ≥ 5, was identified in 237 patients (92.6%). The postoperative mRS was ≤ 2 in 245 patients (95.7%), whereas after subtracting the preoperative baseline mRS, only 9 patients (3.5%) had a worsening in mRS of >1, in the sense of an objectifiable functional deterioration. All the outcome parameters are listed in Table 4. New neurological deficits were not recorded in the external validation set. Similar to the preoperative parameters, the postoperative outcomes also differ significantly from the internal set.

The QDA estimator that best predicted postoperative mRS >2 on our internal test set only achieved a ROC-AUC of 0.61 ± 0.03 in external validation. The LR baseline generalized slightly better to the external set, with a ROC-AUC of 0.66 ± 0.04.

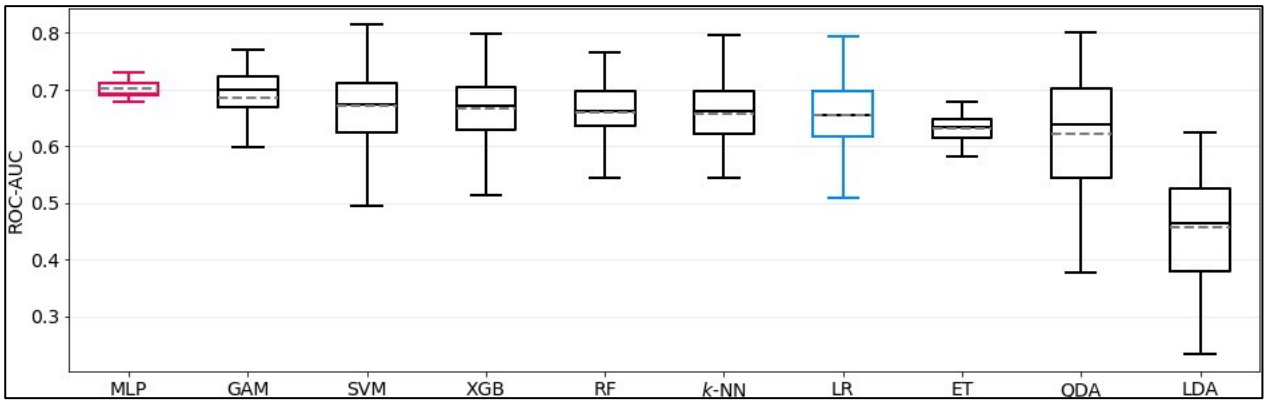

Figure 6: *Bootstrapped test-set ROC-AUC of all models trained to predict postoperative mRS-difference >1, sorted by mean ROC-AUC. MLP is the top-performing model, and LR represents the logistic regression baseline model (both highlighted). mRS = modified Rankin Scale, ROC-AUC = area under Receiver Operating Characteristic curve, MLP = multilayer perceptron, GAM = generalized additive model, SVM = Support Vector Machine, XGB = Extreme Gradient Boosting, RF = Random Forest, KNN = k-Nearest Neighbors, LR = Logistic Regression, ET = Extremely Randomized Trees, QDA = Quadratic Discriminant Analysis, LDA = Linear Discriminant Analysis.*

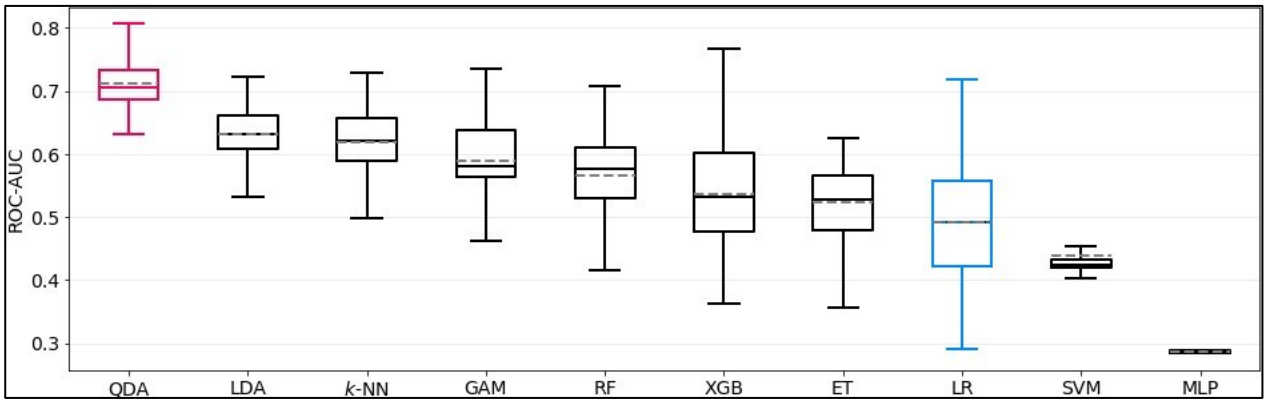

Figure 7: *Bootstrapped test-set ROC-AUC of all models trained to predict permanent new neurological deficit (pnND), sorted by mean ROC-AUC. QDA is the top-performing model, and LR represents the logistic regression baseline model (both highlighted). ROC-AUC = area under Receiver Operating Characteristic curve, QDA = Quadratic Discriminant Analysis, LDA = Linear Discriminant Analysis, KNN = k-Nearest Neighbors, GAM = generalized additive model, RF = Random Forest, XGB = Extreme Gradient Boosting, ET = Extremely Randomized Trees, LR = Logistic Regression, SVM = Support Vector Machine, MLP = multilayer perceptron.*

The MLP estimator that best predicted post- to preoperative mRS difference >1 on our internal test set achieved a ROC-AUC of 0.53 ± 0.01 in external validation. The LR baseline showed equally poor discrimination (0.53 ± 0.03).

The GAM model that best predicted GOS <5 on our internal test set achieved a ROC-AUC of 0.58 ± 0.03 in external validation. It was outperformed by the LR baseline, with 0.62 ± 0.02.

All the performance metrics of external validation are summarized in Table 6. The performance drop of the respective best model and the LR baseline compared to the internal test set is always significant, for each outcome ($p<0.0001$). Figure 10 additionally depicts the ROC-AUC of all trained models on both the internal test set and the external set, illustrating that the best models on the internal test set are always outperformed by other models on the external set. Extra Trees and Random Forests seem to generalize best to the external validation set.

10.1.5. Discussion

In recent years, ML-based predictive models have become increasingly important in medical sciences, including neurosurgery. To date, numerous well-performing prediction models have been published, e.g. for neurooncology[99], spinal research[68,69], and cerebrovascular pathologies. Aneurysm detection using computer-aided diagnosis systems is one example[100-103]. Such models should be regarded as a support or supplement and not as a substitute for the clinical decision process[104,105]. ML has further applications in distinguishing rupture status or rupture risk assessment[72,106,107]. In the study by Zhu et al., ML-based models were shown to be superior to previously established prediction scores (e.g., PHASES score) as well as classic LR analysis[108].

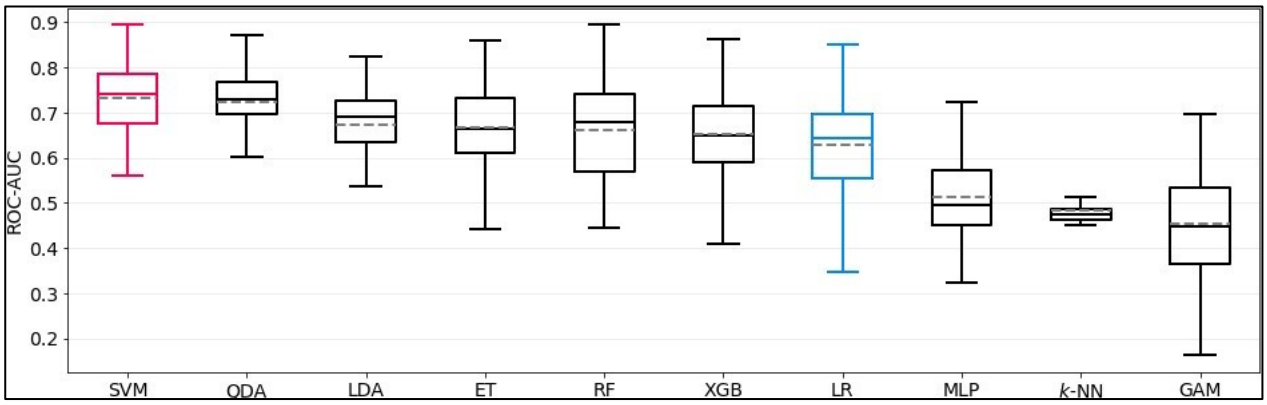

Figure 8: *Bootstrapped test-set ROC-AUC of all models trained to predict transient new neurological deficit (tnND), sorted by mean ROC-AUC. SVM is the top-performing model, and LR represents the logistic regression baseline model (both highlighted). ROC-AUC = area under Receiver Operating Characteristic curve, SVM = Support Vector Machine, QDA = Quadratic Discriminant Analysis, LDA = Linear Discriminant Analysis, ET = Extremely Randomized Trees, RF = Random Forest, XGB = Extreme Gradient Boosting, LR = Logistic Regression, MLP = multilayer perceptron, KNN = k-Nearest Neighbors, GAM = generalized additive model.*

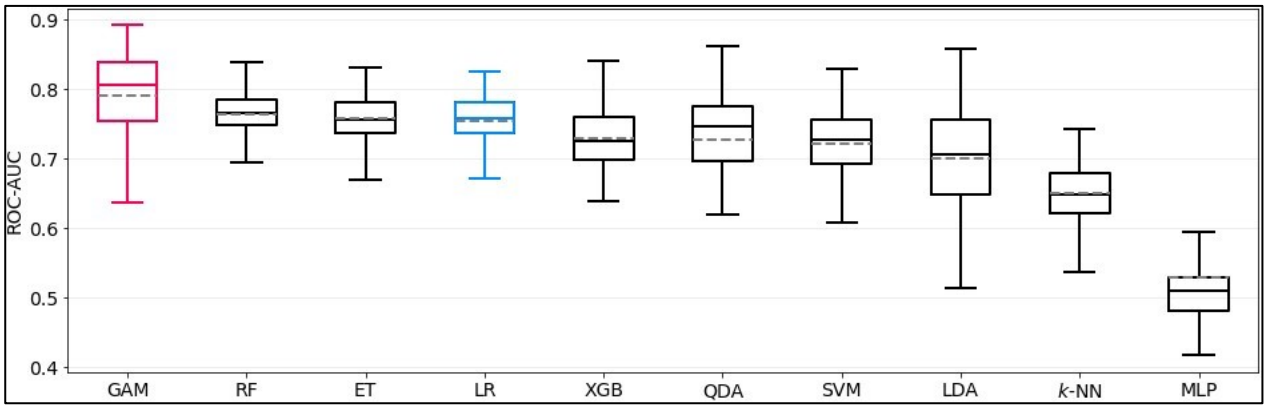

Figure 9: *Bootstrapped test-set ROC-AUC of all models trained to predict GOS <5, sorted by mean ROC-AUC. GAM is the top-performing model, and LR represents the logistic regression baseline model (both highlighted). GOS = Glasgow Outcome Scale, ROC-AUC = area under Receiver Operating Characteristic curve, GAM = generalized additive model, RF = Random Forest, ET = Extremely Randomized Trees, LR = Logistic Regression, XGB = Extreme Gradient Boosting, QDA = Quadratic Discriminant Analysis, SVM = Support Vector Machine, LDA = Linear Discriminant Analysis, KNN = k-Nearest Neighbors, MLP = multilayer perceptron.*

Regarding outcome prediction, several ML models have already been published that focus on functional outcomes after aSAH[74,75,84,86,109,110]. Muscas et al. and Ramos et al. developed relevant models for complication prediction, especially shunt-dependent hydrocephalus and delayed cerebral ischemia, respectively[85,111]. Thus far, prediction models for post-treatment occlusion rates are only available for endovascular-treated aneurysms[112-114]. Postoperative occlusion rates in microsurgically treated aneurysms are traditionally very high[51]. In this series, 98.5% of all treated aneurysms and 100% of those in the test set were completely occluded. Therefore, no prediction models were trained and evaluated for this outcome. Decision-making in diagnosed UIA is complex and always requires balancing the risk of rupture with that of preventive treatment. Strategies to improve risk stratification and outcome prediction remain rare and are therefore highly warranted. Staartjes et al. addressed this issue in their pilot study and were able to demonstrate the feasibility of such predictive models for functional outcomes and postoperative complications[76]. Moreover, Ishankulov et al. published promising predictive models for a functional outcome (mRS) after the treatment of UIAs in a pilot study[77]. However, both studies randomly assigned their patients to either the train or test group (random train-test split)[115].

Owing to the continuous improvement in surgical standards in recent years, we believe that training sets have a clear temporal character, and thus relevant domain shifts must be addressed. Therefore, to guarantee realistic assessments of our prediction models in a clinical setting, we opted to employ a temporal train-test split. Temporal splits allow the approximation of the predictive quality of a model when applied to future patients more accurately than random splits[116], and therefore are the natural candidate for simulating prospective validation in retrospective studies. They do have several drawbacks, though, like producing models with limited generalizability, which necessitates re-training the models on all available data before an actual prospective validation or deployment to clinical practice takes place. Analogous to our modified cross-validation strategy, it may then even be beneficial to pay more attention to more recent samples for further maximizing the generalizability to future data. The temporal validation strategy presented in this work merely seeks to provide honest estimates of what can be expected from a prospective validation. Irrespective of that, any prediction model currently used in clinical practice should be continuously re-evaluated and re-trained when new data become available to account for possible negative effects of domain shifts.

Outcome	Model	ROC-AUC	p-Value	Average Prec.	p-Value	Accuracy	Sensitivity	Specificity	PPV	NPV
mRS > 2	QDA	0.87 ± 0.03*	p<0.0001	0.60 ± 0.13*	p<0.0001	0.72 ± 0.06	0.83 ± 0.08	0.71 ± 0.07	0.24 ± 0.04	0.98 ± 0.01
	Baseline LR	0.77 ± 0.05		0.40 ± 0.08		0.79 ± 0.05	0.51 ± 0.14	0.82 ± 0.06	0.24 ± 0.07	0.94 ± 0.01
mRS-Diff. > 1	MLP	0.70 ± 0.02*	p<0.0001	0.19 ± 0.05	p=0.2561	0.52 ± 0.03	0.74 ± 0.07	0.50 ± 0.04	0.13 ± 0.00	0.95 ± 0.01
	Baseline LR	0.65 ± 0.06		0.19 ± 0.06		0.66 ± 0.07	0.50 ± 0.16	0.67 ± 0.08	0.14 ± 0.03	0.93 ± 0.02
perm. nND	QDA	0.71 ± 0.04*	p<0.0001	0.26 ± 0.08*	p<0.0001	0.60 ± 0.10	0.65 ± 0.24	0.60 ± 0.12	0.11 ± 0.02	0.96 ± 0.02
	Baseline LR	0.49 ± 0.09		0.08 ± 0.02		0.69 ± 0.07	0.19 ± 0.16	0.73 ± 0.08	0.05 ± 0.04	0.92 ± 0.01
trans. nND	SVM	0.73 ± 0.07*	p<0.0001	0.15 ± 0.05*	p=0.0116	0.90 ± 0.03	0.00 ± 0.02	0.97 ± 0.03	0.22 ± 0.41	0.93 ± 0.00
	Baseline LR	0.63 ± 0.11		0.19 ± 0.10		0.74 ± 0.05	0.41 ± 0.19	0.77 ± 0.08	0.12 ± 0.06	0.95 ± 0.02
GOS < 5	GAM	0.79 ± 0.08*	p<0.0001	0.45 ± 0.09	p=0.0879	0.73 ± 0.05	0.69 ± 0.12	0.73 ± 0.06	0.30 ± 0.05	0.93 ± 0.02

	Baseline LR	0.75 ± 0.04		0.43 ± 0.09		0.74 ± 0.05	0.57 ± 0.13	0.77 ± 0.06	0.30 ± 0.06	0.92 ± 0.02

Table 5: *Test-set performance of the best model and baseline logistic regression model for each outcome, displayed as mean ± std.dev. Statistically significant differences between best- and baseline models in terms of ROC-AUC and Average Precision are marked as * (Mann-Whitney U test, alpha=0.05). The QDA and GAM models for mRS >2, permanent nND and GOS <5 perform best in terms of Average Precision, too. mRS = modified Rankin Scale, GOS = Glasgow Outcome Scale, nND = new neurological deficit, LR = logistic regression, QDA = quadratic discriminant analysis, MLP = multilayer perceptron, SVM = support vector machine, GAM = generalized additive model, ROC-AUC = area under receiver operating characteristic curve, PPV = positive predictive value, NPV = negative predictive value.*

Outcome	Model	ROC-AUC	Average Prec.	Accuracy	Sensitivity	Specificity	PPV	NPV
mRS > 2	QDA	0.61 ± 0.03	0.08 ± 0.01	0.57 ± 0.04	0.59 ± 0.06	0.57 ± 0.05	0.06 ± 0.01	0.97 ± 0.01
	Baseline LR	0.66 ± 0.04	0.16 ± 0.04	0.69 ± 0.07	0.55 ± 0.10	0.69 ± 0.07	0.08 ± 0.01	0.97 ± 0.01
mRS-Diff. > 1	MLP	0.53 ± 0.01	0.05 ± 0.01	0.54 ± 0.05	0.44 ± 0.04	0.54 ± 0.05	0.03 ± 0.01	0.96 ± 0.00
	Baseline LR	0.53 ± 0.03	0.11 ± 0.05	0.64 ± 0.09	0.48 ± 0.12	0.65 ± 0.09	0.05 ± 0.01	0.97 ± 0.00
GOS < 5	GAM	0.58 ± 0.03	0.12 ± 0.02	0.59 ± 0.07	0.49 ± 0.13	0.60 ± 0.09	0.09 ± 0.01	0.94 ± 0.01
	Baseline LR	0.62 ± 0.02	0.16 ± 0.03	0.67 ± 0.05	0.47 ± 0.09	0.68 ± 0.06	0.11 ± 0.01	0.94 ± 0.01

Table 6: *External validation performance of the best model (on the internal test set) and baseline logistic model for each outcome, displayed as mean ± std.dev. Note that transient nND was not recorded in the external data, so no results are available for that outcome. mRS = modified Rankin Scale, GOS = Glasgow Outcome Scale, nND = new neurological deficit, LR = logistic regression, QDA = quadratic discriminant analysis, MLP = multilayer perceptron, SVM = support vector machine, GAM = generalized additive model, ROC-AUC = area under receiver operating characteristic curve, PPV = positive predictive value, NPV = negative predictive value.*

Our models showed an excellent or at least acceptable discrimination performance for the most important outcome parameters, such as permanent nND, postoperative mRS, and mRS difference. Currently, ROC-AUC is regarded as a reliable parameter for comparing different ML models[117,118].

In our study, the prediction model for postoperative mRS scores reached a value of 0.87 ± 0.03 and shows therefore excellent discrimination.[119] This is the highest reported ROC-AUC in ML studies investigating postoperative clinical outcomes in patients with UIAs[76].

As not every patient had an mRS score of 0 preoperatively, we further introduced the mRS difference into our models, which may be another clinically relevant outcome parameter.

Our MLP model revealed a ROC-AUC of 0.70 ± 0.02. Similarly, a permanent postoperative neurological deficit may be another important parameter that was predicted with a ROC-AUC of 0.71 ± 0.04. Moreover, compared with classical LR, our models revealed a significantly better performance ($p<0.0001$).

To our knowledge, this is the first study to present ML-based prediction models for functional and clinical outcomes in a large sample of microsurgically treated UIAs using a temporal split.

The pronounced class imbalance in all five outcomes, in conjunction with the relatively small dataset, led to a large variance in the bootstrapped model performance. This also means that the specific train-test split utilized for training and evaluating models can have a huge impact on the final results, as we observed in preliminary experiments with multiple random splits (data not shown). This in turn justifies the nonrandom temporal split.

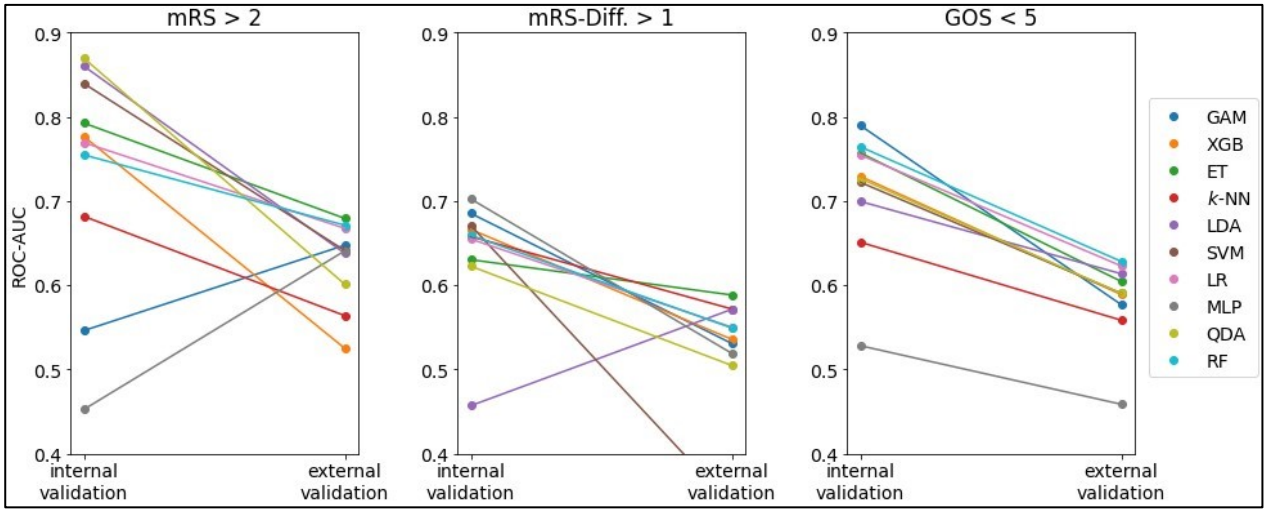

Figure 10: *ROC-AUC of all models on both the internal (left column in each subplot) and external (right column in each subplot) test set. One can clearly observe the pronounced performance drop, especially of the model with the highest ROC-AUC on the internal test set. ROC-AUC = area under Receiver Operating Characteristic curve, mRS = modified Rankin Scale, GOS = Glasgow Outcome Scale, GAM = Generalized Additive Model, XGB = Extreme Gradient Boosting, ET = Extremely Randomized Trees, k-NN = k-Nearest Neighbors, LDA = Linear Discriminant Analysis, SVM = Support Vector Machine, LR = Logistic Regression, MLP = Multilayer Perceptron, QDA = Quadratic Discriminant Analysis, RF = Random Forest.*

So far, only a few neurosurgical ML studies were published with an external validation of their models. Good generalisability of external validation is seen in the radiological diagnosis of UIAs[120] or in the prediction of intracranial aneurysm rupture risk based on multi-omics factors[121]. Fuse et al. published an external validation of their preoperative prediction model for postoperative outcomes after chronic subdural hematoma evacuation and external validation revealed an excellent ROC-AUC of 0.860.[122] However, no external validation of a preoperative prediction model for microsurgically treated UIAs has been published so far.[76,77,113]

In this study, external validation of the best internally validated models shows ROC-AUC values of 0.61, 0.53 and 0.58 respectively for predicting a postoperative mRS >2, a pre- and postoperative difference in mRS >1 point and a GOS <5. This is a poor discrimination of the models in the external validation and therefore the models are not applicable to this tested external dataset from the Department of Neurosurgery at the University Medical Centre Hamburg-Eppendorf.

The prediction models are all based on preoperative parameters. Our SHAP analysis (see Figure 5a-e) showed that especially the parameters location, symptoms and preoperative mRS have a strong influence on the best-performing models. When these parameters are compared between the internal training and test set and the external validation set (p-values in Table 2 and Table 3), a significant difference in the underlying population can be seen. The reason for this difference remains unknown and points to the importance of individual centre-specific factors, such as different surgical strategies among different surgeons and

different intra- and perioperative setups. As all of the models are trained on the data in a specific setup of a microsurgical high-volume centre, our results clearly show that it has only good predictability for this particular centre. Moreover, our results also clearly demonstrate, that the parameters obtained in the SHAP analysis can be used to check in advance whether a model is not applicable to a certain population. Trustworthiness and transparency as part of a safety net are important for the use of predictive models. Careful validation and adaptation are important when implementing predictive tools in different healthcare settings.

Consistent with the typical distribution of UIAs, this surgical cohort included a large number of middle cerebral artery (MCA) bifurcation aneurysms (n=309). Aside from Nussbaum et al., it is therefore one of the largest published monocentric registries of microsurgically treated unruptured MCA bifurcation aneurysms[51]. Microsurgical treatment by clipping remains the gold standard for the management of unruptured MCA bifurcation aneurysms, reflecting the clinical importance of our data analysis.

10.1.6. Limitations

The retrospective nature of the data collection has a limiting effect on the quality of the data registry. All the prediction models were based on a monocentric database over a period of 19 years. Since there were several neurosurgeons with different experiences involved over such a long time, the good results indicate robust predictive models. The diagnostic options and, consequently, the treatment indications for UIAs have changed over the long observation period from 2002 to 2020 and can thus be considered a potential selection bias.

In addition, any prediction model for postoperative outcome parameters based on preoperative parameters underestimates the intraoperative component. The experience or individual decisions of the treating neurosurgeon might have an impact on the outcome. By definition, intraoperative parameters would be possible confounders and thus may not be taken into account in preoperative prediction models.

The chosen outcome parameters were ascertainable and easily comparable. For comprehensive neurocognitive outcome evaluation, a detailed postoperative neurocognitive examination is required.

From a modeling perspective, the feature set was limited to a handful of numerical and categorical variables that could be acquired easily preoperatively. It lacks unstructured information such as imaging data, free-text notes, and medication prescriptions that hold the potential to carry useful information for the prediction tasks considered in this study. Furthermore, one could speculate that ensemble models that combine the decisions of multiple base estimators into one final decision are more accurate than the single-estimator models presented in this study. However, initial experiments with training and tuning ensembles of up to 25 different base estimators led to no or only negligible performance improvements (data not shown) at the cost of considerably more complex, hardly interpretable models.

10.1.7. Conclusion

In conclusion, the results show excellent and acceptable performances in predicting functional and clinical outcomes after microsurgical therapy of UIAs in the internal validation data set, especially for the main outcome parameters mRS and permanent nND. The application of a temporal train-test split is feasible for this specific question and is unique.

Unfortunately, the excellent models could not be generalized in the external validation data set of an independent neurosurgical department due to major differences between the treated patients and aneurysms in the departments.

The implementation of newly available data and the merging of larger databases to form more broad-based predictive models is imperative.

10.2. Global Outcomes for Microsurgical Clipping of Unruptured Intracranial Aneurysms: A Benchmark Analysis of 2245 Cases

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10.2.1. Abstract

10.2.1.1. Background and Objectives

Benchmarks represent the best possible outcome and help to improve outcomes for surgical procedures. However, global thresholds mirroring an optimal and reachable outcome for microsurgical clipping of unruptured intracranial aneurysms (UIA) are not available. This study aimed to define standardized outcome benchmarks in patients who underwent clipping of UIA.

10.2.1.2. Methods

A total of 2245 microsurgically treated UIA from 15 centers were analyzed. Patients were categorized into low- (“benchmark”) and high-risk (“nonbenchmark”) patients based on known factors affecting outcome. The benchmark was defined as the 75th percentile of all centers’ median scores for a given outcome. Benchmark outcomes included intraoperative (eg, duration of surgery, blood transfusion), postoperative (eg, reoperation, neurological status), and aneurysm-related factors (eg, aneurysm occlusion). Benchmark cutoffs for aneurysms of the anterior communicating/anterior cerebral artery, middle cerebral artery, and posterior communicating artery were determined separately.

10.2.1.3. Results

Of the 2245 cases, 852 (37.9%) patients formed the benchmark cohort. Most operations were performed for middle cerebral artery aneurysms (53.6%), followed by anterior communicating and anterior cerebral artery aneurysms (25.2%). Based on the results of the benchmark cohort, the following benchmark cutoffs were established: favorable neurological outcome (modified Rankin scale ≤2) ≥95.9%, postoperative complication rate ≤20.7%, length of postoperative stay ≤7.7 days, asymptomatic stroke ≤3.6%, surgical site infection ≤2.7%, cerebral vasospasm ≤2.5%, new motor deficit ≤5.9%, aneurysm closure rate ≥97.1%, and at 1-year follow-up: aneurysm closure rate ≥98.0%. At 24 months, benchmark patients had a better score on the modified Rankin scale than nonbenchmark patients.

10.2.1.4. Conclusion

This study presents internationally applicable benchmarks for clinically relevant outcomes after microsurgical clipping of UIA. These benchmark cutoffs can serve as reference values for other centers, patient registries, and for comparing the benefit of other interventions or novel surgical techniques.

10.2.1. Introduction

In recent years, performance monitoring and quality assessment have become increasingly important in the medical field. Particularly in surgical disciplines, there is an increased interest in evaluating outcomes after surgery to improve long-term patient safety. Nevertheless, to date, quality measurements are mainly available from national databases or from cohorts of individual centers, which lack a standardized method of analysis and hampers comparisons between different centers and countries.[65,124,125] To address this issue, the concept of benchmarking was introduced to the field of surgery by Staiger et al in 2018.[82] Since then, standardized benchmark outcomes for several surgical techniques have been established.[126-129] Benchmarking represents the best achievable outcome of a given procedure and is the desirable goal to achieve.[82] The ambition to achieve this best possible outcome should lead to a reduction in postoperative morbidity and mortality of patients after surgery and enables a worldwide comparison of defined benchmark cutoffs for certain procedures.[82,130] The methodology and recommendations were further refined in a Delphi process.[130] This standardized method was successfully described for many surgical techniques, such as liver transplantation[129] and pancreaticoduodenectomy[126], with technique-specific outcomes described in addition to general morbidity and mortality. These efforts provide reason to expect that surgical benchmarking will emerge as an effective tool to collect patient-reported outcomes in a standardized format and to improve outcomes in the long term.[131] However, the concept of benchmarking has not yet been applied to neurosurgical interventions.

One challenging neurosurgical procedure is microsurgical clipping of unruptured intracranial aneurysms (UIA). Due to the increasing use of MRI and computed tomography (CT) diagnostics, UIAs are being diagnosed with increasing frequency and affect 3% - 5% of the adult population.[15,132,133] Because UIA rupture is known to occur in up to 6.0% of patients during a follow-up period of 24 months, preventive microsurgical or endovascular treatment of aneurysms is a potential option, although the optimal choice of treatment poses challenges to clinicians.[2,134,135] Available data report a risk of unfavorable outcome in 6.7% and a mortality of 1.7% after microsurgical clipping.[136] However, the literature on microsurgical treatment of UIA is heterogeneous and does not follow standardized methods, making comparison with other modalities such as endovascular treatment difficult.

With this in mind, we aimed to define the best possible outcome by assessing benchmark cutoffs for microsurgical clipping of UIA in 15 centers on 4 continents. We selected 23 patient-centered perioperative outcome variables and defined benchmark cutoffs for each variable. These results can serve as a reference for other centers by establishing milestones to strive for and facilitating comparison with other treatment modalities or novel surgical techniques and even help in the discussion of centralization of complex procedures to ensure quality associated with case volume.

10.2.2. Methods

10.2.2.1. Study design

The aim of this study was to establish benchmarks for microsurgical clipping of untreated UIA and followed the standardized methodology published by Staiger et. al.[82] We performed a multicenter, retrospective cohort study based on institutional databases. The patient population was stratified according to their preoperative risk profile, using defined high-risk criteria (Figure 11). Once a patient fulfilled a single high-risk criterion, he was assigned to the high-risk (hereafter referred as “nonbenchmark”) cohort. Consequently, patients not fulfilling a high-risk criterion were used to define the low-risk (hereafter referred as “benchmark”) cohort (Figure 11).

Next, outcomes were defined for specific variables covering surgery- and aneurysm-related outcome. For each outcome, a benchmark cutoff (indicating the "best achievable" outcome) was calculated as the 75th percentile of the median values for all centers separately for the benchmark and nonbenchmark cohorts.

The study was registered with ClinicalTrials.gov (NCT 05029947), and ethical approval was granted by the Medical Ethics Committee of the Hamburg Medical Association (2021-300063-WF). A patient consent exemption was granted because of the retrospective nature of the study. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.[137]

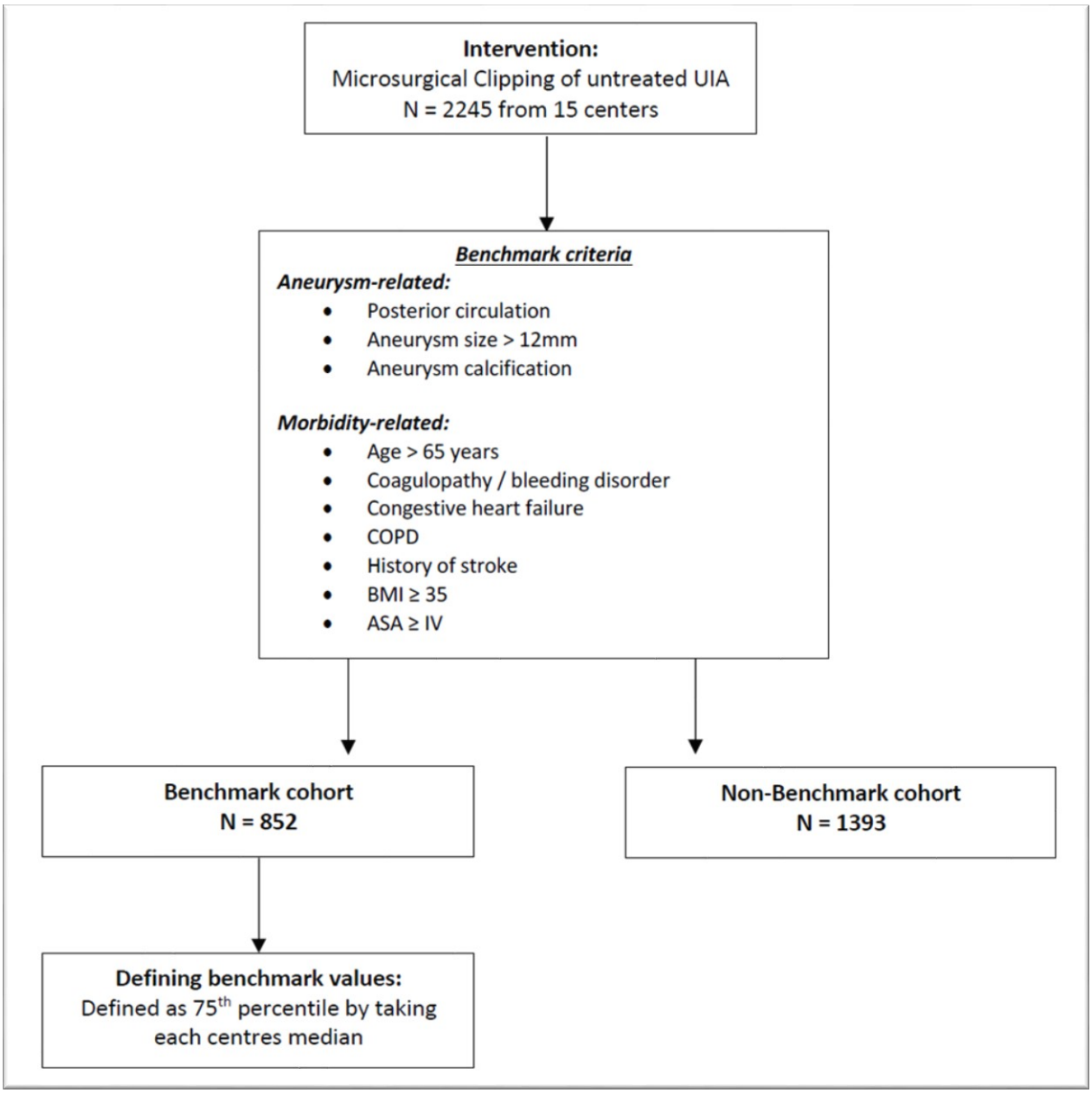

Figure 11: *Study flow diagram.*

10.2.2.2. Patient and Hospital Selection

The final collaborative consortium included 15 centers: 7 from Europe (Hamburg, Berlin, Munich, Mainz (all Germany), Vienna, Linz (all Austria), Milan (Italy)), 5 from North America (Phoenix, San Francisco, San Antonio, Thomas Jefferson Philadelphia, and Penn Medicine Philadelphia (all United States of America)), 2 from Asia (Novosibirsk (Russian Federation), Pohang (South Korea)) and 1 from South America (Sao Paulo (Brazil)). All centers were

specialized in cerebrovascular treatment defined as possibility for open and endovascular treatment as well as availability of neurosurgical intensive care unit (ICU) ward. From the 15 included centers, consecutive patients who were above 18 years of age and underwent elective microsurgical clipping of untreated UIA between January 2016 and December 2020 were selected. Additionally, the number of endovascular-treated UIA in each center during the study period was recorded.

10.2.2.3. Performance Metrics of Benchmarking

Aiming for a homogeneous group of patients as a mandatory prerequisite for benchmarking, we defined high-risk criteria (Figure 11), which are known factors that negatively affect outcomes after microsurgical clipping of UIA: age at surgery above 65 years, aneurysm of the posterior circulation, aneurysm diameter above 10 mm, aneurysm calcification, irregular aneurysm configuration, chronic obstructive pulmonary disease, coagulopathy or bleeding disorder, history of congestive heart failure, history of stroke, American Society of Anesthesiology physical status of IV or higher, and body mass index above 40 kg/m^2.[136,138-145] After having defined the cohort of benchmark patients, which accordingly had a "low-risk profile", these were used to determine benchmark cutoffs representing the following clinically relevant outcomes: operating duration, blood transfusion, intraoperative aneurysm rupture, wrapping adjunct to clipping, any deviation from the ideal postoperative course, stroke, surgical site infection, meningitis, hydrocephalus, cerebral vasospasm, intracerebral hemorrhage, subdural hematoma, new-onset seizure, pulmonary or cardiac complication, pulmonal embolism, new motor or sensory deficit, new aphasia, length of hospital and ICU stay, in-hospital mortality, and aneurysm occlusion assessed by CT angiography or digital subtraction angiography. In addition, the neurological outcome was assessed using the modified Rankin Scale (mRS) by the treating neurosurgeon. Benchmark cutoffs, calculated as the 75th percentile of each center's median, were used to indicate the best achievable outcomes.

10.2.2.4. Statistical Analysis

As first step we calculated the median values of continuous parameters and the proportional values of categorical variables for each participating center as described previously.[82] Next,

the median and IQR of center-specific values were calculated. As determined in the Delphi process,[130] we selected the 75th percentile as the benchmark cutoff. For further statistical analyses, we performed the Shapiro-Wilk normality test for confirming Gaussian distribution. The 2-tailed Student's t-test or 1-way analysis of variance with post hoc tests was performed for examining pairwise differences of parametric data.

Kaplan-Meier plot was used to visualize the aneurysm closure rates during follow-up and statistical difference was assessed by log-rank test. A p-value less than 0.05 was considered as statistically significant. All analyses were performed using SPSS Inc. (Version 27). Data illustrations were performed using GraphPad Prism 9.

10.2.3. Results

10.2.3.1. Study Population

Data were available for a total of 2245 cases from the 15 centers that participated in this study (Figure 12). Of the 2245 cases, 1675 (74.6%) were women and 570 (25.4%) were men, with a mean (SD) age of 57.3 (11.1) years (Table 7). Most clippings were performed for MCA aneurysms (53.6%), followed by anterior cerebral artery (ACA) and anterior communicating artery (ACOM) aneurysms (25.2%) (Table 7). Of the 2245 cases, 540 (24.1%) patients had more than 1 aneurysm clipped in a single operation, and 77 (3.4%) patients also underwent bypass (Table 7).

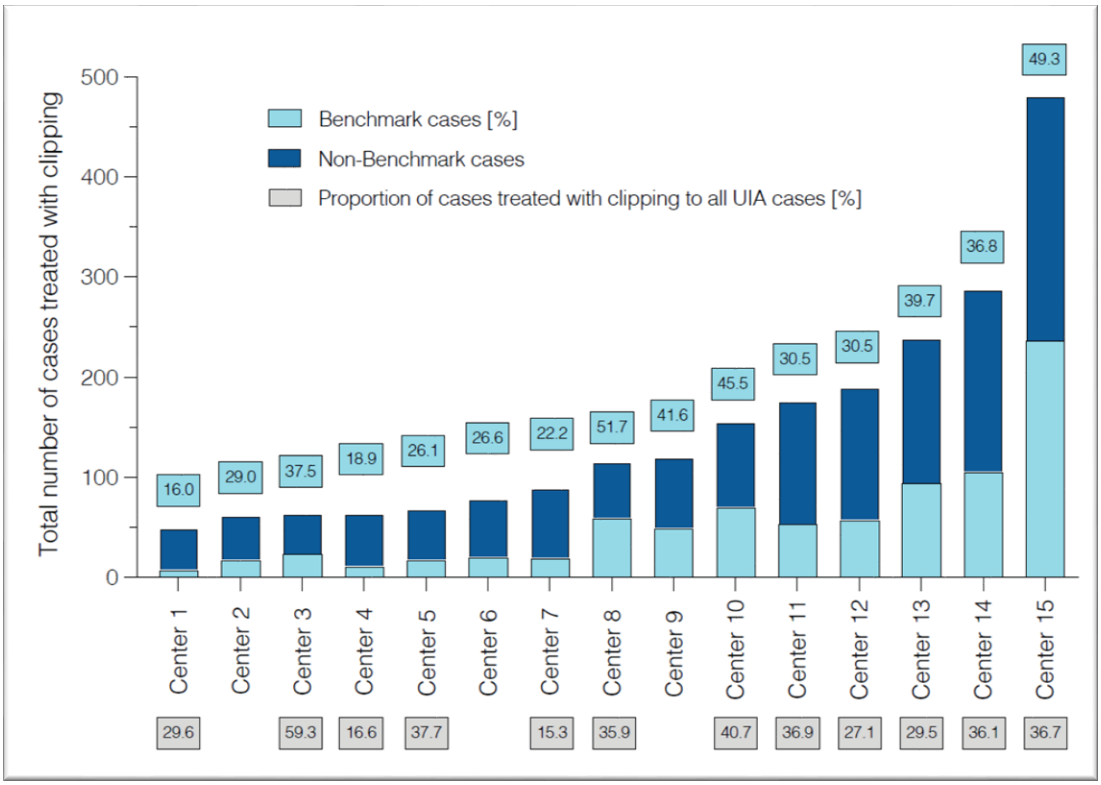

Figure 12: *Variations in the proportion of benchmark cases performed across the 15 centers.*

Characteristic	N=2245	Low-risk cohort (N=852)	High-risk cohort (N=1393)	*P* value
Age, [years], mean (SD)	57.2 (11.1)	53.2 (9.1)	59.8 (11.5)	**<0.01**
Gender, n (%)				
Female	1675 (74.6)	667 (78.3)	1008 (72.4)	**<0.01**
Male	570 (25.4)	185 (21.7)	385 (27.6)	
ASA, n (%)				
I	211 (9.4)	120 (14.1)	91 (6.5)	**<0.01**
II	1169 (52.1)	526 (61.7)	643 (46.2)	**<0.01**
III	814 (36.3)	206 (24.2)	608 (43.6)	**<0.01**
IV	51 (2.3)	0 (0.0)	51 (3.7)	**<0.01**
BMI, [kg/m^2], mean (SD)	27.1 (5.4)	26.4 (4.2)	27.6 (5.4)	**<0.01**
Hypertension, n (%)	1433 (63.8)	474 (55.6)	959 (66.9)	**<0.01**
Congestive heart failure, n (%)	118 (5.3)	0 (0.0)	118 (8.5)	**<0.01**
COPD, n (%)	120 (5.3)	0 (0.0)	120 (8.6)	**<0.01**
Diabetes mellitus, n (%)	210 (9.4)	52 (6.1)	158 (11.3)	**<0.01**
Previous stroke, n (%)	293 (13.1)	0 (0.0)	293 (21.0)	**<0.01**
Coagulopathy, n (%)	47 (2.1)	0 (0.0)	47 (3.4)	**<0.01**
Reason for imaging, n (%)				
Incidental	1840 (82.0)	745 (87.4)	1095 (78.6)	**<0.01**
Cranial nerve deficit	190 (8.5)	54 (6.3)	136 (9.8)	**<0.01**
Thromboembolic event	81 (3.6)	0 (0.0)	81 (5.8)	**<0.01**
Epilepsy	36 (1.6)	9 (1.1)	27 (1.9)	0.11
Migraine	30 (1.3)	2 (0.2)	28 (2.0)	**<0.01**
Aneurysm location, n (%)				
Anterior communicating artery	429 (19.1)	183 (21.5)	246 (17.7)	**0.03**
ACA A1	36 (1.6)	15 (1.8)	21 (1.5)	0.64
ACA A2	50 (2.2)	24 (2.8)	26 (1.9)	0.14
ACA A3	45 (2.0)	18 (2.1)	27 (1.9)	0.76
ACA A4	5 (0.2)	1 (0.1)	4 (0.3)	0.66
MCA M1	759 (33.8)	282 (33.1)	477 (34.2)	0.58
MCA M2	421 (18.8)	161 (18.9)	260 (18.7)	0.91
MCA M3	20 (0.9)	8 (0.9)	12 (0.9)	**<0.01**
MCA M4	3 (0.1)	1 (0.1)	2 (0.1)	0.87
ICA pars cerebralis	94 (4.2)	47 (5.5)	47 (3.4)	**0.02**
ICA pars cavernosus	49 (2.2)	22 (2.6)	27 (1.9)	**0**.37

Ophthalmic artery	116 (5.2)	61 (7.2)	55 (3.9)	**<0.01**
Anterior choroidal artery	39 (1.7)	19 (2.2)	20 (1.4)	0.18
Posterior communicating artery	126 (5.6)	10 (1.2)	116 (8.3)	**<0.01**
Posterior cerebral artery	17 (0.8)	0 (0.0)	17 (1.2)	**<0.01**
Basilar artery	16 (0.7)	0 (0.0)	16 (1.1)	**<0.01**
Vertebral artery	20 (0.9)	0 (0.0)	20 (1.4)	**<0.01**
Aneurysm calcification, n (%)	212 (9.4)	0 (0.0)	212 (15.2)	**<0.01**
Aneurysm morphology, n (%)				
Regular	1646 (73.3)	852 (100.0)	794 (56.9)	**<0.01**
Irregular or lobular	599 (26.7)	0 (0.0)	599 (41.6)	
Aneurysm multiplicity, n (%)	938 (41.8)	372 (43.7)	566 (40.6)	0.16
Neck diameter, [mm], mean (SD)	3.7 (2.1)	3.2 (1.3)	3.9 (2.2)	**<0.01**
Maximum diameter, [mm], mean (SD)	6.7 (4.9)	5.4 (2.4)	7.5 (5.6)	**<0.01**
Size of parent vessel, [mm], mean (SD)	2.3 (0.6)	2.2 (0.5)	2.4 (0.6)	**0.03**
Simultaneous clipping of > 1 aneurysm, n (%)	540 (24.1)	223 (26.2)	317 (22.8)	0.07
Simultaneous bypass, n (%)	77 (3.4)	5 (0.6)	72 (5.2)	**<0.01**

Table 7: *Characteristics of all patients included in this study. ASA: American Society of Anesthesiology score; BMI: body mass index; COPD: chronic obstructive pulmonary disease; ACA: anterior cerebral artery; MCA: middle cerebral artery; ICA: internal carotid artery*

10.2.3.2. Benchmark Cohort

From the main cohort of 2245 cases, 852 (37.9%) patients were identified as benchmark patients after applying the high-risk criteria (Figure 11) and constitute the benchmark cohort (Table 14). The proportion of benchmark patients in the final cohort varied from 16.0% to 49.3% depending on the centre (Figure 12).

In this benchmark cohort, the mean (SD) age was 53.2 (9.1) years, and 78.3% of patients were female. As expected, patients in the benchmark cohort were significantly less multimorbid than nonbenchmark patients ($p < 0.01$). Most aneurysms were detected incidentally (87.4%, Table 7) and were located at the MCA (53.0%). The mean (SD) aneurysm diameter was 5.4 (2.4) mm (Table 7). Of the 852 patients, 372 (43.7%) patients had multiple cerebral aneurysms, of whom 223 (26.2%) had their aneurysms clipped in 1 surgical session. Benchmark outcome cutoffs are shown in Table 8. The median (range) operative time was 196.2 (87.4-319.0) minutes, and intraoperative aneurysm rupture

occurred in 1.6% of cases. The overall complication rate was 13.6% (Table 8). Closure of the clipped aneurysm was achieved in 98.4% at the time of discharge.

	Low-risk cohort *Median (range) across centers*	**Benchmark Cutoff** *75th percentile of medians*	**High-risk cohort** *Median (range) across centers*
Aneurysm-related outcome			
Operating duration	196.2 (87.4-319.0) min	≤ 210.8 min	234.3 (95.0 – 236.0) min
Intraoperative blood transfusion	0.0 (0.0 – 6.4) %	≤ 0.4 %	1.6 (0.0 – 17.3) %
Intraoperative aneurysm rupture	1.6 (0.2 – 11.7) %	≤ 3.8 %	4.1 (0.0 – 12.5) %
Wrapping	0.0 (0.0 – 16.8) %	≤ 6.4 %	4.6 (1.8 – 38.2) %
Occlusion of aneurysm	98.4 (84.5 – 100.0) %	≥ 97.1 %	94.6 (79.2 – 100.0) %
Postoperative outcome			
Any complication	13.6 (1.2 – 39.2) %	≤ 20.7 %	21.9 (3.0 – 48.2) %
In-hospital mortality	0.0 (0.0 – 2.1) %	≤ 0.0 %	0.6 (0.0 – 6.2) %
Favorable neurological outcome mRS ≤ 2	98.5 (90.8 – 100.0) %	≥ 95.9 %	92.7 (84.1 – 98.5) %
New motor deficit	0.0 (0.0 – 7.7) %	≤ 5.9 %	9.1 (1.6 – 27.1) %
New sensory deficit	0.0 (0.0 – 6.3) %	≤ 0.3 %	2.1 (0.0 – 7.1) %
New aphasia	0.0 (0.0 – 5.4) %	≤ 3.2 %	2.6 (0.0 – 6.8) %
Stroke			
Asymptomatic	1.8 (0.0 – 12.9) %	≤ 3.6 %	4.9 (1.3 – 19.9) %
Symptomatic	0.0 (0.0 – 3.4) %	≤ 0.3 %	1.5 (0.0 – 8.7) %
Cerebral vasospasm	0.0 (0.0 – 11.9) %	≤ 2.5 %	3.6 (0.0 – 15.7) %
Intracerebral hemorrhage	0.0 (0.0 – 6.9) %	≤ 1.4 %	2.7 (0.0 – 9.0) %
Subdural hematoma	0.0 (0.0 – 3.2) %	≤ 0.5 %	1.5 (0.0 – 9.8) %
Surgical site infection	0.0 (0.0 – 6.9) %	≤ 2.7 %	1.2 (0.0 – 6.8) %
Reoperation rate	0.0 (0.0 – 9.1) %	≤ 1.7 %	3.9 (0.0 – 19.4) %
New-onset Seizure	0.0 (0.0 – 9.4) %	≤ 0.9 %	3.1 (0.0 – 6.4) %
Pulmonary complication	0.0 (0.0 – 4.8) %	≤ 0.9 %	1.1 (0.0 – 13.1) %
Pulmonal embolism	0.0 (0.0 – 6.9) %	≤ 0.2 %	0.0 (0.0 – 4.3) %
Length of ICU stay	1.0 (0.0 – 2.0) days	≤ 1.0 days	1.0 (0.0 – 4.0) days
Length of hospital stay	6.0 (1.0 – 11.0) days	≤ 7.7 days	6.0 (1.0 – 14.4) days
12 months outcome			
Occlusion of aneurysm	99.0 (80.0 - 100.0) %	≥ 98.0 %	94.5 (43.1 – 100.0) %

Table 8: *Outcome benchmarks after microsurgical clipping of UIA from 15 international centers. ICU: intensive care unit*

10.2.3.3. Benchmark Outcome Cutoffs

We defined 23 benchmark variables to describe the best achievable outcomes (Table 8). Intraoperative benchmark variables were operative time ≤210.8 min, blood transfusion ≤0.4%, aneurysm rupture ≤3.8%, and wrapping ≤6.4%. The benchmark cutoff for length of hospital stay was ≤7.7 days and for length of ICU stay ≤1.0 day. Aneurysm closure is targeted in ≥97.1% at discharge and in ≥98.0% 12 months after surgery. When the outcomes of the nonbenchmark cohort were analyzed, 18 of 23 (78.3%) benchmark values did not reach the cutoff confirming correct stratification of the main cohort (Table 8, Table 9).

	Low-risk cohort *Interquartile range*	**Benchmark Cutoff** *75th percentile of medians*
Aneurysm-related outcome		
Operating duration	162.3 – 210.8 min	≤ 210.8 min
Intraoperative blood transfusion	0.0 – 0.4 %	≤ 0.4 %
Intraoperative aneurysm rupture	0.0 – 3.8 %	≤ 3.8 %
Wrapping	0.0 – 6.4 %	≤ 6.4 %
Occlusion of aneurysm	97.1 – 98.3 %	≥ 97.1 %
Postoperative outcome		
Any complication	6.7 – 20.7 %	≤ 20.7 %
In-hospital mortality	0.0 – 0.0 %	≤ 0.0 %
Neurological outcome mRS ≤ 2	95.9 – 100.0 %	≥ 95.9 %
New motor deficit	0.4 – 5.9 %	≤ 5.9 %
New sensory deficit	0.0 – 0.3 %	≤ 0.3 %
New aphasia	0.0 – 3.2 %	≤ 3.2 %
Stroke		
Asymptomatic	0.2 – 3.6 %	≤ 3.6 %
Symptomatic	0.0 – 0.3 %	≤ 0.3 %
Cerebral vasospasm	0.0 – 2.5 %	≤ 2.5 %
Intracerebral hemorrhage	0.0 – 1.4 %	≤ 1.4 %

Subdural hematoma	0.0 – 0.5 %	≤ 0.5 %
Surgical site infection	0.2 – 2.7 %	≤ 2.7 %
Reoperation rate	0.0 – 1.7 %	≤ 1.7 %
New-onset Seizure	0.0 – 0.9 %	≤ 0.9 %
Pulmonary complication	0.1 – 0.9 %	≤ 0.9 %
Pulmonal embolism	0.0 – 0.2 %	≤ 0.2 %
Length of ICU stay	1.0 – 1.0 days	≤ 1.0 days
Length of hospital stay	3.8 – 7.7 days	≤ 7.7 days
12 months outcome		
Occlusion of aneurysm	98.0 – 100.0 %	≥ 98.0 %

Table 9: *Interquartile range (25th to 75th percentile) of outcome benchmarks in the low-risk cohort. ICU: intensive care unit*

10.2.3.4. Neurological Status After Microsurgical Clipping

Patients were assessed during follow-up using the mRS (Figure 13). A favorable neurological outcome was defined as mRS ≤2, which was 99.52% in the benchmark cohort before surgery (Figure 13). Of these benchmark patients, 4.1% had an unfavorable neurological status (mRS >2) at the time of discharge, with an in-hospital mortality of 0.62%. During follow-up, neurological recovery was seen in many patients, whereas the rate of mRS >2 decreased to 1.99% at 12 months and 2.03% at 24 months after surgery (Figure 13). In conclusion, 97.98% of benchmark patients had satisfactory neurological outcome at 24 months after surgery. Higher rates of unfavorable neurological outcome were observed in the nonbenchmark patients (Figure 13).

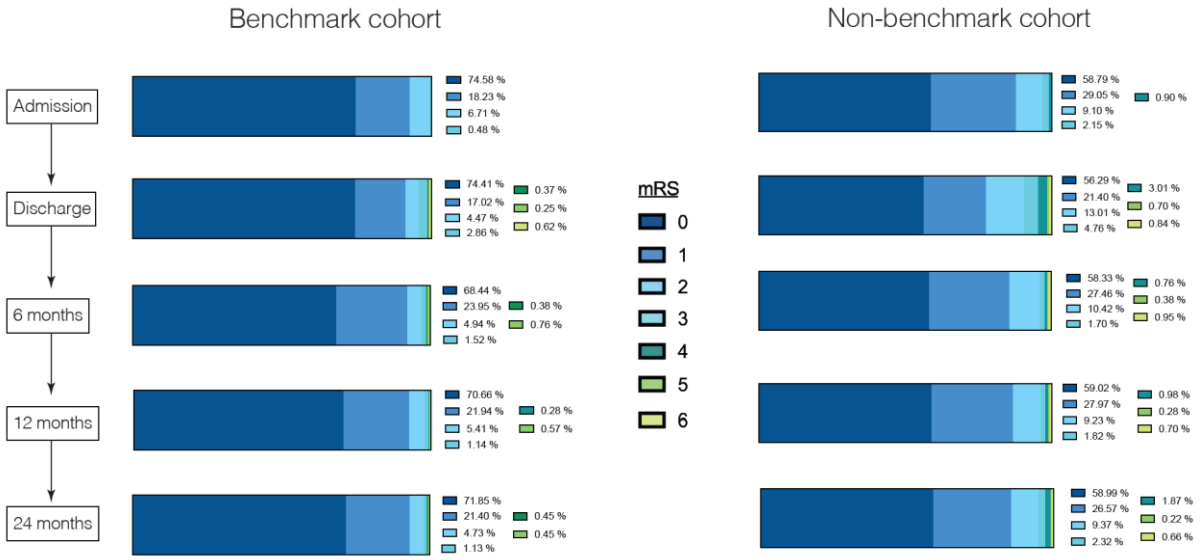

Figure 13: *Stacked bar charts of modified Rankin scale (mRS) results at admission, discharge, 6 months, 12 months, and 24 months in the a) benchmark and b) nonbenchmark cohort after surgical clipping.*

10.2.3.5. Aneurysm Occlusion

To further describe surgical success after microsurgical clipping, the rate of aneurysm occlusion is undeniably an important parameter, especially when comparing different treatment modalities. To investigate this aspect, we documented the closure rates at discharge and during follow-up in 1091 (48.6%) patients. In 364 benchmark patients, the benchmark cutoffs for aneurysm closure of ≥97.1% at the time of discharge and ≥98.0% 12 months after surgery was calculated (Table 8). Aneurysm closure rates were highest after clipping of MCA aneurysms and lowest for posterior communicating (PCOM) aneurysms (Table 10). After exclusion of aneurysms of the posterior circulation and PCOM, comparable aneurysm closure rates were seen between benchmark and nonbenchmark patients during follow-up (p = 0.17, Figure 14).

Feature	Benchmark cutoff (75th percentile of centers median)		
	ACOM / ACA (N = 241)	**MCA (N = 452)**	**PCOM (N = 10)**
Aneurysm-related outcome			
Operating duration	≤ 256.0 min	≤ 306.2 min	≤ 248.9 min
Intraoperative blood transfusion	≤ 0.1 %	≤ 0.1 %	≤ 0.4 %
Intraoperative aneurysm rupture	≤ 1.3 %	≤ 5.8 %	≤ 4.7 %
Wrapping	≤ 0.0 %	≤ 7.4 %	≤ 0.1 %
Occlusion of aneurysm	≥ 94.8 %	≥ 97.6 %	≥ 88.2 %
Postoperative outcome			
Any complication	≤ 30.1 %	≤ 21.9 %	≤ 23.9 %
In-hospital mortality	≤ 0.0 %	≤ 0.0 %	≤ 0.0 %
New motor deficit	≤ 2.4 %	≤ 3.2 %	≤ 7.3 %
New sensory deficit	≤ 0.0 %	≤ 0.2 %	≤ 0.2 %
New aphasia	≤ 3.9 %	≤ 6.4 %	≤ 1.6 %
Stroke			
Asymptomatic	≤ 5.9 %	≤ 2.4 %	≤ 4.6 %
Symptomatic	≤ 0.2 %	≤ 0.0 %	≤ 0.3 %
Cerebral vasospasm	≤ 0.1 %	≤ 4.1 %	≤ 0.0 %
Intracerebral hemorrhage	≤ 3.2 %	≤ 2.1 %	≤ 3.8 %
Subdural hematoma	≤ 0.3 %	≤ 0.2 %	≤ 2.9 %
Surgical site infection	≤ 0.5 %	≤ 3.2 %	≤ 0.3 %
Reoperation rate	≤ 0.0 %	≤ 1.1 %	≤ 1.3 %
New-onset Seizure	≤ 2.3 %	≤ 0.0 %	≤ 0.0 %
Length of ICU stay	≤ 1.0 days	≤ 1.0 days	≤ 1.0 days
Length of hospital stay	≤ 8.6 days	≤ 7.4 days	≤ 4.4 days

Table 10: *Outcome benchmarks stratified according to aneurysm location. ICU: intensive care unit*

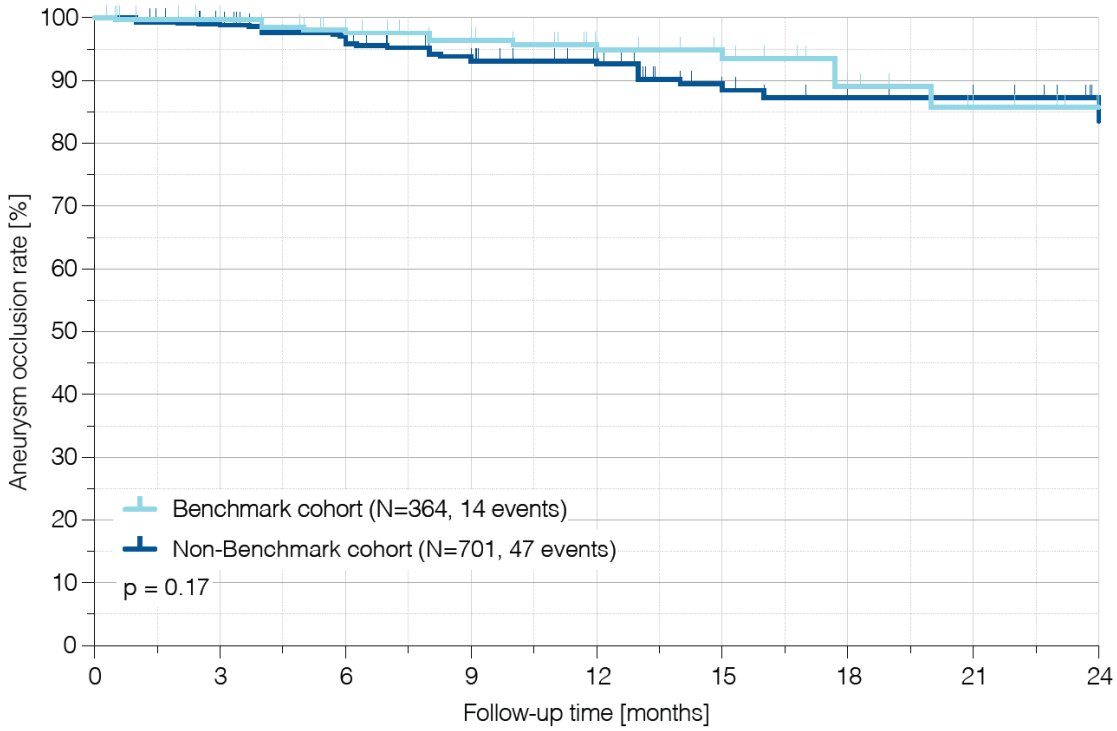

Figure 14: *Representation of occlusion rates from time of discharge until 24 months after surgical clipping. Aneurysms of the posterior circulation and the posterior communicating artery were excluded in this analysis.*

10.2.3.6. Location-Specific Benchmark Values

Because it is well known that the outcome after clipping may differ depending on the location of the aneurysm and therefore influences the decision for or against microsurgical treatment, we further subdivided the benchmark cohort depending on the location of the aneurysm. Table 10 shows the three most treated aneurysm localizations in our patient cohort: ACOM/ACA, MCA, and PCOM. As done previously, we calculated separate benchmark cutoffs for each localization using the benchmark cohort. This showed that aneurysms of the ACOM/ACA and PCOM had shorter operative times, less temporary vessel occlusion, and less intraoperative aneurysm rupture (Table 10). Nevertheless, the rates of overall complication, stroke, and intracerebral hemorrhage were lowest after clipping of MCA aneurysms (Table 10).

10.2.3.7. Correlation of the Benchmark Proportions With the Centers' Volume

To further understand the differences in the proportions of benchmark cases between centers, we correlated them with the number as well as the proportion of cases that were treated with clipping (Figure 15). This showed an increased proportion of benchmark cases in centers with higher case volume (p = 0.03, Figure 15A) and proportion of cases treated with clipping when compared proportionally with endovascular cases (p = 0.09, Figure 15B). Nevertheless, there was no correlation between the percentage of cases treated with clipping and the number of endovascular patients (p = 0.36, Figure 15C), suggesting that the preference for a particular method depends on the center's practice rather than the overall caseload.

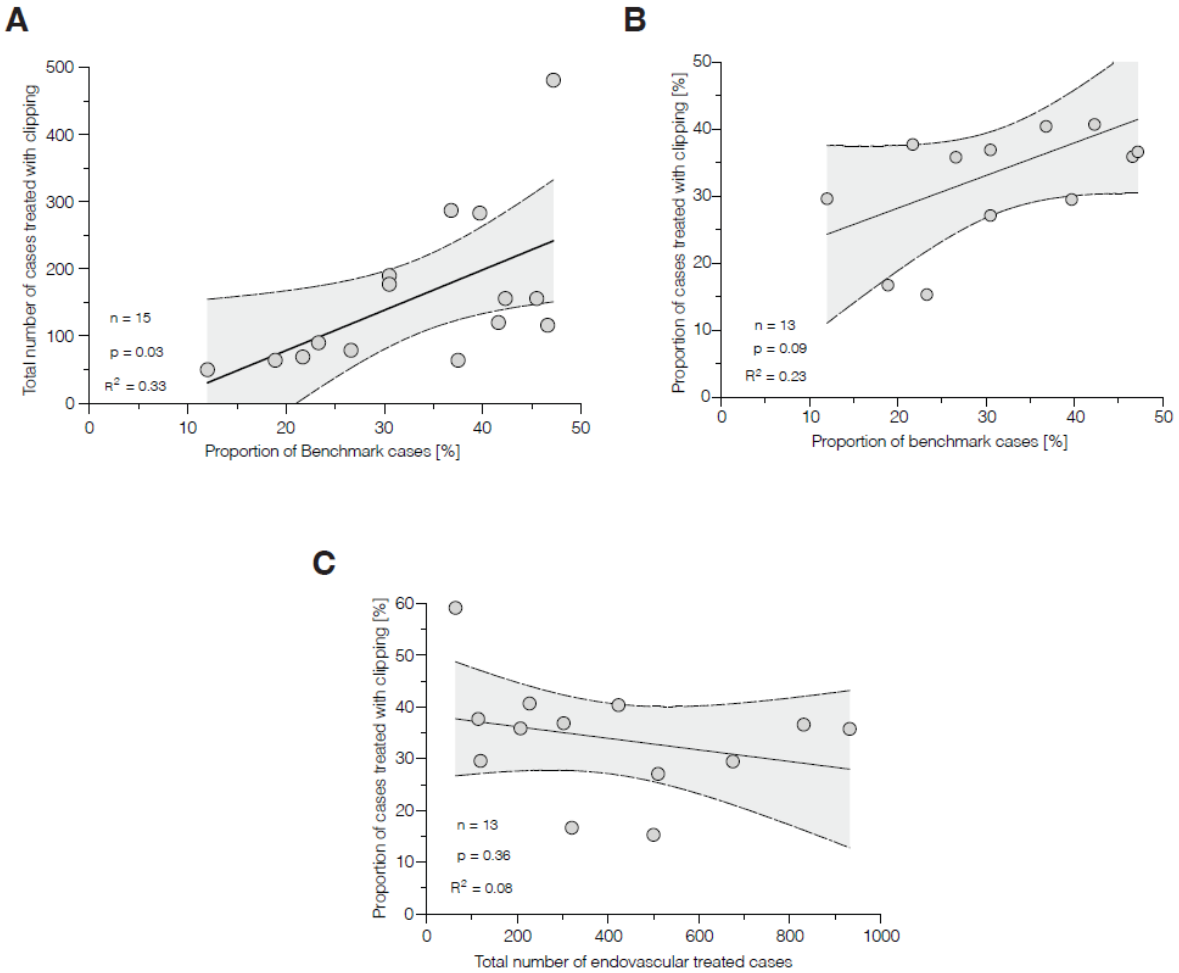

Figure 15 (A-C): *Correlation between proportion of benchmark cases and* ***A)*** *total number of cases treated with clipping in 15 centers, and* ***B)*** *percentage of cases treated with clipping to all UIA cases in 13 centers.* ***C)*** *Correlation between percentage of cases treated with clipping and total number of endovascular treated patients.*

10.2.4. Discussion

Although surgery is an essential part of UIA treatment and outcomes are of great importance to patients, there is no standardized reporting of surgical outcomes. This multicenter study describes the best possible outcomes after microsurgical clipping of UIA using an international cohort by establishing benchmark cutoffs for several outcome variables. In addition, we report the expected neurological outcome and location-specific aneurysm closure rate up to 2 years after treatment.

Intracranial aneurysms are diagnosed with increased frequency in recent years because of improved imaging.[15] Because of mostly absent symptoms, as in our study, but a risk for growth and associated increasing rupture risk, the optimal management of a UIA presents clinicians with challenging decisions.[138,146,147] For this decision making, it is highly relevant to know what outcome can be expected after treatment. Therefore, with this study we present internationally applicable benchmark cutoffs, which may be considered in the process of decision-making, may serve to reflect on the performance of any given center in the context of certifications, and allow for comparison between alternative treatment modalities and new endovascular technologies.

To test the internal validity of the benchmarks, we compared the high-risk, nonbenchmark patients with the defined benchmark cutoffs and observed that the median of the nonbenchmark cohort was inferior to the cutoff in most outcomes. Therefore, the high-risk criteria, and outcomes with cutoffs can be assessed as sensitive to represent the best possible outcome. The literature to date on the complication rates after microsurgical treatment of unruptured aneurysms is very heterogeneous, so that morbidity varies between 4.1% and 10.9% and the mortality between 0.5% and 2.6%.[136,148-151] This variation is mainly due to a heterogeneous patient population and different proportions of the different

aneurysm locations. Most of the data presented here fit well into previous studies, for example, the low mortality rate or a benchmark cutoff of ≤3.8% for intraoperative aneurysm rupture.[136,151] Complementary to the current literature, we present the neurological outcome assessed by the mRS up to 24 months after clipping. An unfavorable neurological outcome (mRS ≥3) of 4.1% at discharge and 2.03% at 24 months after clipping demonstrates an acceptable outcome and correlates with the previous findings of Wiebers and colleagues.[138]

Another benchmark variable of particular interest is length of hospital stay after clipping, which in our study has a benchmark cutoff of ≤7.7 days. Given the ambition to reduce health care costs worldwide in recent years and, consequently, to shorten the length of stay as one major cost factor,[152] this cutoff seems comparatively long. Recent studies have described a significant decrease in length of stay after management of an UIA from approximately 8-5 days within the past 20 years in the United States.[153,154] However, this strong trend is not evident from administrative databases of European countries with, in addition, generally longer hospital stays after interventional procedures when compared to U.S. hospitals.[155,156] Because our study reflects data from centers on 4 continents, the cutoff represents a global practice pattern but is not specific to any healthcare system. Nevertheless, it is highly conceivable that the cutoffs presented here can be transferred to national registries (such as National Surgical Quality Improvement Program)[157] in future studies and serve as reference values. A direct calculation of benchmark cutoffs from different national registries is not recommended in view of inhomogeneous variables in international comparison and often limited postoperative follow-up (eg, 30-day outcome).[131]

An ongoing discussion is the choice between microsurgical or endovascular aneurysm closure.[15,134] The paucity of randomized controlled trials hampers the comparison of treatment risks and general recommendations in favor of one treatment modality or another.[124,146,151] Recent pooled analyses were able to reveal location-specific risk factors, such as an increased risk of complications in posterior circulation aneurysms for microsurgical therapy or for broad-neck aneurysm for endovascular therapy.[140] To further reflect location-specific outcomes after microsurgical clipping, benchmark cutoffs for different aneurysm locations are reported separately in our study. These can be used to

compare the location-specific outcome with that of other modalities in more detail and can aid in decision-making.

In addition, our study provides data on aneurysm closure rates for various time points up to 2 years after surgical clipping. This is a valuable contribution to the current literature, because data on occlusion rates are mostly lacking in publications investigating surgically treated aneurysms.[158,159] A meta-analysis by Kotowski et al[136] found that 82.2% of clipped aneurysms had missing data for closure rate. Of the available data, an overall closure rate of 91.8% was reported although the modality of assessment was mostly unclear.[136] Another meta-analysis by Smith et al[160] examined unruptured MCA aneurysms which reported failure of aneurysm closure in 3.0% of surgically treated cases, assessed by postoperative digital subtraction angiography. Our study sets the benchmark cutoff for aneurysm closure at ≥97.1% at discharge and ≥98.0% at 24 months in benchmark patients, as assessed by CT angiography, but also provides separate closure rates for ACOM, MCA, and PCOM aneurysms. These data demonstrate excellent closure rates for surgically treated ACOM, ACA, and MCA aneurysms both postoperatively and 12 months after clipping. When putting these data into context of current literature, these occlusion rates are superior to endovascular-treated aneurysm and aid in the decision-making on the right treatment depending on the aneurysm localization.[161-164]

10.2.5. Limitations

The present work is subject to limitations. First, this study includes patients from a retrospective data analysis rather than a prospective randomized clinical trial. These data may have been collected and recorded differently at different sites. Second, we focused on surgical outcome after index surgery with a follow-up period of 24 months and could not report on long-term outcome and the failure of aneurysm occlusion after this period. In addition, the high number of patients lost to follow-up must be mentioned at this point. Third, we did not consider the number of cases performed per neurosurgeon but only per center, which needs to be investigated in further studies.

10.2.6. Conclusion

In conclusion, this global multicenter study is the first to apply the concept of benchmarking in microsurgical clipping of UIA and to present internationally valid benchmark cutoffs for key outcomes. These cutoffs reflect the surgical and neurological outcome after clipping for different subgroups and can serve as reference values for other interventions as well as for comparing potential benefits of future techniques.

10.3. Microsurgical Clipping of Unruptured Anterior Circulation Aneurysms-A Global Multicenter Investigation of Perioperative Outcome

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10.3.1. Abstract

10.3.1.1. Background and Objectives

Microsurgical aneurysm repair by clipping continues to be highly important despite increasing endovascular treatment options, especially because of inferior occlusion rates.

This study aimed to present current global microsurgical treatment practices and to identify risk factors for complications and neurological deterioration after clipping of unruptured anterior circulation aneurysms.

10.3.1.2. Methods

Fifteen centers from 4 continents participated in this retrospective cohort study. Consecutive patients who underwent elective microsurgical clipping of untreated unruptured intracranial aneurysm between January 2016 and December 2020 were included. Posterior circulation aneurysms were excluded. Outcome parameters were postsurgical complications and neurological deterioration (defined as decline on the modified Rankin Scale) at discharge and during follow-up. Multivariate regression analyses were performed adjusting for all described patient characteristics.

10.3.1.3. Results

Among a total of 2192 patients with anterior circulation aneurysm, complete occlusion of the treated aneurysm was achieved in 2089 (95.3%) patients at discharge. The occlusion rate remained stable (94.7%) during follow-up. Regression analysis identified hypertension ($p<0.02$), aneurysm diameter ($p<0.001$), neck diameter ($p<0.05$), calcification ($p<0.01$), and morphology ($p=0.002$) as pre-existing risk factors for postsurgical complications and neurological deterioration at discharge. Furthermore, intraoperative aneurysm rupture (OR 2.863 (CI 1.606 – 5.104); $p<0.01$) and simultaneous clipping of more than 1 aneurysm (OR 1.738 (CI 1.186 – 2.545); $p<0.01$) were shown to be associated with an increased risk of postsurgical complications. Yet, none of the surgical-related parameters had an impact on neurological deterioration. Analyzing volume-outcome relationship revealed comparable complication rates ($p=0.61$) among all 15 participating centers.

10.3.1.4. Conclusion

Our international, multicenter analysis presents current microsurgical treatment practices in patients with anterior circulation aneurysms and identifies preexisting and surgery-related risk factors for postoperative complications and neurological deterioration. These findings

may assist in decision-making for the optimal therapeutic regimen of unruptured anterior circulation aneurysms.

10.3.2. Introduction

Unruptured intracranial aneurysms (UIAs) are detected incidentally at an increasing rate because of improved quality and higher frequency of neuroimaging for nonspecific symptoms.[15,132,133] To date, several scores are available for risk stratification of affected patients to facilitate the decision for or against the necessity of aneurysm repair.[8,49] Owing to recent technical innovations and improvements of endovascular therapy options, patients' characteristics and indications for open procedures have changed.[166] For instance, aneurysms of the posterior circulation as a complication-prone subgroup are now most commonly treated by endovascular procedures.[167,168]

However, surgical clipping continues to be of great importance in the treatment of incidental aneurysms, especially in complex, irregular, wide-neck aneurysms. A major advantage of microsurgical aneurysm repair is a high and long-lasting occlusion rate[169] and the lack of need for subsequent anticoagulation, often necessary after placement of endovascular devices. Recently, technical innovations in neurosurgery and neuroanesthesia (eg, quantitative intraoperative fluorescence angiography) have pushed the limits of surgical feasibility and safety[170], thus expanding the repertoire of open aneurysm repair.

In this study, we investigate the current practice of microsurgical aneurysm repair in specialized neurovascular centers using an international, multicenter dataset and provide extensive data on risk factors for postoperative morbidity and mortality.

The main objective aimed to analyze surgical approaches and intraoperative events in relation to preexisting patient-specific and aneurysm-specific characteristics affecting outcomes after microsurgical clipping for UIAs of the anterior circulation.

10.3.3. Methods

10.3.3.1. Study design

This study used a large multicenter, retrospectively collected dataset with 2245 patients from 15 international neurosurgery centers with cerebrovascular specialization. The analysis

presented here is based on a subset of the data collected from the centers mentioned below as part of a benchmark analysis. A standardized questionnaire was provided for all institutions to ensure uniform data collection. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards and local laws. Institutional review board approval was acquired from each site independently as well as a central approval (Medical Ethics Committee of the Hamburg Medical Association [2021-300063-WF]). A patient consent exemption was granted because of the retrospective nature of the study.

10.3.3.2. Patient and Hospital Selection

The final collaborative consortium included 15 centers: 7 from Europe (Hamburg, Berlin, Munich, Vienna, Linz, Mainz, and Milan), 5 from the United States (Phoenix, San Francisco, San Antonio, Thomas Jefferson Philadelphia, and Penn Medicine Philadelphia), 2 from Asia (Novosibirsk and Pohang), and 1 from South America (Sao Paulo) as described before.[123] All consecutively treated patients age older than 18 years who underwent elective microsurgical clipping of an untreated UIA between January 2016 and December 2020 were included. Posterior circulation aneurysms (n=53) were excluded from further analyses because of the rare and highly individual decision for clipping. All participating centers were specialized in cerebrovascular treatment defined as possibility for open and endovascular treatment as well as availability of neurosurgical intensive care unit (ICU) ward as previously described.[123] The decision whether and how to treat an unruptured aneurysm was made in an interdisciplinary cerebrovascular board of the treating center. In all centers, treatment of UIAs was performed by board-certified neurosurgeons with a cerebrovascular specialization (defined as successful completion of a cerebrovascular fellowship after residency).

10.3.3.3. Outcome Parameters and Statistical Analyses

Patients underwent computed tomography (CT) angiography after microsurgical clipping to assess closure of the treated aneurysm. In case of uncertain assessment or relevant remnant, an additional angiogram was performed in these patients. The postoperative angiograms and CT angiographies were assessed by a board-certified neuroradiologist and

a neurosurgeon with a cerebrovascular specialization of the corresponding institution. Neurological complications and worsening of modified Rankin Scale (mRS) at the day of discharge compared with admission were defined as outcome parameters. A neurological complication was defined as the postoperative occurrence of 1 or more of the following during hospital stay: evidence of ischemic stroke on multimodality CT or MRI, evidence of intracerebral hemorrhage on CT or MRI, intracranial hematoma requiring surgical relief, and new neurological deficit (defined as new impairment of any cranial nerve function, motor function, or sensory function assessed by a board-certified neurosurgeon or neurologist at discharge) as previously described.[123] Ischemic strokes were further subdivided into minor strokes without clinical symptoms and major strokes that resulted in neurological deterioration. The mRS value of each patient was assessed by the attending neurosurgeon, who was not the operative surgeon, as previously described.[62] The length of stay in the hospital and ICU was counted from the day of surgery to the day of discharge from the index hospital. The presence of a subdural hematoma was recorded when a threshold of 5 mm was reached. Surgical removal of an intracerebral hemorrhage or subdural hematoma was based on an individual, patient-specific decision by the treating center. Preoperative assessment was performed using the American Society of Anesthesiology score.

Statistical analyses were performed using IBM SPSS® v.25 (IBM Corporation). Numerical variables were given as mean and SD, ordinal variables as median and interquartile range, and nominal variables as number and percentage (Table11). A logistic regression (Table 12 and 13) was calculated independently for each patient characteristic adjusted for age and sex (Tables 12A and 13A). In a next step, the variables of the surgical procedure were tested in a multivariate regression analysis adjusted for all described patient characteristics (Tables 12B and 13B). A Pearson correlation matrix and variance inflation factors were used to test all patient characteristics for multicollinearity. The selection of patient characteristics for regression analysis was based on the results of the collinearity analysis. All statistical analyses were reviewed by an experienced statistician of the Department of Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf.

Patient-, aneurysm- and surgery-related characteristics of 2192 patients who underwent microsurgical clipping of unruptured aneurysm of the anterior circulation.

Sex – no. (%)	
male	**553 (25.2)**
female	**1639 (74.8)**
Age (years) – mean (SD)	**57.3 (11.1)**
Hypertension – no. (%)	**1402 (64.0)**
ASA classification – median (IQR)	**2 (1)**
Autosomal polycystic kidney disease – no. (%)	**37 (1.7)**
BMI – mean (SD)	**27.1 (5.5)**
Coagulopathy or thrombophilic disorder – no. (%)	**46 (2.1)**
Congestive heart failure – no. (%)	**116 (5.3)**
COPD – no. (%)	**118 (5.4)**
Current cigarette smoking - no. (%)	**530 (24.2)**
Diabetes mellitus – no. (%)	**204 (9.3)**
Family history of UIA or SAH - no. (%)	**146 (6.7)**
mRS at presentation – median (IQR)	**0 (1)**
mRS at discharge – median (IQR)	**0 (1)**
Previous SAH from another aneurysm – no. (%)	**213 (9.7)**
Previous stroke – no. (%)	**281 (12.8)**
Incidental finding – no. (%)	**1900 (86.7)**
Aneurysm location – no. (%)	
ACA/Acom	**565 (25.8)**
MCA	**1203 (54.9)**
ICA	**259 (11.8)**
PCOM/AChoA	**165 (7.5)**
Aneurysm calcification – no. (%)	**211 (9.6)**
Aneurysm maximum diameter [mm] – mean (SD)	**6.67 (4.92)**
Neck diameter [mm] – mean (SD)	**3.63 (2.06)**
Morphology – no. (%)	
Regular	**1607 (73.3)**
Irregularity or lobulation	**585 (26.7)**
Multiple aneurysms – no. (% of cases)	**917 (41.8)**
INTRAOPERATIVE	
Intraoperative rupture – no. (%)	**74 (3.4)**
Repositioning of initial clip – no. (%)	**349 (15.9)**
Use of more than 1 clip – no. (%)	**1128 (51.5)**
Simultaneous clipping of more than 1 aneurysm – no. (%)	**532 (24.3)**
Temporary vessel occlusion – no. (%)	**642 (29.3)**
Simultaneous bypass – no. (%)	**73 (3.3)**
POSTOPERATIVE	
Cardiac complication – no. (%)	**20 (0.9)**

Intracerebral hemorrhage – no. (%)	**59 (2.7)**
Meningitis – no. (%)	**11 (0.5)**
New neurological deficit – no. (%)	**216 (9.9)**
Pulmonary complication – no. (%)	**39 (1.8)**
Seizure – no. (%)	
focal	**38 (1.7)**
generalized	**18 (0.8)**
Subdural hematoma – no. (%)	
yes, without evacuation	**21 (1.0)**
yes, requiring evacuation	**16 (0.7)**
Stroke – no. (%)	
minor	**77 (3.5)**
major	**45 (2.1)**
none	**2070 (94.4)**
Surgical site infection – no. (%)	**40 (1.8)**
Length of ICU stay [days] – mean (SD)	**2.12 (4.98)**
Length of postoperative hospital stay [days] – mean (SD)	**8.20 (9.31)**
In-hospital mortality – no. (%)	**17 (0.8)**
Complete occlusion at discharge – no. (%)	**2089 (95.3)**
mRS difference admission to discharge – median (IQR)	**0 (0)**
Neurological deterioration / mRS worsening – no. (%)	**340 (15.5)**

Table 11: *Patient-, aneurysm- and surgery-related characteristics of 2192 patients who underwent microsurgical clipping of unruptured aneurysm of the anterior circulation. ACA = anterior cerebral artery, AChoA = anterior choroidal artery; ACOM = anterior communicating artery; ASA = American Society of Anesthesiologists; BMI = body mass index; COPD = chronic obstructive pulmonary disease;ICU = intensive care unit; ICA = internal carotid artery; MCA = media cerebral artery; mRS = Modified Rankin Scale; PCOM = posterior communicating artery; UIA = unruptured intracranial aneurysm; SAH = subarachnoid hemorrhage; SD = standard deviation*

	No complication (n=1898)	**Complication (n=294)**	**OR (CI)**	***P* value**
Sex – no. (%)			0.88 (0.66 – 1.17)	0.373
male	485 (25.6)	68 (23.1)		
female	1413 (74.4)	226 (76.9)		
Age (years) – mean (SD)	57.1 (11.0)	58.8 (11.4)	1.01 (1.00 – 1.03)	**0.016**
(A) LOGISTIC REGRESSION ADJUSTED FOR SEX AND AGE				

Hypertension – no. (%)	1191 (62.8)	211 (71.8)	1.44	**0.011**
ASA classification – median (IQR)	2 (1)	2 (1)	1.13 (0.93 – 1.38)	0.219
Autosomal polycystic kidney disease – no. (%)	26 (1.4)	11 (3.7)	3.00 (1.46 – 6.16)	**0.003**
BMI – mean (SD)	27.1 (5.5)	27.2 (5.7)	1.00 (0.98 – 1.02)	0.937
Coagulopathy or thrombophilic disorder – no. (%)	36 (1.9)	10 (3.4)	1.81 (0.89 – 3.70)	0.104
Congestive heart failure – no. (%)	95 (5.0)	21(7.1)	1.42 (0.86 – 2.36)	0.175
COPD – no. (%)	94 (5.0)	24 (8.2)	1.60 (1.00 – 2.56)	0.052
Current cigarette smoking – no. (%)	458 (24.1)	72 (24.5)	1.10 (0.75 – 1.37)	0.936
Diabetes mellitus – no. (%)	172 (9.1)	32 (10.9)	1.11 (0.74 –1.66)	0.631
Family history of UIA or SAH – no.(%)	126 (8.8)	20 (9.3)	1.08 (0.66 – 1.78)	0.762
mRS at presentation – median (IQR)	0 (1)	0 (1)	1.36 (1.17 –1.57)	**<0.001**
Previous SAH from another aneurysm – no. (%)	186 (9.8)	27 (9.2)	1.05 (0.69 – 1.61)	0.817
Previous stroke – no. (%)	234 (12.3)	47 (16.0)	1.31 (0.93 – 1.85)	0.129
Incidental finding – no. (%)	1666 (87.8)	234 (79.6)	1.80 (1.31 – 2.48)	**<0.001**
Aneurysm location – no. (%) ACA/Acom MCA ICA PCOM/AChoA	 484 (25.5) 1051 (55.4) 217 (11.4) 146 (7.7)	 81 (27.6) 152 (51.7) 42 (14.3) 19 (6.5)	 Ref. 0.86 (0.64 – 1.15) 1.18 (0.78 – 1.79) 0.77 (0.45 – 1.33)	 Ref. 0.301 0.434 0.352
Aneurysm calcification – no. (%)	169 (8.9)	42 (14.3)	1.63 (1.13 – 2.36)	**0.009**
Aneurysm maximum diameter [mm] – mean (SD)	6.4 (4.6)	8.2 (6.3)	1.06 (1.04 – 1.08)	**<0.001**
Aneurysm neck diameter [mm] – mean (SD)	3.6 (2.0)	4.0 (2.3)	1.09 (1.04 – 1.15)	**0.001**
Morphology– no. (%) Regular Irregularity or lobulation	 1414 (74.5) 484 (25.5)	 193 (65.6) 101 (34.4)	 1.52 (1.16 – 1.98)	 **0.002**
Multiple aneurysms – no. (% of cases)	787 (41.5)	130 (44.2)	1.07 (0.83 – 1.37)	0.623
(B) MULTIVARIABLE REGRESSION ADJUSTED FOR ALL PARAMETERS ABOVE				
Intraoperative rupture – no. (%)	51 (2.7)	23 (7.8)	2.86 (1.61 – 5.10)	**<0.001**
Repositioning of initial clip – no. (%)	292 (15.4)	57 (19.4)	1.31 (0.92 – 1.86)	0.136
Use of more than 1 clip – no. (%)	972 (51.2)	156 (53.1)	0.96 (0.72 – 1.27)	0.768
Simultaneous clipping of more than 1 aneurysm – no. (%)	438 (23.1)	94 (32.0)	1.74 (1.19 – 2.55)	**0.005**
Temporary vessel occlusion – no. (%)	546 (28.8)	96 (32.7)	0.96 (0.70 – 1.32)	0.794
Simultaneous bypass – no. (%)	52 (2.7)	21 (7.1)	1.72 (0.77 – 3.81)	0.186

Table 12: *Regression analysis for postoperative neurological complications. % = % within complications/no complication; ACA = anterior cerebral artery, AChoA = anterior choroidal artery; ACOM = anterior communicating artery; ASA = American Society of Anesthesiologists; BMI = body mass index; COPD = chronic obstructive pulmonary disease;*

ICA = internal carotid artery; IQR = interquartile range; MCA = media cerebral artery; mRS = Modified Rankin Scale; PCOM = posterior communicating artery; UIA = unruptured intracranial aneurysm; SAH = subarachnoid hemorrhage; SD = standard deviation;

	no mRS worsening (n=1852)	**mRS worsening (n=340)**	**OR (CI)**	***P* value**
Sex – no. (%)			0.88 (0.67 – 1.16)	0.358
male	474 (25.6)	79 (23.2)		
female	1378 (74.4)	261 (76.8)		
Age (years) – mean (SD)	57.2 (10.9)	57.9 (11.8)	1.01 (1.00 – 1.02)	0.328
(A) LOGISTIC REGRESSION ADJUSTED FOR SEX AND AGE				
Hypertension – no. (%)	1163 (62.8)	239 (70.3)	1.37 (1.06 – 1.79)	**0.017**
ASA classification – median (IQR)	2 (1)	2 (1)	1.28 (1.06 – 1.53)	**0.009**
Autosomal polycystic kidney disease – no. (%)	23 (1.2)	14 (4.1)	3.49 (1.77 – 6.88)	**<0.001**
BMI – mean (SD)	27.1 (5.5)	27.4 (5.9)	1.01 (0.99 – 1.03)	0.412
Coagulopathy or thrombophilic disorder – no. (%)	25 (1.3)	21 (6.2)	4.71 (2.60 – 8.54)	**<0.001**
Congestive heart failure – no. (%)	92 (5.0)	24 (7.1)	1.46 (0.90 – 2.35)	0.125
COPD – no. (%)	95 (5.1)	23 (6.8)	1.30 (0.81 – 2.09)	0.278
Current cigarette smoking – no. (%)	439 (23.7)	91 (26.8)	1.10 (0.84 – 1.46)	0.488
Diabetes mellitus – no. (%)	157 (8.5)	47 (13.8)	1.65 (1.15 – 2.35)	**0.006**
Family history of UIA or SAH	123 (6.6)	23 (6.8)	1.02 (0.64 – 1.62)	0.925
mRS at presentation – median (IQR)	0 (1)	0 (1)	1.01 (0.86 – 1.18)	0.933
Previous SAH from another aneurysm – no. (%)	176 (9.5)	37 (10.9)	1.17 (0.81 – 1.71)	0.406
Previous stroke – no. (%)	240 (13.0)	41 (12.1)	0.89 (0.62 – 1.28)	0.538
Incidental finding – no. (%)	1615 (87.2)	285 (83.8)	1.30 (0.94 – 1.80)	0.108
Aneurysm location – no. (%)				
ACA/Acom	481 (26.0)	84 (24.7)	Ref.	0.866
MCA	1019 (55.0)	184 (54.1)	1.02 (0.77 –1.36)	
ICA	216 (11.7)	43 (12.6)	1.11 (0.74 – 1.67)	
PCOM/AChoA	136 (7.3)	29 (8.5)	1.19 (0.75 – 1.91)	
Aneurysm calcification – no. (%)	162 (8.7)	49 (14.4)	1.72 (1.21 – 2.44)	**0.002**
aneurysm maximum diameter [mm] – mean (SD)	6.5 (4.7)	7.8 (5.7)	1.05 (1.03 – 1.07)	**<0.001**
aneurysm neck diameter [mm] – mean (SD)	3.6 (2.1)	3.9 (2.1)	1.06 (1.01 – 1.12)	**0.021**
Morphology			1.50 (1.17 – 1.93)	**0.002**
Regular	1382 (74.6)	225 (66.2)		
Irregularity or lobulation	470 (25.4)	115 (33.8)		

Multiple aneurysms – no. (% of cases)	756 (40.8)	161 (47.4)	1.26 (1.00 – 1.60)	0.051
(B) MULTIVARIABLE REGRESSION ADJUSTED FOR ALL PARAMETERS ABOVE				
Intraoperative rupture – no. (%)	54 (2.9)	20 (5.9)	1.75 (0.95 – 3.22)	0.075
Repositioning of initial clip – no. (%)	287 (15.5)	62 (18.2)	1.22 (0.87 – 1.72)	0.240
Use of more than 1 clip – no. (%)	955 (51.6)	173 (50.9)	0.82 (0.63 – 1.07)	0.149
Simultaneous clipping of more than 1 aneurysm – no. (%)	426 (23.0)	106 (31.2)	1.38 (0.97 – 1.95)	0.070
Temporary vessel occlusion – no. (%)	528 (28.5)	114 (33.5)	1.12 (0.83 – 1.51)	0.463
Simultaneous bypass – no. (%)	52 (2.8)	21 (6.2)	1.48 (0.65 – 3.36)	0.347

***Table 13**: Regression analysis for postoperative neurological deterioration. % = % within mRS worsening/ no mRS worsening; ACA = anterior cerebral artery, AChoA = anterior choroidal artery; ACOM = anterior communicating artery; ASA = American Society of Anesthesiologists; BMI = body mass index; COPD = chronic obstructive pulmonary disease; ICA = internal carotid artery; IQR = interquartile range; MCA = media cerebral artery; mRS = Modified Rankin Scale; PCOM = posterior communicating artery; UIA = unruptured intracranial aneurysm; SAH = subarachnoid hemorrhage; SD = standard deviation*

10.3.4. Results

10.3.4.1. Patient Characteristics

A total of 2245 patients from 15 centers on 4 continents were entered into the database. A mean (SD) of 146 (110) patients were included per center (Figure 16). After exclusion of aneurysms of the posterior circulation, 2192 (97.6%) patients remained for further analyses. The mean (SD) patient age was 57.3 (11.1), and 74.8% (n=1639) were women (Table 11). Patients' baseline characteristics and comorbidities as well as aneurysm-specific and surgery-specific data are presented in Table 11. Overall, the in-hospital mortality rates were 0.8% and 0.9% during follow-up (Table 14). A complete occlusion of the treated aneurysm was achieved in 2089 patients (95.3%).

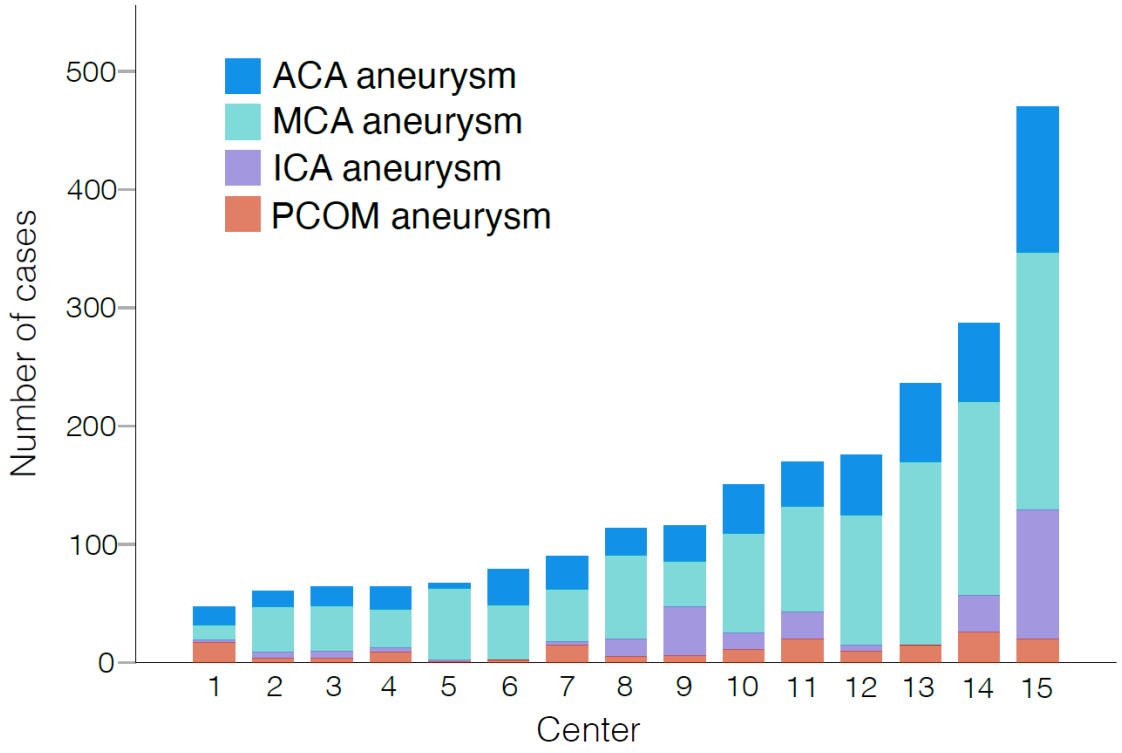

Figure 16: *Total number of procedures performed per center during the study period. Color coded represents the proportion of aneurysms with respect to their localization.*

FOLLOW-UP	
Months after surgery – mean (SD)	12.94 (13.82) (n=1566)
Complete Occlusion of Aneurysm – no. (%)	1291 (1364 valid)
Retreatment of Aneurysm – no. (%)	30 (1.91) (1568 valid)
cSDH – no. (%)	30 (1.92) (1560 valid)
Mortality – no. (%)	14 (0.89) (1569 valid)
mRS – median (IQR)	0 (1) (1568 valid)
mRS difference to admission – median (IQR)	0 (0) (1568 valid)

Table 14*: Follow-Up.*

10.3.4.2. Risk Analysis for Postoperative Complications

As a next step, we investigated the association between patient-specific and aneurysm-specific characteristics and the occurrence of postsurgical complications (Table 12). Here, age, hypertension, autosomal dominant polycystic kidney disease, mRS at presentation, symptomatic aneurysm, aneurysm diameter, neck diameter, calcification of the aneurysm, and morphology of the aneurysm were shown to be preexisting risk factors for the occurrence of any complication. In addition, intraoperative aneurysm rupture and concomitant clipping of more than 1 aneurysm, adjusted for all patient characteristics, were shown to be associated with an increased risk of complication (odds ratio 2.863 [CI 1.606 – 5.104]; p<0.001 and odds ratio 1.738 [CI 1.186 – 2.545]; p=0.005, respectively) (Table 12). By contrast, for example, temporary vessel occlusion, a discussed parameter, was not shown to be associated with an increased risk of complication.

10.3.4.3. Risk Factors for Neurological Deterioration

Additional analyses were performed for neurological deterioration as an outcome parameter defined as mRS worsening at discharge (Table 13). Risk factors identified were hypertension, American Society of Anesthesiology score, autosomal dominant polycystic kidney disease, coagulopathy or thrombophilic disorder, diabetes mellitus, aneurysm calcification, morphology, diameter, and neck diameter. Here, patients with a calcified aneurysm had a 1.72-fold higher risk of mRS worsening at discharge than patients with non-calcified aneurysms (CI 1.213 - 2.435; p=0.002). None of the surgical-related parameters had an impact on mRS worsening. Table 15 provides a detailed analysis of adverse events within the patients with worsened mRS.

Adverse event	**no. (%)**
Stroke	
minor	57 (16.8)
major	43 (12.6)
Intracerebral hemorrhage	42 (12.4)
Subdural hematoma requiring evacuation	6 (1.8)

New motor/sensory/speech deficit	
Motor deficit	104 (30.6)
Sensory deficit	12 (3.5)
Speech deficit	34 (10.0)
Combination of the above	19 (5.6)
Cerebral vasospasm	30 (8.8)
Postoperative seizures	32 (9.4)
Surgical site infection	9 (2.6)
Postoperative meningitis	3 (0.9)
Postoperative hydrocephalus	13 (3.8)
Pulmonary complication including embolism	24 (7.1)
Cardiac complication	10 (2.9)
In-hospital mortality	17 (5.0)

***Table 15**: Adverse events in patients with mRS worsening (n=340). Multiple events possible.*

10.3.4.4. Volume-outcome relationship

Because caseload and volume-outcome relationship analyses are of increasing importance across all surgical specialties, we further analyzed the same in our study.[171] All centers of our study were specialized cerebrovascular centers defined as possibility for open and endovascular treatment as well as availability of neurosurgical ICU ward. The number of surgeons involved in microsurgical treatment of unruptured aneurysms at the participating institutions ranged from 1 to 3.

To address this, we examined the association of the centers' respective caseload with the incidence of complications and neurologic deterioration (Figure 17). Here, we could not find a significant correlation between the number of cases treated in the respective center and the rate of complications (ρ=-0.123; p=0.661). There tended to be a lower rate of neurologic deterioration in centers with a higher number of cases. However, this tendency did not remain statistically significant (ρ=-0.475; p=0.073).

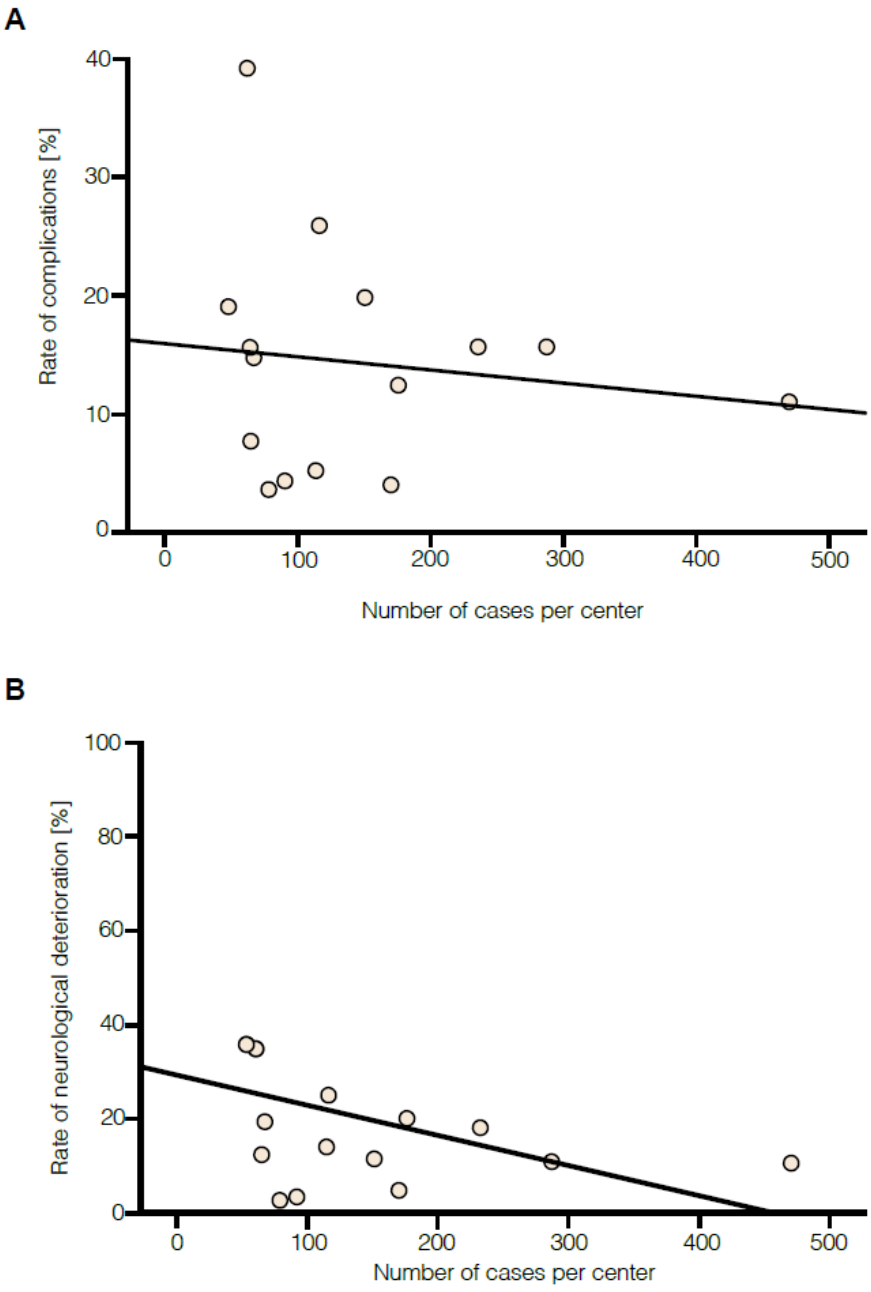

Figure 17: *Volume-outcome relationship for frequency of postoperative complications and neurological deterioration at time of discharge*

10.3.5. Discussion

The treatment of UIA continues to be an interdisciplinary challenge. To achieve the best possible results, assessment and evaluation of many factors are required. We sought to

examine the current global state of the art of microsurgical clipping of anterior circulation aneurysms and to identify patient-centered and surgery-centered risk factors for postoperative morbidity and neurological outcome.

Our study reports a complete aneurysm occlusion rate of 95.3% at discharge and 94.6% at follow-up which is in accordance with previous neurosurgical studies.[160] At this point, it is worth mentioning that valid results on complication rates after neurosurgical treatment are underreported and hence our multicenter study reveals much-needed rates from a large real-word data set.[136] Our data show a high occlusion rate and high durability of microsurgical aneurysm occlusion. In meta-analyses of aneurysms treated endovascularly by coiling, an adequate aneurysm occlusion rate of up to about 92.1% is reported for aneurysms of the anterior circulation.[172] For aneurysms treated with flow-diverters or endosaccular flow disruption devices occlusion rates of 76% - 80% are found.[173,174] Compared with these data, our analysis suggests an advantage of microsurgical treatment over endovascular methods in terms of occlusion rates. This assumption is supported by the prospective trial by Darsaut et al who found a residual saccular aneurysm in only 7% of microsurgically treated aneurysms. By contrast, the rate of residual saccular aneurysms in the endovascularly treated group was 15%.[175] Furthermore, some studies suggest that clipping may be a more cost-effective method of treatment.[176-178] In addition, we confirmed several known patient-specific and aneurysm-specific risk factors. Patients' age and arterial hypertension have been described earlier to be associated with postoperative complications.[140,143,145,179] Orz et al found an aneurysm size > 15mm to be a risk factor for poor outcome.[180] In line, our analyses show increasing aneurysm size as a risk factor for postoperative complications and mRS deterioration at discharge. The size of the aneurysms treated in our database was comparable with large prospective randomized trials on ruptured and unruptured aneurysms and considered representative.[175,181]

In general, reports on complication rates vary in the literature. However, the rates in our study are comparable to those in large meta-analyses.[136,140]

In this work, special emphasis is given to the study of intraoperative events and surgical techniques as well as their significance for affecting patients' outcome. Intraoperative aneurysm rupture and simultaneous clipping of more than 1 aneurysm during surgery were

independent risk factors for the occurrence of postoperative complications. However, with respect to neurological deterioration at discharge, these parameters did not reach statistical significance and are in line with the results of smaller series.[182,183] Presumably, the risks of simultaneous clipping of multiple aneurysms are additive, and it can be assumed that this additive effect is similar to the risk of a 2-stage procedure and the then respective risks of the individual operations.

Another subject of growing importance in recent years is the volume-outcome relationship[171] and an interhospital heterogeneity in outcomes.[184] The correlation between caseload and postoperative outcome as well as learning curves is reported differently between the available studies.[185-187] However, there was no significant difference in terms of postsurgical outcome between our centers. The lack of association between caseload and rate of complications as well as neurological deterioration might reflect the homogeneous selection of study centers with high expertise in the cerebrovascular field.

10.3.6. Conclusion

In summary, our global multicenter study emphasizes the relevance of preexisting patient-related and aneurysm-related risk factors that need to be considered in decision-making for the best therapeutic regimen. The surgery-related factors were associated with postoperative morbidity but did not represent a significant risk factor for neurological deterioration. Improving the intraoperative setting with novel techniques may lead to the reduction of surgery-related morbidity in the future. Lastly, microsurgical treatment of anterior circulation aneurysms leads to excellent occlusion rates at acceptable risk of neurological deterioration.

The risk of neurological deterioration at discharge is primarily affected by patient comorbidities and aneurysmal factors.

10.3.6.1. Strengths

The strength of this work is the large, global, and multicenter-based data set, which contains patients treated in a recent period since many larger studies date from past decades and may no longer adequately reflect the current collective of patients. Our study represents a

real-world cross-section of patients treated by clipping in an era of growing importance of endovascular treatment. Complementary to meta-analyses, we were able to specifically address the topics of morbidity and mortality regarding a large number of well-documented potential risk factors. All consecutively treated patients were included to avoid selection bias.

10.3.6.2. Limitations

This study is subject to limitations. As described, this is a retrospective data analysis and not a prospective randomized study or registry. These data may, therefore, be collected and recorded differently at the various sites. Furthermore, the short follow-up is a limitation because this study primarily investigates perioperative morbidity. In addition, our follow-up analyses do not include data on the patients' quality of life. A variable not assessed in the current analysis was surgeon experience, which has been found to be positively associated with outcomes in other neurosurgical procedures. There was no comparison with endovascular-treated patients possible because data were obtained from a microsurgery-centered data set, and the outcomes after endovascular treatment was not subject of this study.

11. Discussion

The findings of this cumulative dissertation and the three complementary studies offer a comprehensive perspective on the challenges and advancements in managing UIAs. Each study contributes unique insights into critical areas, including predictive modeling through ML, benchmarking for standardized quality assessment, and evaluating surgical practices and outcomes. Together, these works form a framework for addressing longstanding issues in UIA management and advancing the field of cerebrovascular neurosurgery.

The discussion aims to integrate these themes, highlighting connections between predictive analytics, outcome benchmarks, and surgical paradigms. The findings provide tools for improving patient outcomes and optimizing clinical decision-making.

Clinical Outcomes and Associated Risk Factors

Nowadays, the management of UIAs is interdisciplinary, with a fundamental role of microsurgical clipping and its proven efficacy and durability, particularly for complex aneurysms and aneurysms in the anterior circulation.[33,188] The high occlusion rates after microsurgical clipping mentioned in the literature >90%,[51,52,160,189,190] were reproducible in the findings of this cumulative dissertation. In the multicenter cohort of the third study ("*Microsurgical Clipping of Unruptured Anterior Circulation Aneurysms-A Global Multicenter Investigation of Perioperative Outcome*") with 2192 patients who underwent microsurgical clipping of unruptured aneurysms in the anterior circulation, a complete occlusion at discharge was seen in 95.2% of the cases. Also, in the cohort of the first study ("*Machine learning based outcome prediction of microsurgically treated unruptured intracranial aneurysms*") on which the ML outcome prediction tools were based, a complete occlusion rate of 98.5% of all treated aneurysms and 100% of those in the test set was seen. In the second study cohort ("*Global Outcomes for Microsurgical Clipping of Unruptured Intracranial Aneurysms: A Benchmark Analysis of 2245 Cases*"), the complete occlusion rate after 12 months in the low-risk cohort was 99%. The findings are comparable with long-term

occlusion rates in the literature >95% and underscore the importance of microsurgical clipping in achieving long-term aneurysm stability and reducing retreatment rates.[52,191,192]

Recent research suggests that the occlusion rate after endovascular management, like coiling or flow-diversion (FD), is considerably lower.[172-174]

Looking particularly at MCA aneurysms, the long-term closure rates for coiling are ~30%[193,194], for endosaccular devices after 3 years up to 60%[195], and for FD up to 80%[196] had an “adequate” but not complete occlusion, after 12 months. Therefore, the findings suggest an advantage of microsurgical clipping. These findings are particularly significant in healthcare cost control, as the need for repeat procedures can impose substantial financial and logistical burdens on patients and healthcare systems.[176,197,198]

Neurological outcomes were a focus across all three studies of the dissertation. The first Study reported a 6.3% incidence of pNNDs, while the multicentric findings of the third study observed a slightly lower rate of 9.9%. This variation may reflect differences in patient selection, surgical techniques, or institutional practices. The proportion of non-permanent deficits in the first study suggests that many patients experience neurological recovery over time. Functional outcomes, measured by the modified Rankin Scale (mRS), further underscore this point. In the first study, 10.3% of patients experienced a decline in mRS of more than one point between admission and discharge, highlighting short-term functional deterioration.

An insight into long-term recovery is provided in the second study's findings, showing that only 4.1% of patients had an unfavorable outcome (mRS ≥3) at discharge, which decreased to 2.0% at 24 months. This improvement underscores the importance of long-term follow-up in assessing the outcome of microsurgical clipping. Furthermore, in the low-risk cohort of study 2, 98.5% of patients achieved a favorable neurological outcome (mRS ≤2) with a benchmark cutoff of 95.9%. These findings reflect the efficacy of microsurgical clipping, particularly for well-selected patients in specialized centers.

The studies also addressed the length of hospital stay. The second study established a benchmark cutoff of ≤7.7 days, representing the cut-off for the best achievable outcome. The third study reported a mean hospital stay of 8.2 days, slightly exceeding the benchmark.

These differences result from variations in center-specific practices and postoperative care protocols. Differences between European and US hospitals concerning the postoperative length of stay after interventional procedures are well-known.[154-156]

Mortality rates across all three cohorts are low, highlighting the safety of microsurgical clipping. Recent studies have described the mortality rate after microsurgical clipping of UIAs as between 0.5% and 2.6%.[136,150] The results of the third study show a mortality rate of 0.8%, while the second study has a comparable rate of 0.6%, even in the high-risk cohort. These findings show that microsurgical clipping can be performed with a low mortality rate in experienced centers, even for patients with certain preoperative risk factors.

The findings also clearly show preoperative parameters linked to a worse postoperative outcome and confirmed pre-existing findings in the literature. In the multicentered investigation of perioperative outcome (third study), preoperative parameters like patients' age, arterial hypertension, or aneurysm-specific parameters like the size of the aneurysm were associated with a worse postoperative outcome.[140,145,180] In addition, the SHAP analysis of the first study shows that the parameters of the location of the aneurysm, preoperative clinical symptoms, and preoperative mRS, as a clinical score, strongly influence the postoperative outcome.

A closer look at intraoperative events is also essential for evaluating a more profound perioperative risk profile for aneurysm patients. That's why a special focus was on intraoperative parameters and events. Although not statistically significant, the multicentric cohorts (second and third study) showed parameters such as an intraoperative aneurysm rupture or the simultaneous clipping of multiple aneurysms as independent risk factors for postoperative complications. While these findings align with existing literature, they also highlight opportunities for improvement.

However, the role of microsurgical clipping of UIAs must be considered within the broader context of evolving treatment paradigms. Endovascular techniques have gained scientific prominence due to their minimally invasive nature and shorter recovery times. While these methods are particularly advantageous for posterior circulation aneurysms and patients with significant comorbidities, their lower occlusion rates and the need for long-term anticoagulation represent notable disadvantages. These therapy difficulties underscore the

importance of a multidisciplinary approach to UIA management, integrating neurosurgeons, interventional radiologists, neurologists, and patient preferences.

Quality assessment

The results of endovascularly and microsurgically treated UIAs must be compared with each other despite all the differences in methodology. Objective tools are necessary to evaluate postoperative complications and outcomes between different treatment strategies. A reasonable quality assessment is essential to improve objectivity. Quality assessment and benchmarking have become more and more critical to advancing surgical disciplines, offering structured methods to evaluate performance, enhance outcomes, and promote transparency.[82]

These tools are essential in neurosurgery, where the stakes are high due to the complexity of procedures. Benchmarking establishes standardized outcome measures by defining best-achievable results for specific procedures, enabling comparisons across institutions and treatment modalities. Such benchmarks are applicable in a therapeutic medical field, such as aneurysm treatment, where variability in surgical and endovascular techniques, case volumes, and institutional practices significantly influence patient outcomes.

For this reason, Benchmarking is another cornerstone of this dissertation, providing a standardized methodology for assessing surgical outcomes. Establishing benchmarks is critical for evaluating and comparing performance across institutions and treatment modalities.

In the second study, based on a multicenter and international cohort of 2245 microsurgically treated UIA patients, the best possible clinical, functional, and radiological outcomes are mentioned by establishing benchmark cutoffs. Benchmarks are set for several outcome variables.

Preoperative well-known risk factors were used to stratify the cohort into high-risk and low-risk groups. Benchmark cutoffs, determined as the 75th percentile of each center’s median, were employed to represent the best achievable outcomes. Key metrics such as

intraoperative rupture rate (≤3.8%), length of hospital stay (≤7.7 days), and unfavorable neurological outcome (≤2.03%), defined as mRS ≥3 at 24 months after surgery, set new standards for quality assessment in UIA management.

A strength of the benchmarking framework is its adaptability to different clinical settings. The study incorporated Data from 15 centers across four continents, and the benchmarks capture global variations in healthcare systems, resource availabilities, and surgical expertise. The international and multicentric data acquisition enhances the generalizability of the findings.

Concerning the ongoing discussion about the treatment choice for UIAs, establishing benchmarks enables direct comparisons between microsurgical and endovascular treatment modalities. Benchmarks facilitate evidence-based discussions on the relative advantages of the respective modalities. For instance, compared to endovascular methods, the superior occlusion rates for microsurgical clipped UIAs (99% at 12 months in the Low-Risk cohort) highlight its continued relevance in specific clinical scenarios.[199]

Integration of ML

The feasibility of ML in the prediction of medical outcomes or as part of clinical decision processes has already been reported in several works.[68,69,99] The application of ML neurosurgery could advance this field, potentially addressing challenges in decision-making and outcome prediction for UIAs. Pilot studies by Staartjes et al.[76] and Ishankulov et al.[77] have already presented promising results and previewed that ML algorithms are a feasible tool for outcome prediction in cerebrovascular neurosurgery.

The first study demonstrates the utility of ML models for predicting functional and clinical outcomes after microsurgical clipping of UIAs. As mentioned above, the mRS score, a functional clinical score assessed postoperatively, is a helpful parameter for evaluating a neurosurgical procedure's clinical outcome. Consequently, predicting such a significant clinical outcome value is of great interest.

The ML model from the first study concerning the prediction of the postoperative mRS score, based on an internal patient cohort - all patients operated microsurgically at the Kepler University Hospital in Linz - represent the best clinical outcome prediction results ever published for microsurgical clipping of UIAs with a ROC-AUC of 0.87 ± 0.03, which means an excellent discrimination in ML.[119]

Likewise, the prediction of a pNND postoperatively proved to be a significant parameter. The presented ML model, predicting a pNND postoperatively in the first study showed a ROC-AUC of 0.71 ± 0.04 in the internal group and outperformed traditional statistical methods like logistic regression ($p < 0.0001$).

These results show that predictive tools can offer neurosurgeons an outcome estimation and a framework to evaluate patient-specific risks for microsurgical clipping of UIAs.

A methodological innovation in this context is the use of temporal train-test splits. Due to the advancements in surgical techniques in recent years and technical advancements like intraoperative angiography, ICG-angiography, and intraoperative neuromonitoring, long-term datasets are often influenced by temporal factors, making it necessary to address domain shifts.[116] A temporal splitting of training and testing groups is feasible to ensure a more realistic evaluation of prediction models.[116]

This method accurately represents a model's predictive performance on future patient data rather than random train-test splits. Given that a prediction model for future patients is based on past patients, this temporal train-test split makes sense. This approach enhances the validity of outcome predictions and bridges the gap between retrospective data and prospective applications. Nevertheless, it should be noted that greater emphasis on more recent samples can further enhance the generalizability of models for future data.

For an objective assessment of the generalizability of ML models, external validation must be performed using an independent dataset. Testing the model on an external dataset from a different hospital makes a performance evaluation under independent patients possible, which is a real-world application. This process ensures that the ROC-AUC values and the performance of the ML model are not limited to the internal training and test data and can reliably generalize to previously unseen data.

The process of external validation of ML models on independent datasets from comparable neurosurgical departments is complex and challenging. These datasets must include identical parameters to ensure compatibility. This requirement likely contributes to the fact that, at the time of the first study, no external validation for ML-based prediction models following microsurgical clipping of UIAs had been published before.

That's why the internally validated ML models with excellent and adequate performances were externally tested on a previously unseen dataset from the Department of Neurosurgery at the University Medical Centre Hamburg-Eppendorf. The external validation results showed ROC-AUC values of 0.61, 0.53, and 0.58 for predicting postoperative mRS > 2, the pre-and postoperative difference in mRS > 1 point, and a GOS < 5.

The SHAP analysis played a key role in a better understanding of the algorithms per se and in evaluating the underlying factors contributing to the limited performance observed in the external validation. The externally tested models demonstrated poor discrimination. This result suggests that although well-calibrated for the internal dataset, the models did not generalize effectively to an independent patient cohort. SHAP analysis was used to investigate which variables had the most significant influence on model predictions. The results indicated that key predictors, such as aneurysm location, symptomatology, and preoperative mRS, differed significantly between the internal and external datasets. These discrepancies suggest that center-specific factors, including surgical techniques, perioperative management strategies, and patient selection criteria, play a crucial role in model applicability.

As mentioned in the second and third studies, multicentric data and interhospital variability are essential to be aware of when processing multicentric data. So-called domain shifts, where differences in patient populations, institutional practices, or data collection methods lead to reduced model performance in new settings, are a fundamental challenge in ML-based predictions.

The SHAP analysis provided insights into these shifts by identifying the most influential predictors and comparing their distributions across datasets. Statistical testing confirmed that these key variables varied significantly between the training and external validation cohorts. This mismatch highlights the necessity for careful adaptation of predictive models

before they can be reliably implemented in different clinical environments. Moreover, SHAP analysis contributes to model transparency and interpretability, which is essential for clinical decision-making. Unlike black-box ML models, SHAP values allow the identification of specific features that drive predictions.

The first study's results demonstrate that while ML models can achieve strong predictive performance in an internal setting, their real-world applicability must be critically assessed. SHAP analysis proved valuable for identifying key differences and understanding why external validation showed reduced performance. However, this reduced performance in the external validation underscores a critical limitation: the need for continuous retraining and local adaptation of these models to accommodate center-specific factors such as surgical protocols, patient populations, and perioperative care.

The potential applications of ML extend beyond risk prediction. By analyzing patterns in large datasets, ML tools can identify subtle predictors of surgical success or complications that may elude conventional statistical analyses. For example, the studies highlight the strong influence of preoperative mRS scores, aneurysm location, and symptomatology on postoperative outcomes, insights that can guide more nuanced clinical decision-making. Future research should focus on expanding the scope of ML models to include multi-modal data, such as advanced imaging features and genetic markers, which may further enhance predictive accuracy.

Multicentric Data and Interhospital Variability

In the processing of big data in the multicentric studies (second and third study) or for external validation of internally validated algorithms, the differences between hospitals are significant to be aware of. The interhospital variability represents a considerable challenge in medical sciences.

The multicenter nature of these studies reveals substantial differences in metrics such as length of hospital stay, complication rates, and neurological outcomes. These variations are due to different hospital practices and the individual surgical experience.

Another challenge is that centers with higher case volumes often report better outcomes; this phenomenon is called a volume-outcome relationship, which is typical in surgical studies.[200] However, this phenomenon was not recognizable in the findings of the third study. The lack of a significant association between caseload and clinical outcomes in the third study could suggest that expertise and standardized protocols may play a more critical role than sheer volume.

The benchmarking framework can address this variability by providing objective criteria for quality assessment. Additionally, the ML models developed in the first study could complement the benchmarks. Besides aneurysm- and patient-specific parameters, the ML algorithms could incorporate additional institution-specific parameters to account for this variability. For subsequent outcome prediction, SHAP analysis would then provide the weighting of the individual institution-specific parameters, offering insights into the inner workings of the ML models.

Future research should explore the integration of benchmarking data with ML tools to develop hybrid frameworks that combine the strengths of both approaches.

Limitations

Several limitations must be acknowledged. A key limitation common to all studies is their retrospective nature, which inherently affects data quality and introduces potential biases. As data were collected over extended periods and across different institutions, variations in data recording practices, surgical techniques, and treatment indications must be considered. The long observational timeframe, particularly in the first study, spanning 19 years, raises concerns regarding changes in diagnostic options, surgical strategies, and decision-making criteria, which may contribute to selection bias.

Another critical limitation is the exclusive reliance on preoperative parameters for predictive modeling. While such models offer valuable insights into risk stratification and outcome prediction, they inherently overlook intraoperative factors that could significantly impact surgical results. For instance, the experience and individual decision-making of the treating neurosurgeon are essential variables that cannot be incorporated into preoperative models,

even though they may influence patient outcomes. Furthermore, surgeon-specific experience and procedural volume per neurosurgeon were not analyzed in detail, limiting the ability to assess their impact on model performance.

The dataset's structure and available features also present limitations. The studies focused on structured numerical and categorical variables, excluding unstructured data sources such as imaging findings, free-text clinical notes, or medication histories. The missing of these additional data could limit the models' accuracy.

Follow-up duration and data completeness further pose significant limitations. One study focused on a follow-up period of 24 months, preventing long-term outcome evaluation, particularly regarding aneurysm occlusion durability. Additionally, many patients were lost to follow-up, which may introduce attrition bias. Another significant limitation is the lack of postoperative quality-of-life assessments, which could provide a more comprehensive perspective on patient recovery beyond neurological and functional outcomes.

Lastly, the studies predominantly relied on microsurgical treatment data, with no direct comparison to endovascularly treated patients. This fact limits generalizability and prevents broader conclusions regarding optimal treatment strategies across different patient populations. External validation efforts also revealed performance discrepancies, emphasizing the impact of center-specific factors such as institutional protocols, perioperative management strategies, and patient selection criteria.

In conclusion, while these studies provide valuable contributions to neurosurgical outcome prediction, future research should address these limitations through prospective study designs, incorporation of unstructured data sources, extended follow-up periods, and improved external validation methodologies. Continuous model recalibration and adaptation will be essential to enhance predictive tools' robustness and clinical applicability.

Perspectives

While the findings of these studies are significant, several opportunities for further research remain.

First, developing predictive models incorporating multi-modal data - including imaging, genetic, and biochemical markers - could enhance their accuracy and clinical relevance. For example, advanced imaging techniques such as 3DRA and perfusion imaging may provide additional insights into aneurysm morphology and hemodynamics, critical determinants of rupture risk, and treatment outcomes.

The benchmarking framework could include endovascular treatments, enabling a more comprehensive evaluation of UIA management strategies. It would facilitate the identification of patient populations most likely to benefit from each modality, promoting personalized treatment planning. Additionally, incorporating patient-reported outcome measures into benchmarking protocols would provide a more holistic assessment of treatment success, encompassing clinical and quality-of-life outcomes.

12. Conclusion

This thesis represents a significant contribution to the field of cerebrovascular neurosurgery by integrating advanced predictive analytics, benchmarking methodologies, and multicenter data. Addressing key challenges in the management of UIAs lays the groundwork for future innovations in treatment planning, quality assessment, and clinical decision-making. The findings underscore the importance of multidisciplinary collaboration, data-driven approaches, and continuous quality improvement in optimizing patient outcomes.

The findings have important implications beyond the academic setting, offering practical value for neurosurgeons. ML-based predictive models may represent a valuable tool for risk stratification and individualized treatment planning, aiding clinicians in making informed decisions regarding the timing and modality of UIA management. These models should be continuously refined with updated data to enhance their clinical applicability.

The proposed benchmarking framework establishes a structured approach for evaluating surgical outcomes in cerebrovascular neurosurgery. Providing evidence-based criteria contributes to standardizing clinical care, reducing treatment variability, and improving patient outcomes. Furthermore, these benchmarks can support certification standards and the centralization of complex procedures in high-volume centers.

Moreover, the results reaffirm the role of microsurgical clipping as an essential treatment modality for UIAs. The high occlusion rates and long-term durability associated with clipping highlight its continued relevance in clinical practice. Treatment selection should be guided by thoroughly evaluating patient-specific factors, aneurysm characteristics, and institutional expertise, supplemented by predictive modeling and benchmarking data.

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